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[Fortsetzung auf der nächsten Seite]

(54) Title: NOVEL BINDER-DRUG CONJUGATES (ADCS) AND THEIR USE

(54) Bezeichnung : NEUE BINDER-WIRKSTOFF KONJUGATE (ADCS) UND IHRE VERWENDUNG

(57) Abstract: The present application relates to novel, anti-C4,4a binder-drug conjugates (ADCs) of N,N-dialkyl auristatins, to effective metabolites of said ADCs, to methods for producing said ADCs, to the use of said ADCs for treating and/or preventing diseases, and to the use of said ADCs for producing pharmaceuticals for treating and/or preventing diseases, in particular hyperproliferative and/or angiogenic diseases, such as cancers. Such treatments can be carried out as monotherapy or in combination with other pharmaceuticals or additional therapeutic measures.

(57) Zusammenfassung: Die vorliegende Anmeldung betrifft neue, gegen das Target C4,4a gerichtete Binder-Wirkstoff-Konjugate (ADCs) von N,N-Dialkylauristatinen, wirksamer Metabolite dieser ADCs, Verfahren zur Herstellung dieser ADCs, die Verwendung dieser ADCs zur Behandlung und/oder Prävention von Krankheiten sowie die Verwendung dieser ADCs zur Herstellung von Arzneimitteln zur Behandlung und/oder Prävention von Krankheiten, insbesondere von hyperproliferativen und/oder angiogenen Erkrankungen wie beispielsweise Krebserkrankungen. Solche Behandlungen können als Monotherapie oder auch in Kombination mit anderen Arzneimitteln oder weiteren therapeutischen Maßnahmen erfolgen.



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- vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eingehen (Regel 48 Absatz 2 Buchstabe h)
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21. März 2013

Novel binder-drug conjugates (ADCs) and their use

The present application relates to new binder-drug conjugates (ADCs) of N,N-dialkylauristatins that are directed against the target C4.4a, 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
5 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.

Cancer diseases are the consequence of uncontrolled cell growth in a wide variety of tissues. In
10 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.

Early-stage tumours may be able to be removed by surgical and radiotherapeutic measures.
15 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.

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
20 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.

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
25 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
30 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.

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 (Erbix) 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

5 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

10 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.

15 Ducry and B. Stump, *Bioconjugate Chem.* 21, 5-13 (2010)].

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 (June 25, 2008)]. Also known are conjugates of cytotoxic drug and addressing ligand

20 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].

Especially suitable for the target-directed addressing of tumour tissue and tumour cells are

25 monoclonal antibodies directed against the antigen C4.4a. C4.4a (gene: LYPD3) was first described as a metastasis-associated, cell surface protein in rat pancreas tumour cells (Rösel M. *et al.*, *Oncogene* 1998,17(15):1989-2002). Human C4.4a was isolated from its placental cDNA library (Würfel, J. *et al.* *Gene* 2001,262:35-41). C4.4a exhibits structural homology with the uPA receptor and contains two LY6 domains, which exhibit the typical three-finger folding pattern and

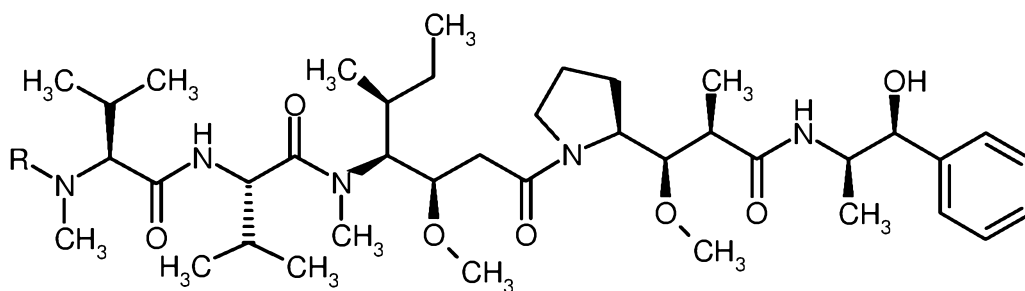
30 are linked via 9 disulphide bridges (Jacobsen B. & Ploug M., *Current Medicinal Chemistry* 2008, 15:2559-2573). C4.4a is anchored in the cell via glycosphosphatidylinositol (GPI). The protein is highly glycosylated and contains numerous N- and O-glycosylation sites. C4.4a exhibits strong expression in tumour cells of lung cancer, large bowel cancer, breast cancer, ovarian cancer, pancreatic cancer, kidney cancer, head-and-neck tumours and melanomas. RNA analyses have

35 shown C4.4a expression in ~ 50% of primary pulmonary tumours and ~ 75% of lung cancer metastases, although expression in healthy lung tissue was not detectable (Würfel J. *et al.*, *Gene*

2001, 262:35-41). C4.4a can be used as a prognostic marker in non-small-cell lung cancer – a high level of C4.4a expression correlates with a poor prognosis (Hansen L. et al., Lung Cancer 2007, 58:260-266). The same is true for large bowel cancer. C4.4a is cleaved off from the surface of the tumour cell and can be used as a prognostic serum marker (K. Konishi et al., Cancer Science 5 2010). A detailed expression analysis of melanomas has shown that C4.4a is expressed in ~ 60% of primary malignant melanomas and in 100% of lymph-node and skin metastases (Seiter S. et al., J Invest Dermatol. 2001, 116(2):344-347). Upregulation of C4.4a gene expression is observed in breast cancer tissue as compared with adjacent normal tissues (Fletcher G.C., Br. J. Cancer 2003, 88(4):579-585). C4.4a is an ideal target protein for a tumour therapy, since C4.4a expression in 10 healthy tissues is confined to skin keratinocytes and oesophageal endothelial cells, and also to placenta cells (Würfel J. et. al., Gene 2001, 262:35-41). WO01/23553 describes the use of a C4.4a inhibitor (e.g. an anti-C4.4a antibody) which in a cancer therapy is able to inhibit C4.4a expression or activity.

The precise function of C4.4a is unknown. In the course of wound healing, it is upregulated in 15 migrating keratinocytes (Hansen L. et al., Biochem J. 2004, 380:845-857). It is thought that C4.4a plays a part in tumour cell invasion, presumably through interaction with the extracellular matrix (Rösel M. et al., Oncogene 1998, 17(15):1989-2002; Paret C. et al., British Journal of Cancer 2007, 97:1146-1156). Potential ligands are laminin 1 and 5, and also galectin 3 (Paret C., Int. J. Cancer 2005, 115:724-733).

20 Auristatin E (AE) and monomethylauristatin E (MMAE) are synthetic analogues of the dolastatins, 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 25 (1998)].



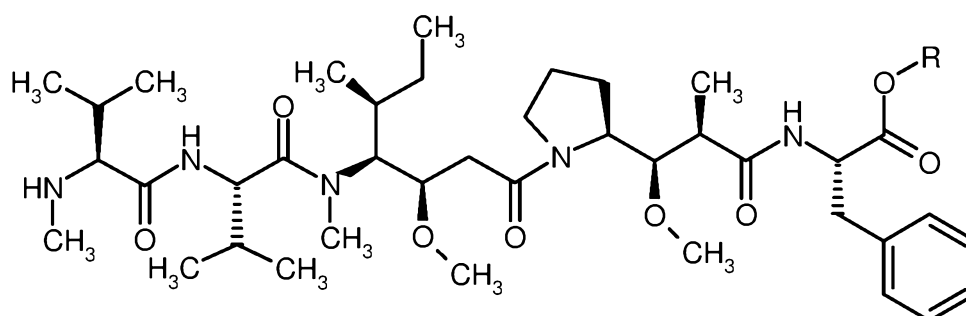
Auristatin E (AE): R = CH₃

Monomethylauristatin E (MMAE): R = H

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.

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

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.



Monomethylauristatin F (MMAF): R = H

Monomethylauristatin F methyl ester (MMAF-OMe): R = CH₃

20

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.

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

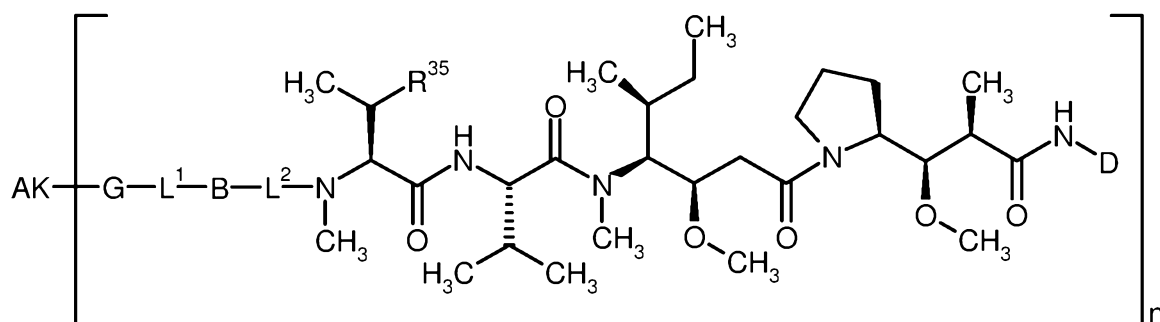
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and WO 2007/008603-A1 claim MMAF analogues which relate to side-chain modifications of the phenylalanine, while WO 2007/008848-A2 claims those in which the carboxyl group of the phenylalanine has been modified. Auristatin conjugates linked via the C-terminus have been recently described in WO 2009/117531-A1 [see also S. O. Doronina *et al.*, *Bioconjugate Chem.* 19, 1960-1963 (2008)].

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.

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.

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



(Ia),

in which

n is a number from 1 to 50,

AK is a binder,

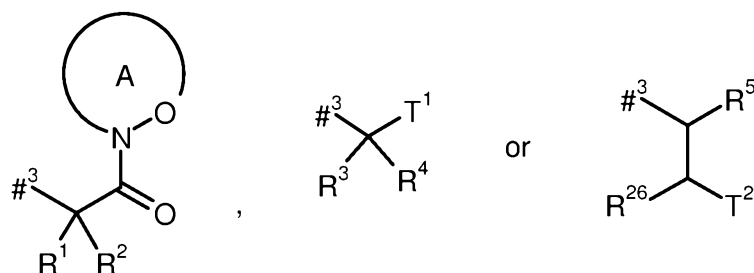
the group §-G-L¹-B-L²-§§ is a linker,

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

5 $\text{\#}^3$ marks the linkage site with the nitrogen atom,

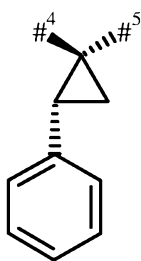
R^1 is hydrogen or methyl,

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, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

10

or

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



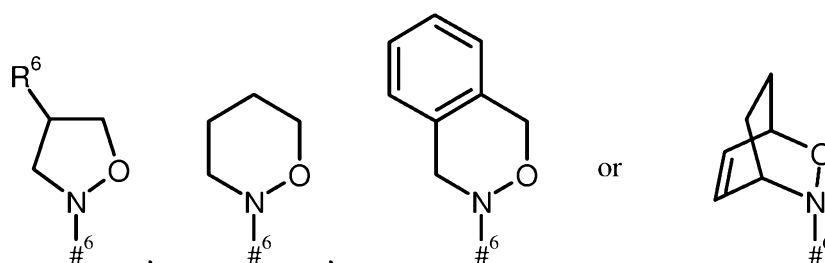
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in which

$\text{\#}^4$ marks the linkage site with the adjacent nitrogen atom,

$\text{\#}^5$ 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,

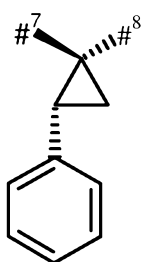
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

10 or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

15 #⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

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,

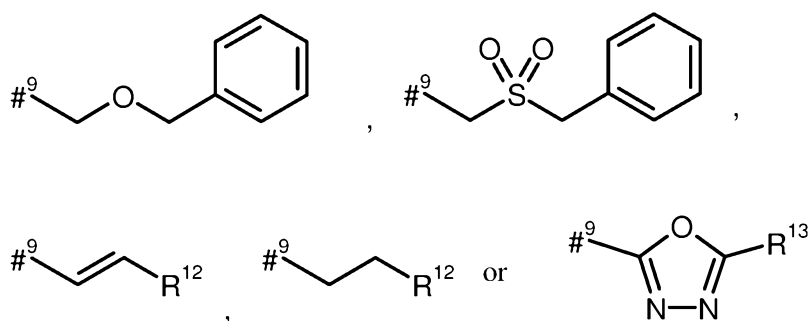
5 or

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,

10 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 $\text{-CHC(R}^{26}\text{)-T}^2$,

15 R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $\text{-S(O)}_2\text{OH}$,

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

R^{26} is hydrogen or hydroxy,

20 T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

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.

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.

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

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 ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}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 ^3H 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.

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
5 for pharmaceutical applications may nevertheless be used, for example, for isolating or purifying the compounds of the invention.

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,
10 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.

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
15 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-
20 ethylenediamine.

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.

25 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).

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

(C₁-C₄)-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.

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),
5 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).

(C₃-C₇)-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
10 cycloheptyl.

The side group of an α -amino acid in the definition of R¹⁹ 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:
15 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-hydroxybenzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl (homoserine), 1-hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (*S*-methylcysteine), 2-
20 mercaptoethyl (homocysteine), 2-methylthioethyl (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
25 groups in the definition of R¹⁹ 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.

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 SO₂ 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
35 ring heteroatoms from the series N and/or O. By way of example, the following may be mentioned:

azetidiny, oxetanyl, pyrrolidiny, pyrazolidiny, tetrahydrofuranyl, thiolanyl, piperidiny, piperaziny, tetrahydropyranyl, tetrahydrothiopyranyl, morpholiny, thiomorpholiny, hexahydroazepiny and hexahydro-1,4-diazepiny. Preference is given to pyrrolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl and morpholiny.

- 5 In the formula of the group which may be represented by A, B, D, G, L¹, L², L⁴, R¹, R², R³, R⁴ and R⁵, respectively, the end point of the line at which the symbol #⁶, *, **, #³, #¹, #², ##¹, ##², ##³, ##⁴, ***, ****, #⁴, #⁵, #⁶, #⁷, #⁸ or #⁹ is located is not a carbon atom or a CH₂ group, but instead is part of the bond to the atom designated in each case, to which the A, B, D, G, L¹, L², L⁴, R¹, R², R³, R⁴ or R⁵ is bonded.
- 10 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.
- 15 In the context of the present invention the terms used, unless otherwise specified, have the following definitions:

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

20 covalently to a drug. Furthermore, linkers may be represented, for example, by divalent chemical units, such as alkylidiyls, arylidiyls, heteroarylidiyls, heterocyclylidiyls, dicarbonyl acid esters, dicarbonyl acid amides.

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-

25 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 (US5,270,163) (review article by Keefe AD., et al., Nat. Rev. Drug Discov. 2010; 9:537-550), or

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

Preferred binders in accordance with the invention are (more particularly human, monoclonal) antibodies or antigen-binding antibody fragments which bind to C4.4a. In the case of anti-C4.4a 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.

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.

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).

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.

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.

5 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
10 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
15 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
20 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.

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
25 antibodies recognize a single antigenic binding site with a high specificity. The term “monoclonal antibody” does not refer to a particular production method.

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 one or more amino acid positions have
30 been altered.

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
35 coupling to a toxophore (see Junutula et al. Nat Biotechnol. 2008 Aug;26(8):925-32).

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
5 been isolated from a library of antibody sequences which are of human origin. One example of such antibodies can be found in Söderlind et al., Nature Biotech. 2000, 18:853-856.

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
10 (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
15 chimeric antibodies, for example, the variable domains of the donor immunoglobulin, or else the entire Fab fraction, in other words VL-CL and VH + CH1, are fused with the constant regions of a human antibody.

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
20 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
25 the variable heavy chain (Kabat et al., Sequences of Proteins of Immunological 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
30 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.

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.
35 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.

- The term “functional fragment” or “antigen-binding antibody fragments” of an 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 CDR1, 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.
- 10 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).
- 15 “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 WO93/17715; WO 92/08802; WO 91/00360; 20 WO 92/05793; Tutt, et al., 1991, J. Immunol. 147:60 69; U. S. Pat. Nos. 4,474,893; 4,7 14,68 1; 4,925,648; 5,573,920; 5,601,8 19; 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.
- 30 “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 Aug;26(8):925-32).
- 35

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 US 4,816,567 or Boss et al US 4,816,397).

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.

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), the purification thereof being such 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.

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.

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
 5 which in a cell-based assay ($K_d = 5 \text{ nM}$) binds the extracellular domains of the human epidermal growth receptor with high affinity. The antibody is produced recombinantly in CHO cells.

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

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

10 n is a number from 1 to 50,

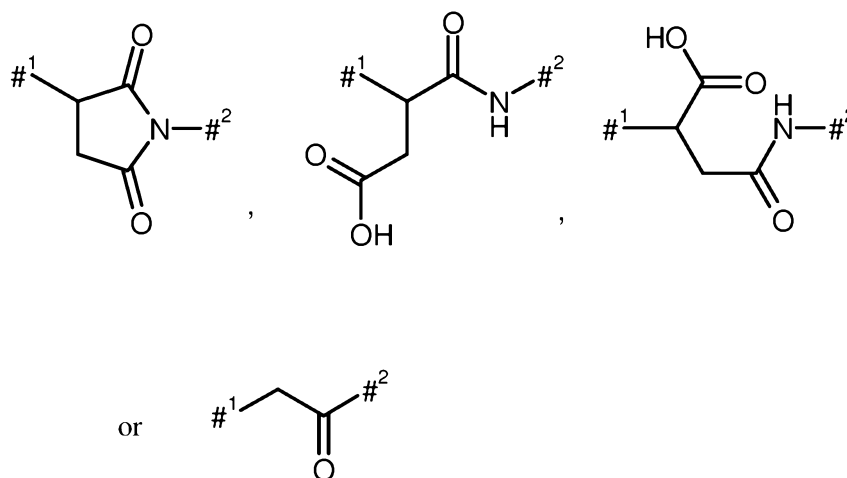
AK is AK_1 or AK_2

where

AK_1 is a binder (preferably an anti-C4.4a antibody) which is bonded via a sulphur atom of the binder to the group G,

15 AK_2 is a binder (preferably an anti-C4.4a antibody) 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

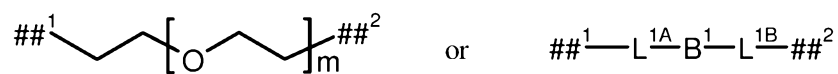
20 #¹ marks the linkage site with the sulphur atom of the binder,

#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



5 where

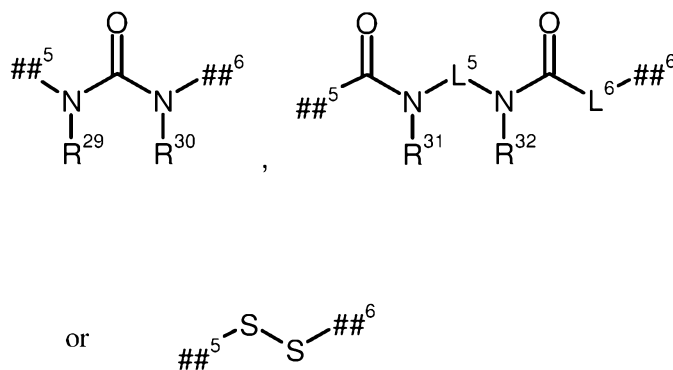
m is a number from 2 to 6,

##^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,

10 B^1 is a group of the formula



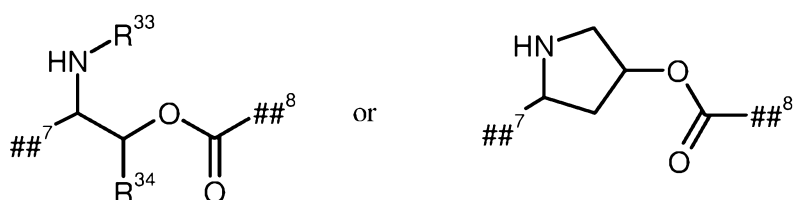
in which

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

15 ##^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},

5 R³³ is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

R³⁰ is hydrogen or (C₁-C₄)-alkyl,

10 or

R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

R³² is hydrogen or (C₁-C₄)-alkyl,

15 or

R³¹ and R³² together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

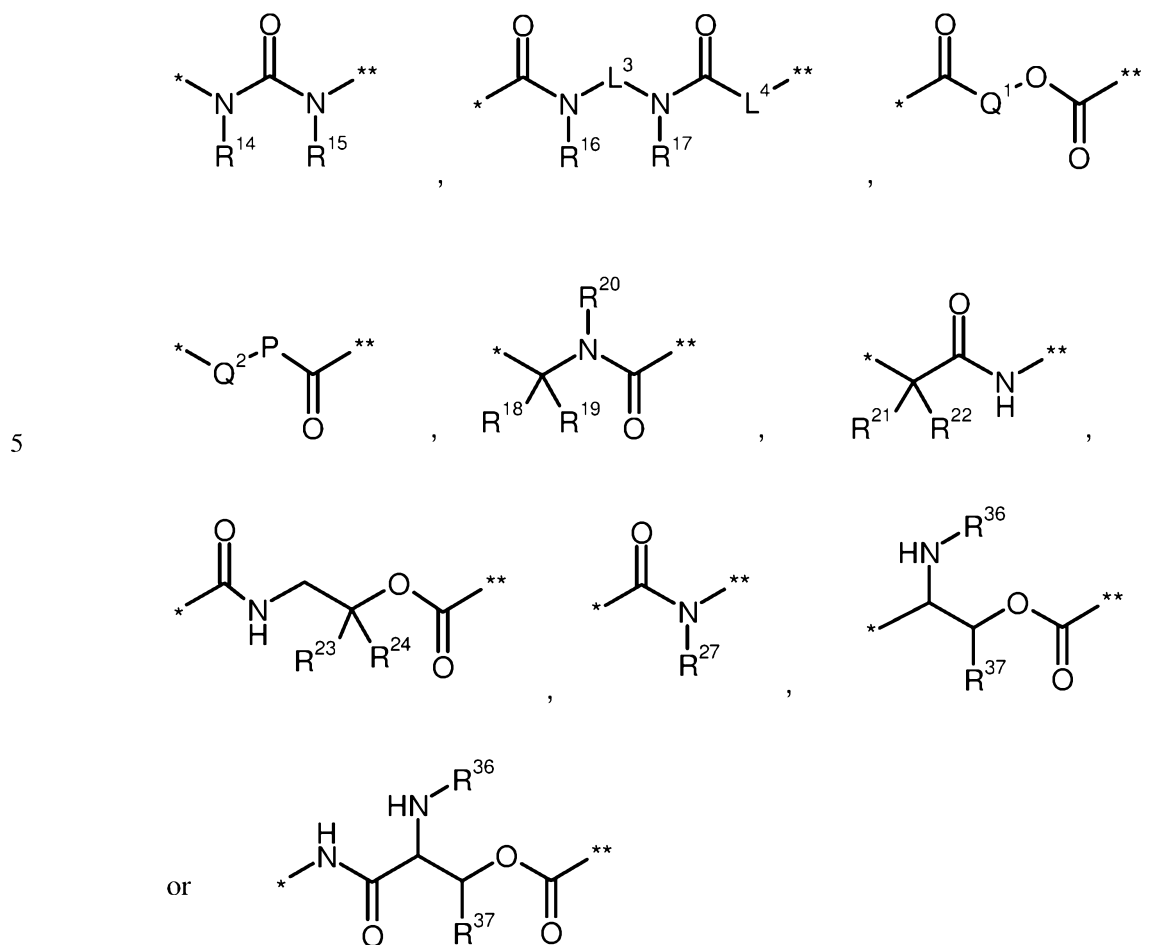
and

20 where (C₁-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



where

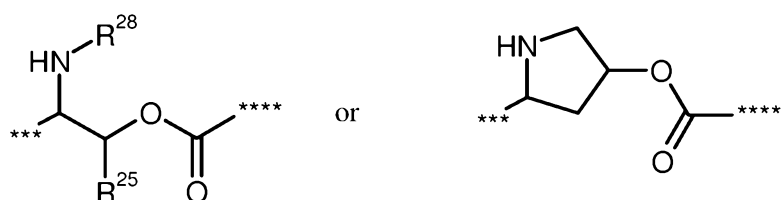
* marks the linkage site with L¹,

** marks the linkage site with L²,

10 P is O or NH,

L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

5 R²⁵ is hydrogen or methyl,

R²⁸ is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

10 R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

15 R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

20 R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-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 (C₁-C₄)-alkyl,

R^{22} is hydrogen or (C₁-C₄)-alkyl,

5 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 (C₁-C₄)-alkyl,

R^{24} is hydrogen or (C₁-C₄)-alkyl,

10 R^{27} is hydrogen or (C₁-C₄)-alkyl,

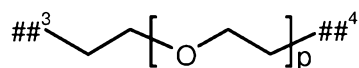
R^{36} is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R^{37} is hydrogen or methyl,

or

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

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

20 ##^3 marks the linkage site with the group B,

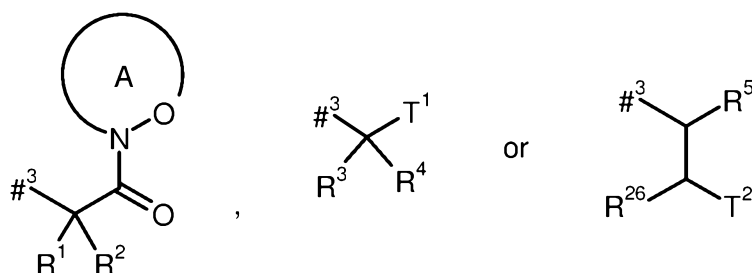
##^4 marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

D is a group of the formula



in which

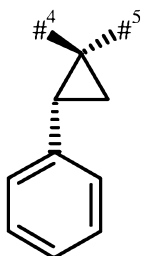
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

10 R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



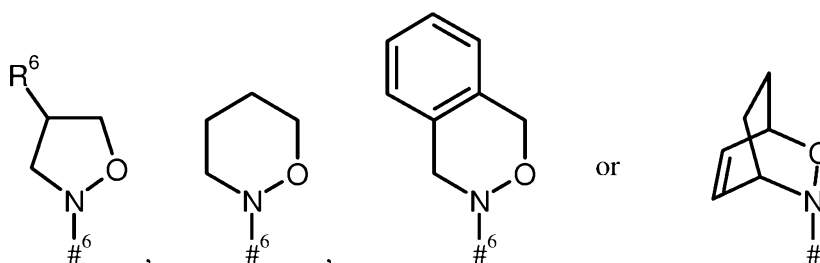
in which

#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

20



in which

#⁶ marks the linkage site with the carbonyl group,

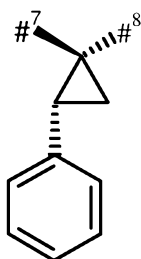
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

10 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

15 #⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

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,

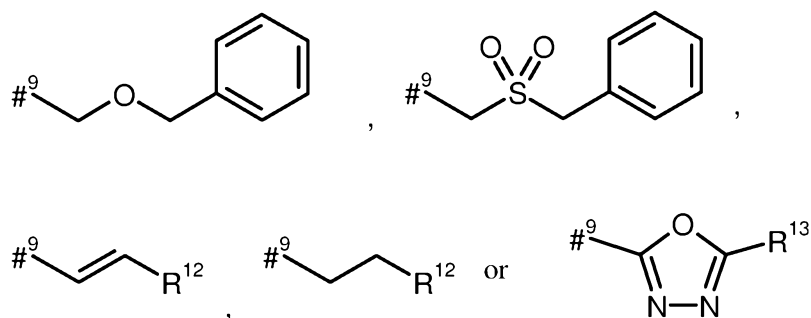
5 or

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,

10 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

15 $\#^9$ marks the linkage site with $\text{-CHC(R}^{26}\text{)-T}^2$,

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

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

R^{26} is hydrogen or hydroxy,

20 T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

A preferred subject of the present invention are binder-drug conjugates of the general formula (Ia) as indicated above, in which

n is a number from 1 to 50,

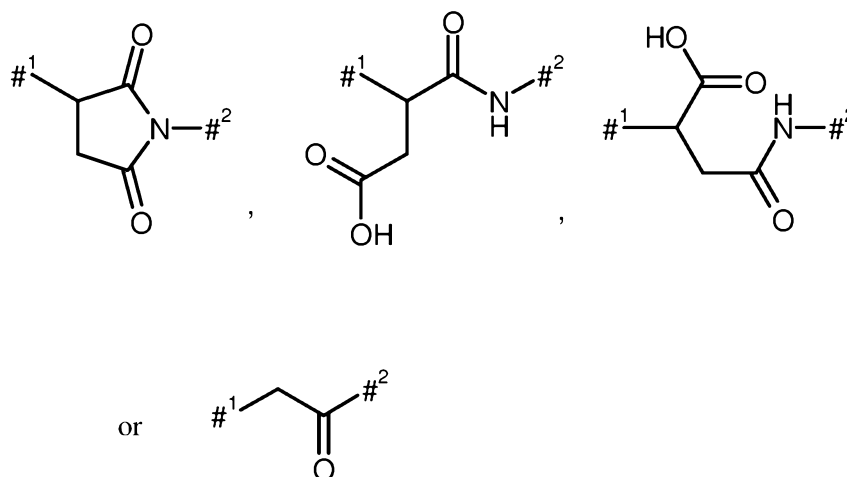
5 AK is AK_1 or AK_2

where

AK_1 is a binder (preferably an anti-C4.4a antibody) which is bonded via a sulphur atom of the binder to the group G,

10 AK_2 is a binder (preferably an anti-C4.4a antibody) 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



in which

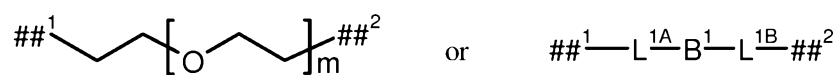
$\#^1$ marks the linkage site with the sulphur atom of the binder,

15 $\#^2$ 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

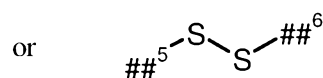
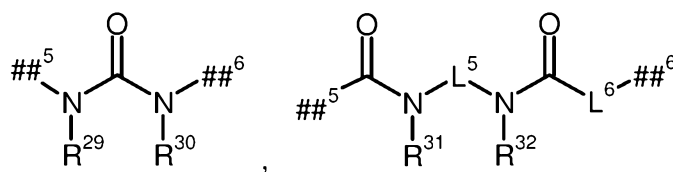
m is a number from 2 to 6,

##^1 marks the linkage site with the group G,

5 ##^2 marks the linkage site with the group B,

L^{1A} is linear (C₂-C₁₀)-alkanediyl,

B^1 is a group of the formula



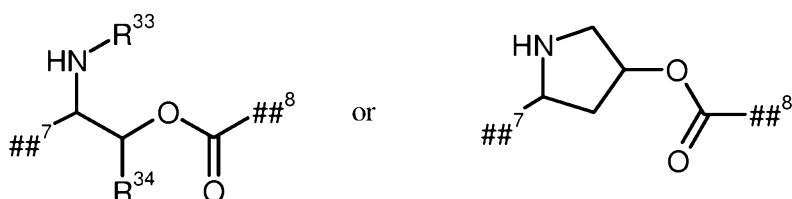
in which

10 ##^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 (C₂-C₄)-alkanediyl,

L^6 is a bond or a group of the formula



15

in which

##⁷ marks the linkage site with the carbonyl group,

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

R³³ is hydrogen (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

5 R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

10 R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

R³² is hydrogen or (C₁-C₄)-alkyl,

or

15 R³¹ and R³² together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

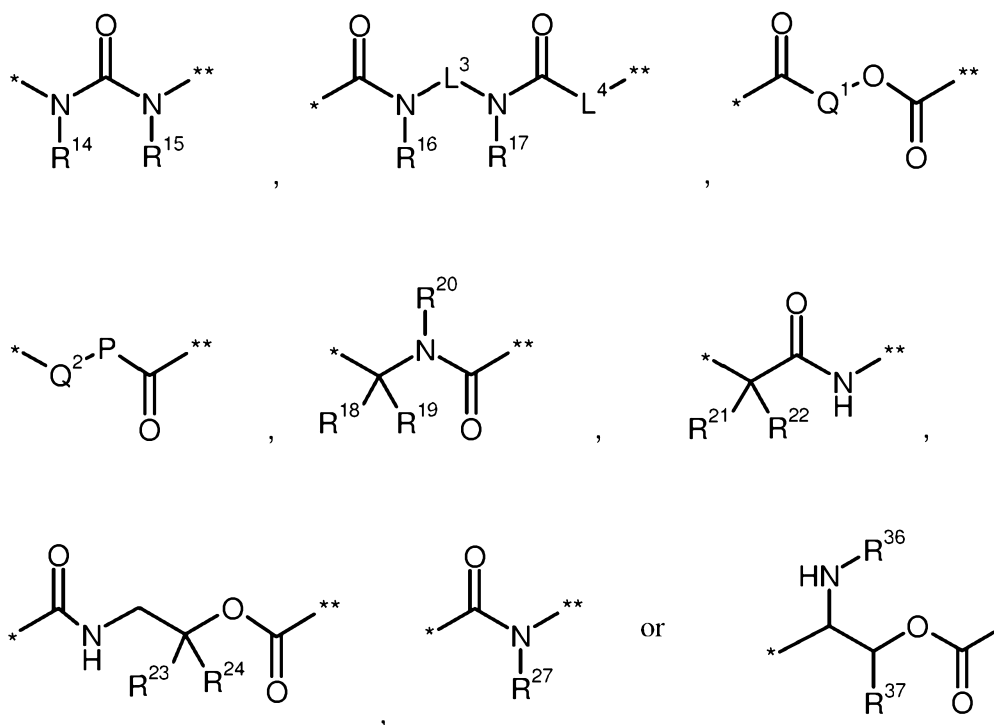
and

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

20 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



where

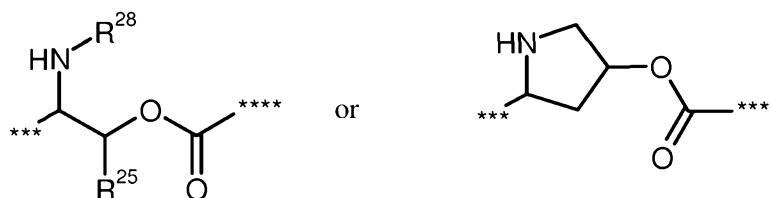
* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

5 P is O or NH,

L^3 is a bond or (C₂-C₄)-alkanediyl,

L^4 is a bond or a group of the formula



10 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, (C₁-C₄)-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,

5 R^{14} is hydrogen or (C₁-C₄)-alkyl,

R^{15} is hydrogen or (C₁-C₄)-alkyl,

or

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

10 R^{16} is hydrogen or (C₁-C₄)-alkyl,

R^{17} is hydrogen or (C₁-C₄)-alkyl,

or

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

15 R^{18} is hydrogen or (C₁-C₄)-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 (C₁-C₄)-alkyl,

or

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

R^{21} is hydrogen or (C₁-C₄)-alkyl,

R^{22} is hydrogen or (C₁-C₄)-alkyl,

or

25 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,

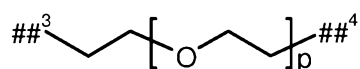
R^{36} is hydrogen, (C_1-C_4) -alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

5 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



10 where

p is a number from 2 to 6,

##^3 marks the linkage site with the group B,

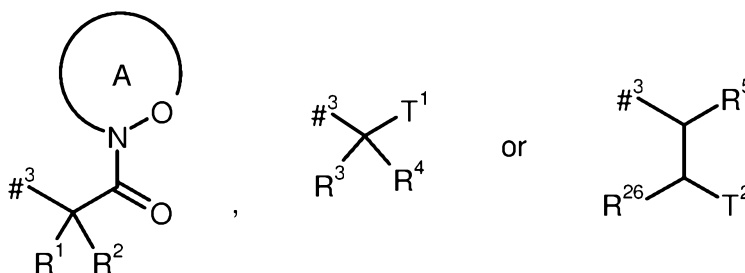
##^4 marks the linkage site with the nitrogen atom,

15 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,

20 D is a group of the formula



in which

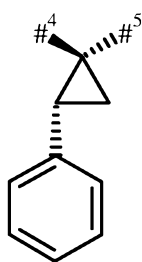
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

5 R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



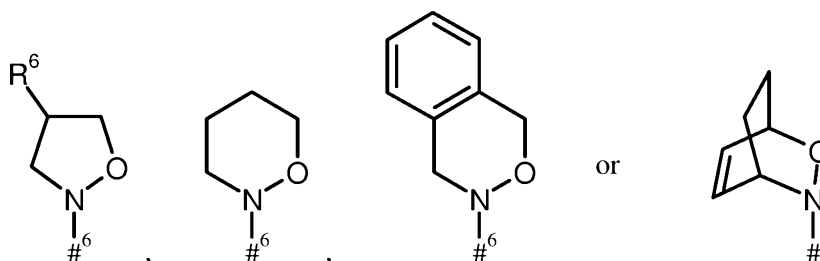
10

in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

15 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,

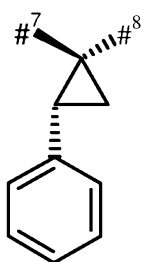
R⁶ is hydrogen, hydroxy or benzyloxy,

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, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

5 or

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



in which

10 $\#^7$ 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

15 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,

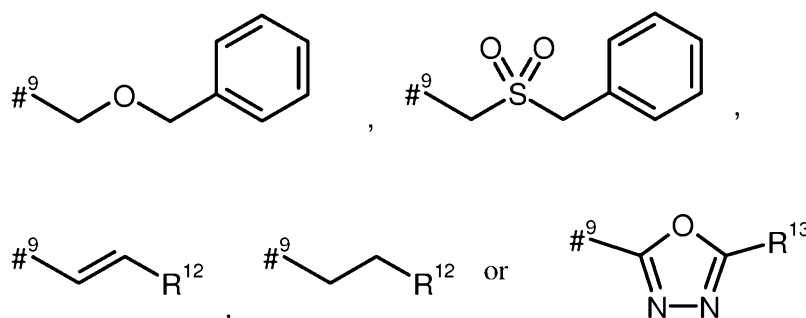
or

20 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



5 in which

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

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

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

10 R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

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

15 n is a number from 1 to 20,

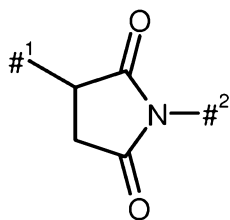
AK is AK_1 or AK_2

where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

20 AK_2 is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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

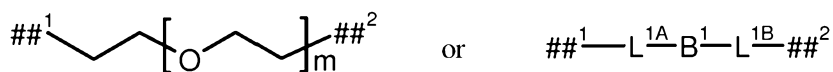
#¹ marks the linkage site with the cysteine residue of the binder,

5 #² marks the linkage site with the group L¹,

or

when $AK = AK_2$, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



10

where

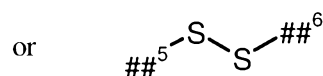
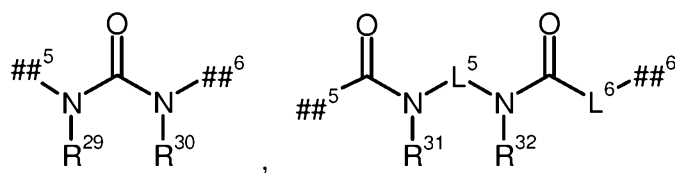
m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

15 L^{1A} is linear (C₂-C₆)-alkanediyl,

B¹ is a group of the formula



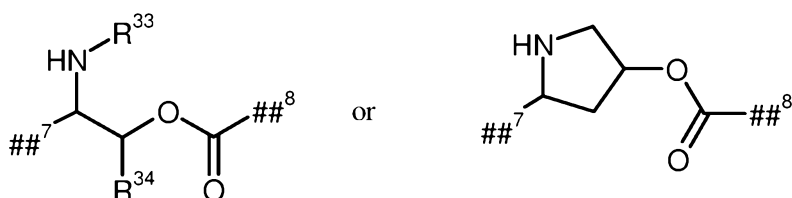
in which

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

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

5 L⁵ is a bond,

L⁶ is a bond or a group of the formula



in which

##⁷ marks the linkage site with the carbonyl group,

10 ##⁸ marks the linkage site with L^{1B},

R³³ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen,

R³⁰ is hydrogen,

15 R³¹ is hydrogen or methyl,

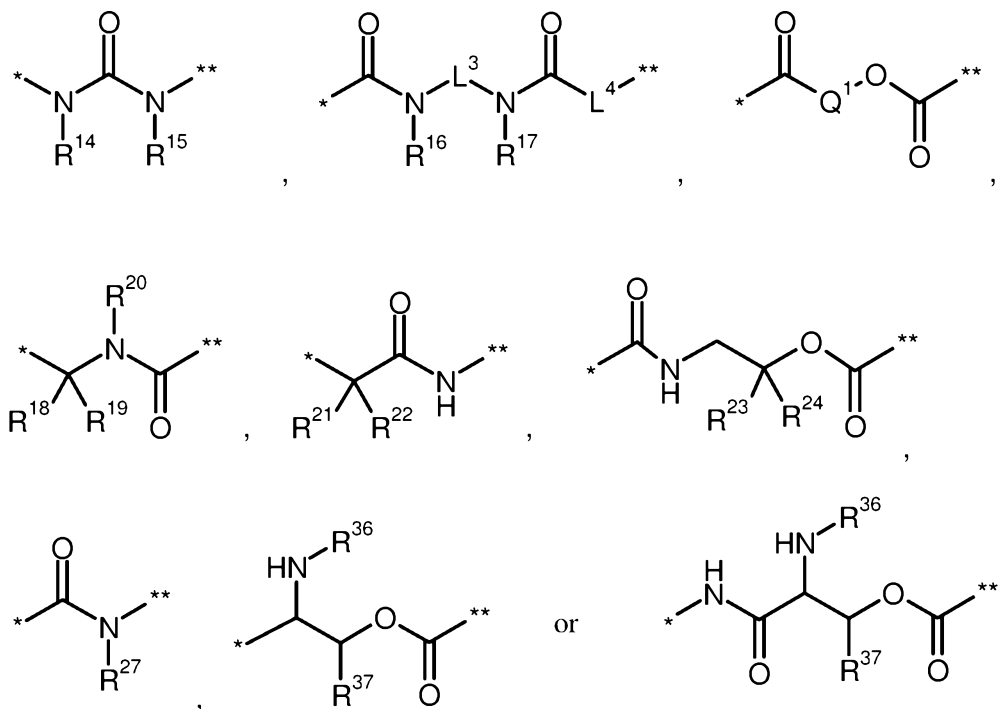
R³² is hydrogen or methyl,

L^{1B} is linear (C₂-C₆)-alkanediyl,

and

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



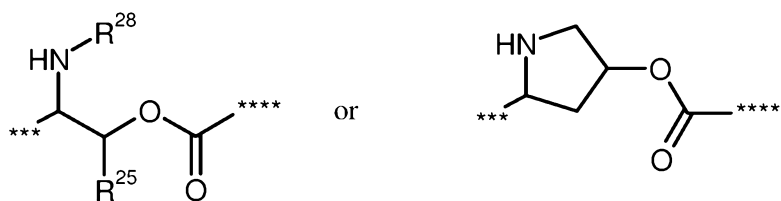
5 where

* marks the linkage site with L¹,

** marks the linkage site with L^2 ,

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

L⁴ 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 ,

R²⁵ is hydrogen or methyl,

R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

Q¹ is a 4- to 7-membered heterocycle,

R¹⁴ is hydrogen,

5 R¹⁵ is hydrogen,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

10 R¹⁸ is hydrogen,

R¹⁹ is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

R²⁰ is hydrogen or methyl,

or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

15 R²¹ is hydrogen or methyl,

R²² is hydrogen or methyl,

or

R²¹ and R²² together with the atoms to which they are bonded form a cyclopropyl ring,

R²³ is methyl,

20 R²⁴ is hydrogen or methyl,

R²⁷ is hydrogen,

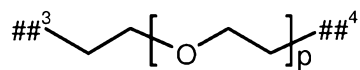
R³⁶ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R³⁷ 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



5 where

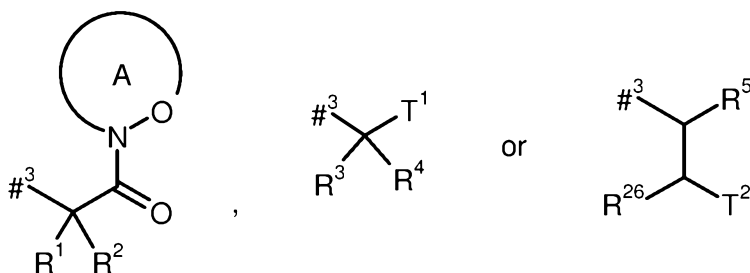
p is a number from 2 to 6,

$##^3$ 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,

10 D is a group of the formula



where

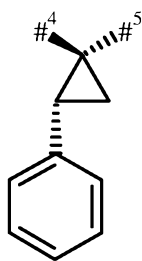
$##^3$ marks the linkage site with the nitrogen atom,

15 R^1 is hydrogen,

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

or

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

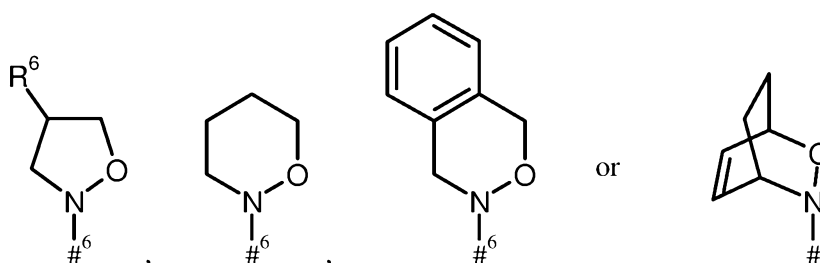


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

10 #⁶ marks the linkage site with the carbonyl group,

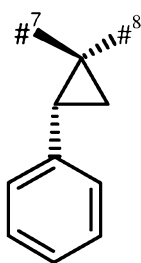
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

15 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

- 5 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

- 10 R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

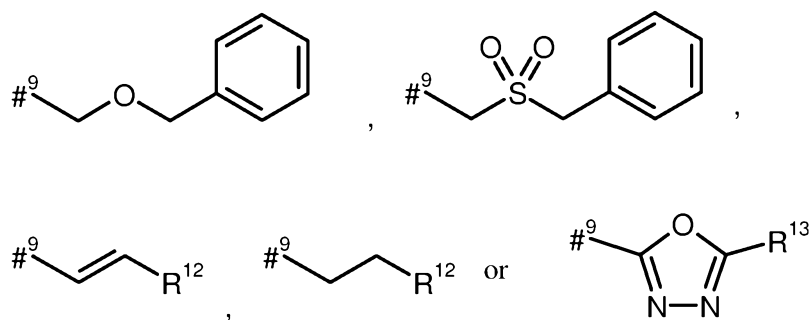
or

- 15 R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



in which

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

5 R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $-\text{S}(\text{O})_2\text{OH}$,

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

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

n is a number from 1 to 20,

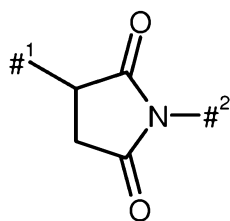
AK is AK_1 or AK_2

15 where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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 C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

20 G when $\text{AK} = \text{AK}_1$, is a group of the formula



in which

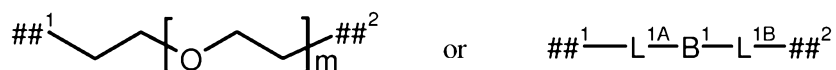
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

5 or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



10 where

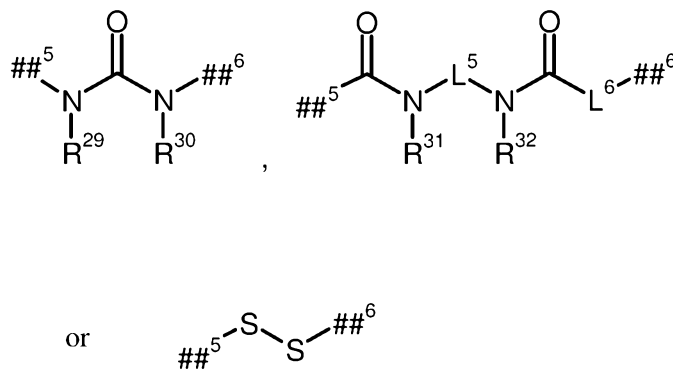
m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₆)-alkanediyl,

15 B¹ is a group of the formula



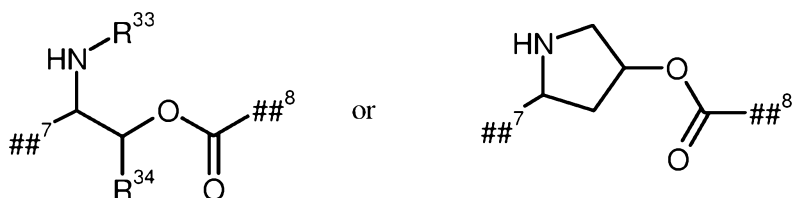
in which

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

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

L⁵ is a bond,

5 L⁶ 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},

10 R³³ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen,

R³⁰ is hydrogen,

R³¹ is hydrogen or methyl,

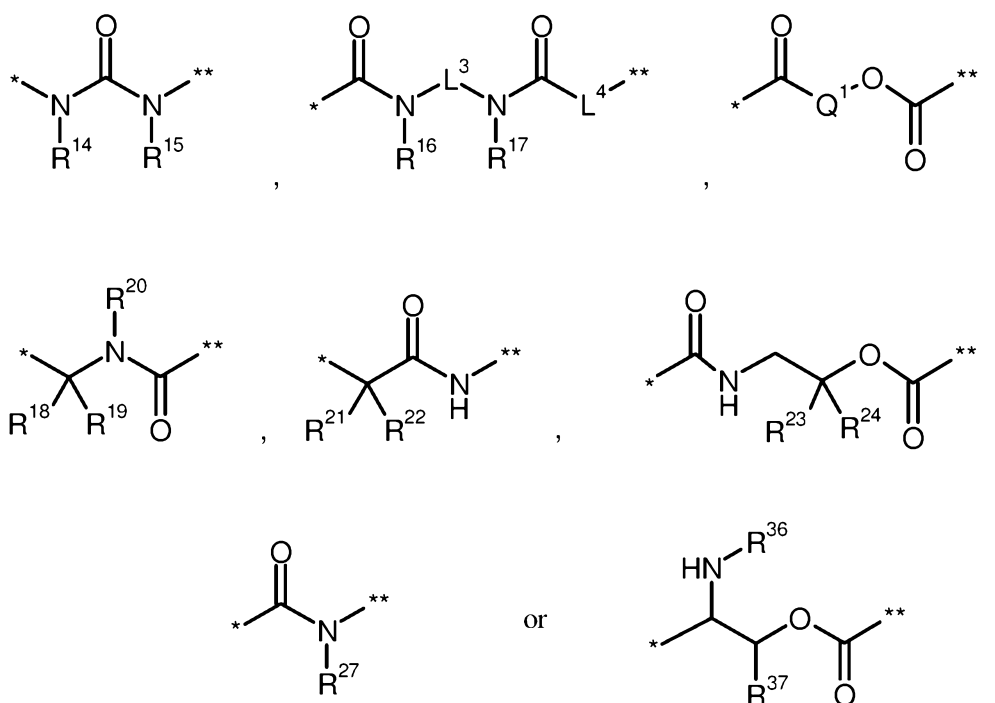
15 R³² is hydrogen or methyl,

L^{1B} is linear (C₂-C₆)-alkanediyl,

and

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



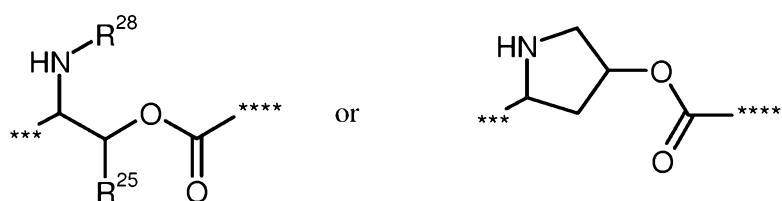
where

* marks the linkage site with L¹,

** marks the linkage site with L^2 ,

5 L^3 is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

10 **** marks the linkage site with L^2 ,

R²⁵ is hydrogen or methyl,

R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

Q¹ is a 4- to 7-membered heterocycle,

R¹⁴ is hydrogen,

R¹⁵ is hydrogen,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

5 or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

R¹⁸ is hydrogen,

R¹⁹ is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

R²⁰ is hydrogen or methyl,

10 or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or methyl,

R²² is hydrogen or methyl,

or

15 R²¹ and R²² together with the atoms to which they are bonded form a cyclopropyl ring,

R²³ is methyl,

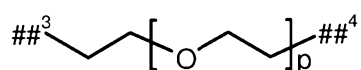
R²⁴ is hydrogen or methyl,

R²⁷ is hydrogen,

R³⁶ is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl, or benzyloxycarbonyl,

20 R³⁷ is hydrogen or methyl,

L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



where

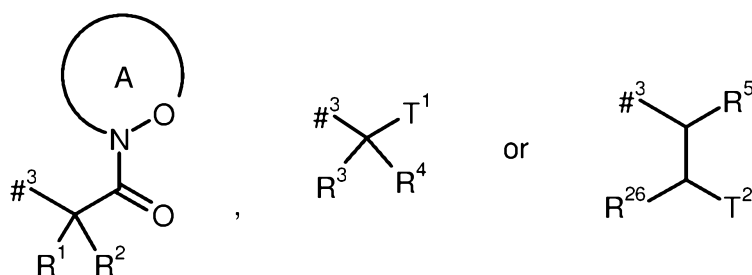
p is a number from 2 to 6,

##³ marks the linkage site with the group B,

##⁴ marks the linkage site with the nitrogen atom,

5 where (C₂-C₁₀)-alkanediyl may be substituted by 1 or 2 methyl substituents,

D is a group of the formula



where

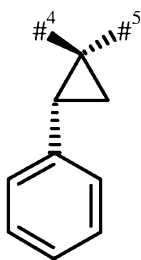
10 #³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

15 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



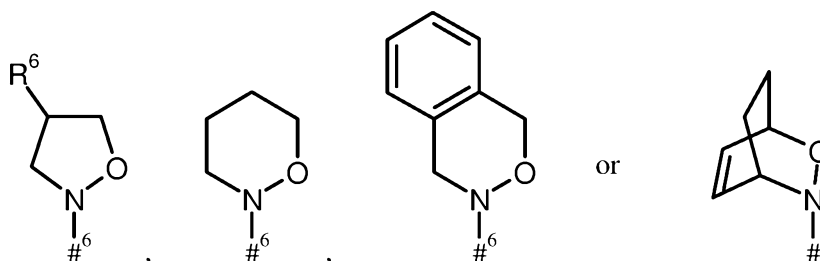
in which

#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

5



in which

#⁶ marks the linkage site with the carbonyl group,

R⁶ is hydrogen, hydroxy or benzyloxy,

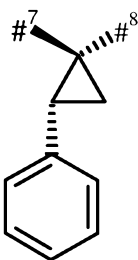
10 R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

15



in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

5

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

10

or

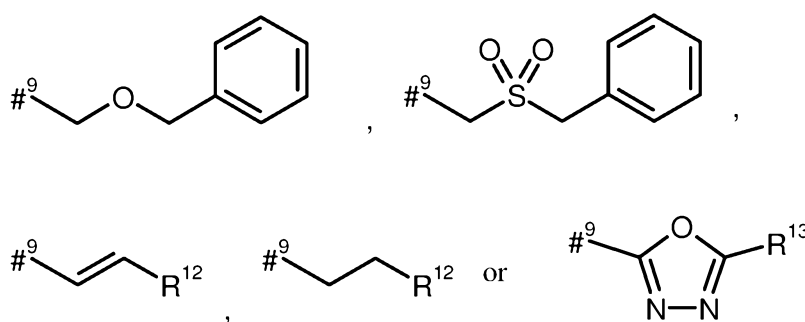
R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

15

R⁵ is hydrogen, methyl or a group of the formula



in which

#⁹ marks the linkage site with -CHC(R²⁶)-T²,

20

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula -S(O)₂OH,

R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R²⁶ is hydrogen or hydroxy,

T² is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R³⁵ is methyl or hydroxy,

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

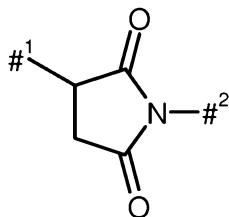
- 5 Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia), in which

n is a number from 1 to 10,

AK is AK₁ or AK₂

where

- 10 AK₁ 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 sulphur atom of a cysteine residue of the binder to the group G,
- 15 AK₂ 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,
- 20 G when AK = AK₁, is a group of the formula



in which

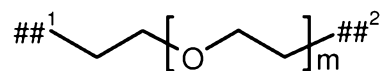
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



5

where

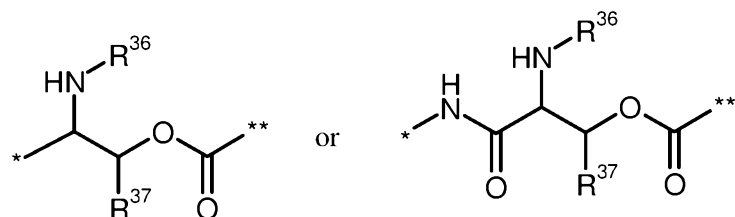
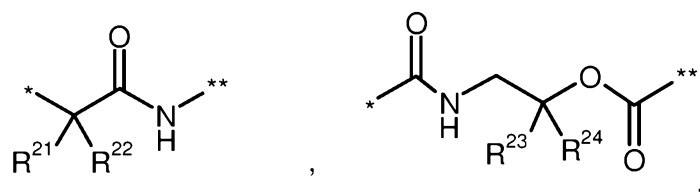
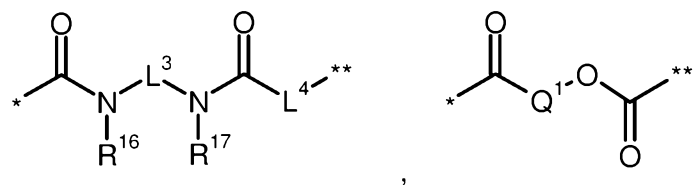
m is a number 2 or 3,

#¹ marks the linkage site with the group G,

#² marks the linkage site with the group B,

10 where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



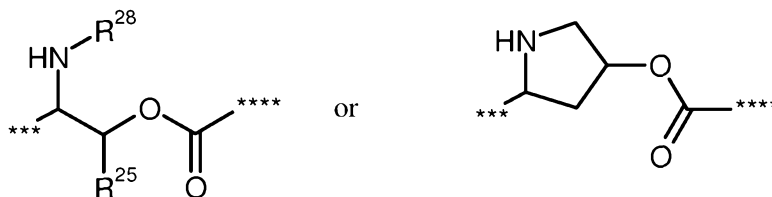
where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



5 in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is methyl,

R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

10 Q¹ is piperidine-1,4-diyl,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

15

R²¹ is hydrogen or methyl,

R²² is hydrogen or methyl,

or

R²¹ and R²² together with the atoms to which they are bonded form a cyclopropyl ring,

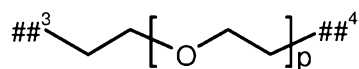
20 R²³ is methyl,

R²⁴ 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



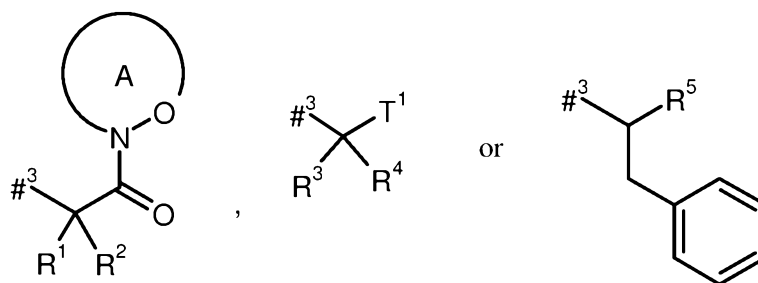
5 where

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



10

where

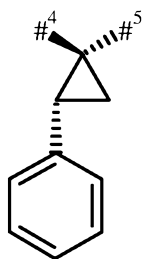
$##^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

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

15 or

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

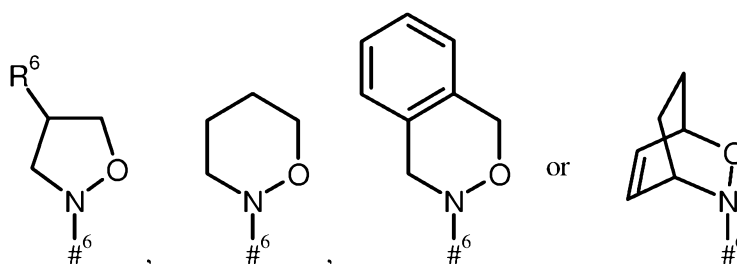


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

5 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,

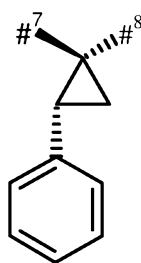
10 R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

15 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

5 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹ or -CH₂-O-R¹¹,

in which

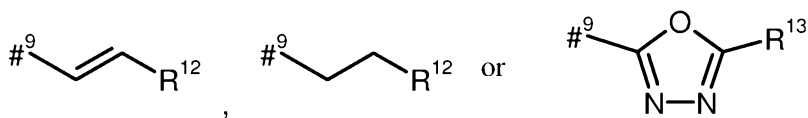
R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

10 R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



15 in which

#⁹ marks the linkage site with -CHCH₂phenyl,

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula -S(O)₂OH,

20 R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R³⁵ is methyl or hydroxy,

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

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

n is a number from 1 to 10,

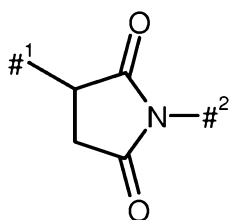
5 AK is AK_1 or AK_2

where

10 AK_1 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 sulphur atom of a cysteine residue of the binder to the group G,

15 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



20 in which

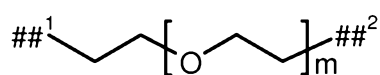
$\#^1$ marks the linkage site with the cysteine residue of the binder,

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

or

when $AK = AK_2$, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



where

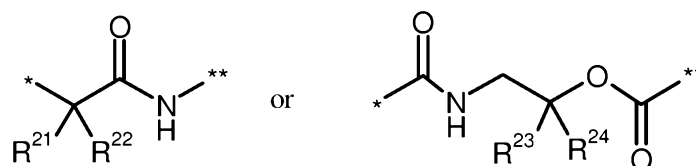
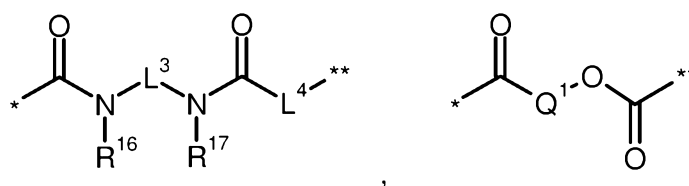
m is a number 2 or 3,

5 ##¹ marks the linkage site with the group G,

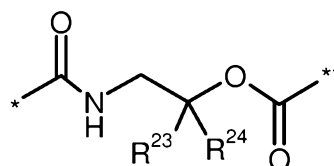
##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



or



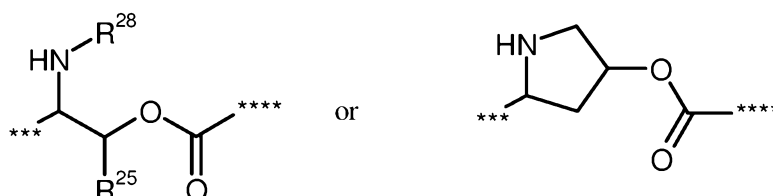
10 where

* marks the linkage site with L¹,

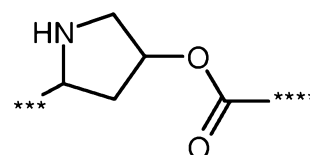
** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



or



15

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2 ,

R^{25} is methyl,

5 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

10 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,

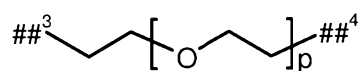
or

15 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 or is a group of the formula



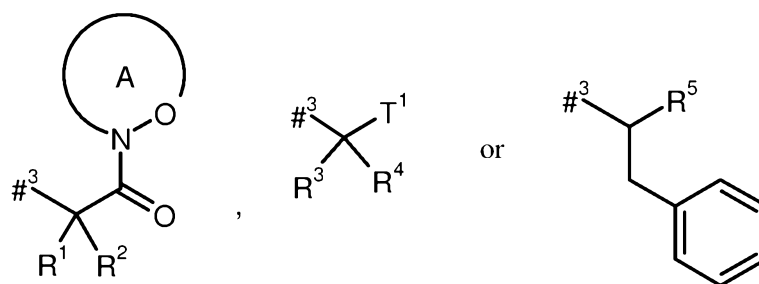
20 where

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

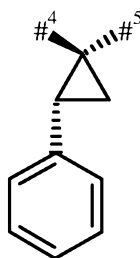
#³ marks the linkage site with the nitrogen atom,

5 R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 1-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

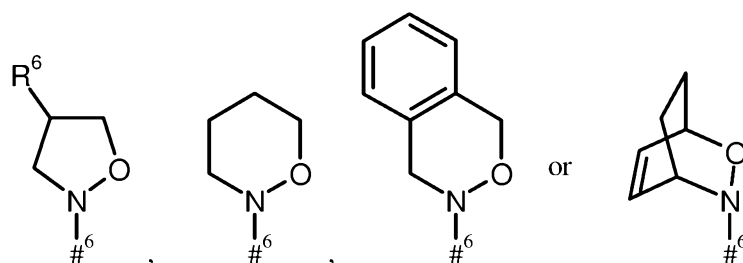
#⁴ marks the linkage site with the adjacent nitrogen atom,

#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

15

substituted heterocycle of the formula



in which

#⁶ marks the linkage site with the carbonyl group,

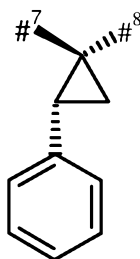
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen,

R⁴ is benzyl, 1-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹ or -CH₂-O-R¹¹,

15

in which

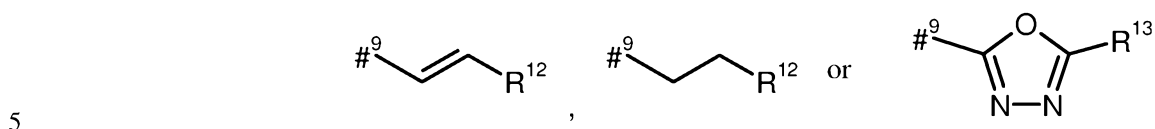
R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ 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 $-\text{CHCH}_2\text{phenyl}$,

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

10 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.

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

15 n is a number from 1 to 10,

AK is AK_2 ,

where

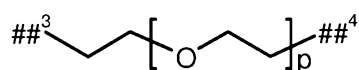
20 AK_2 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10, M31-B01 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6, and is bonded via the NH side group of a lysine residue of the binder to the group G,

G is carbonyl,

L^1 is a bond,

25 B is a bond,

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



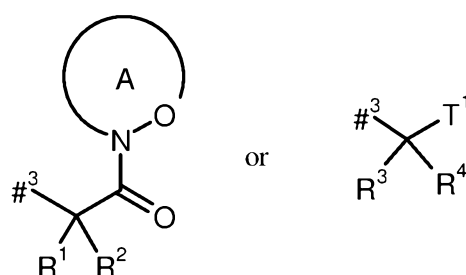
where

p is a number 2 or 3,

5 $##^3$ 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

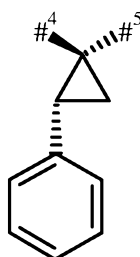
10 $#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl or 1*H*-indol-3-ylmethyl,

or

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

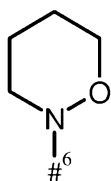


in which

#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



5

in which

#⁶ marks the linkage site with the carbonyl group,

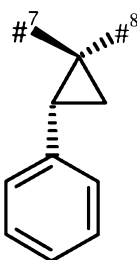
R³ is hydrogen,

R⁴ is benzyl or 1*H*-indol-3-ylmethyl,

10

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

15

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

20

R^8 is hydrogen,

R^9 is hydrogen or benzyl,

R^{35} is methyl,

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

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

n is a number from 1 to 10,

AK is AK_2 ,

where

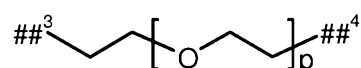
10 AK_2 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10, M31-B01 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6, and is bonded via the NH side group of a lysine residue of the binder to the group G,

15 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



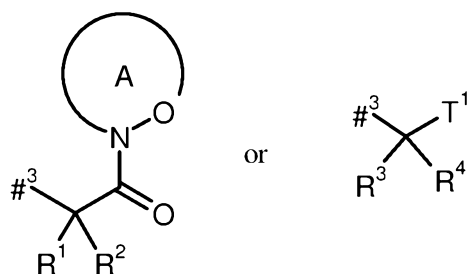
20 where

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

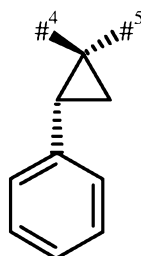
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

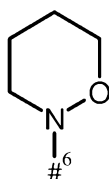


10 in which

#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



15

in which

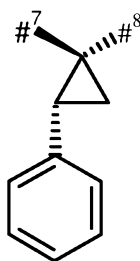
#⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

5 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

10 #⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

15 R⁸ is hydrogen,

R⁹ is hydrogen or benzyl,

R³⁵ is methyl,

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

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

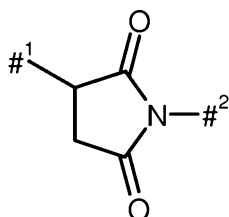
n is a number from 1 to 10,

AK is AK₁,

where

AK₁ 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 sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula

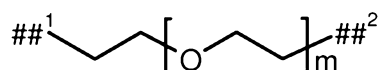


where

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

#² marks the linkage site with the group L¹,

L¹ is a bond, linear (C₃-C₅)-alkanediyl or a group of the formula



where

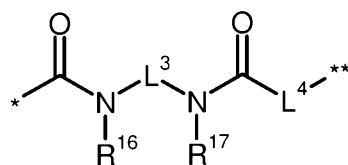
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

20 where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



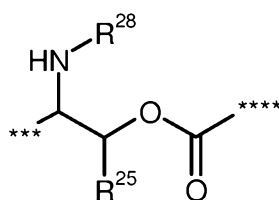
where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

5 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,

10 **** marks the linkage site with L^2 ,

R^{25} is methyl,

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

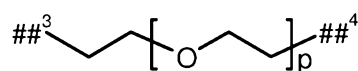
R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

15 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



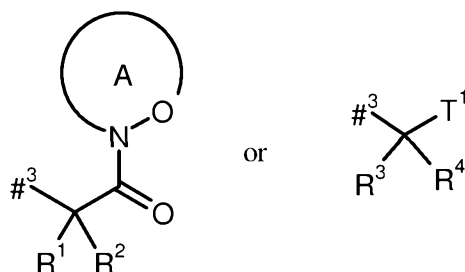
where

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,

5 D is a group of the formula



where

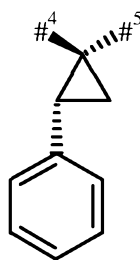
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

10 R^2 is benzyl or 1*H*-indol-3-ylmethyl,

or

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

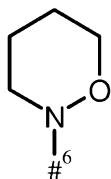


15 in which

$\#^4$ 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

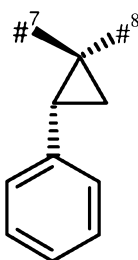
5 #⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

R⁴ is benzyl or 1*H*-indol-3-ylmethyl,

or

10 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

15 T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen,

20 R⁹ is hydrogen or benzyl,

R³⁵ is methyl,

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

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

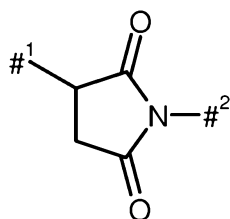
n is a number from 1 to 10,

AK is AK₁,

where

AK₁ 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 sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula

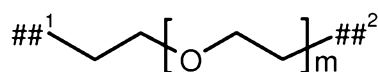


where

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

#² marks the linkage site with the group L¹,

L¹ is a bond, linear (C₃-C₅)-alkanediyl or a group of the formula



where

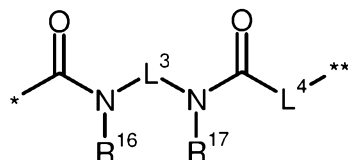
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



5

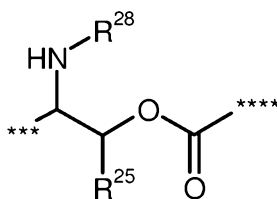
where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

10 L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

15 R²⁵ is methyl,

R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

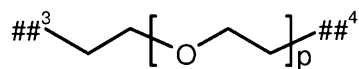
R¹⁶ is hydrogen or methyl,

R¹⁷ 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



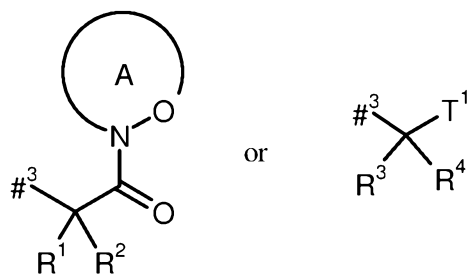
5 where

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



10

where

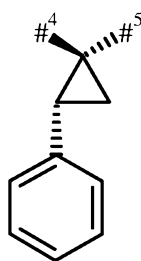
$#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

15 or

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

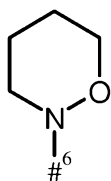


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

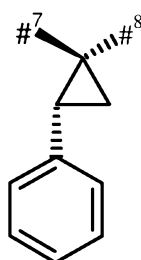
#⁶ marks the linkage site with the carbonyl group,

10 R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

5 R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

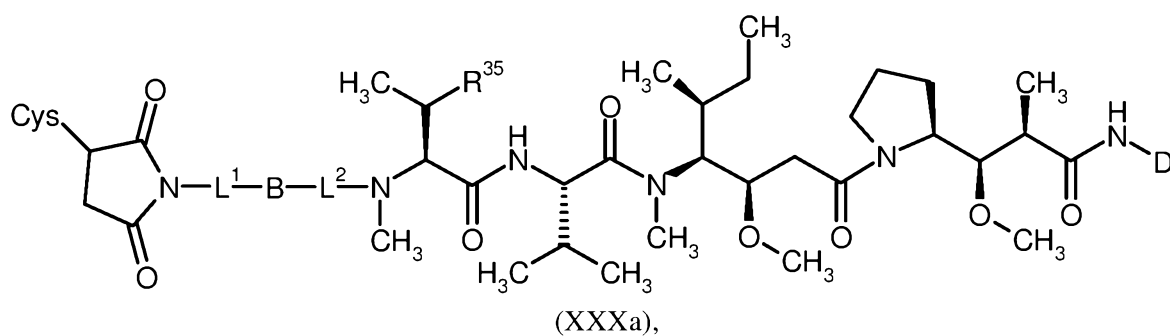
R⁸ is hydrogen,

R⁹ is hydrogen or benzyl,

R³⁵ is methyl,

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

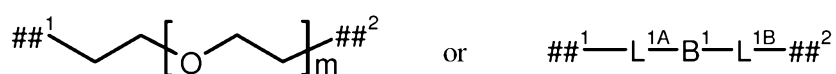
Additionally provided by the present invention are compounds of the formula (XXXa)



in which

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

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl, a group of the formula



where

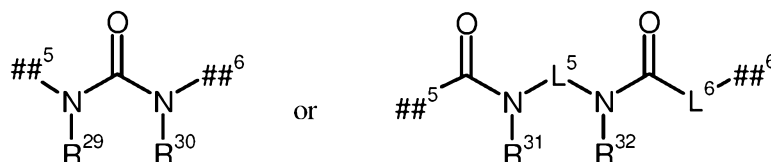
20 m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₁₀)-alkanediyl,

B¹ 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},

L⁵ is a bond or (C₂-C₄)-alkanediyl,

10 L⁶ is a bond,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

15 R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

R³² is hydrogen or (C₁-C₄)-alkyl,

or

20 R³¹ and R³² together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

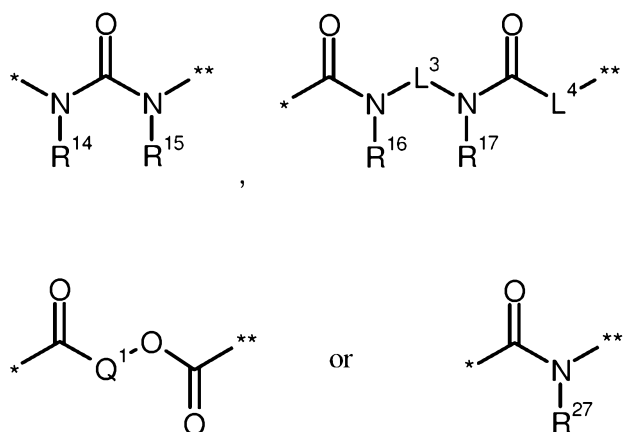
and

where (C₁-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



where

* marks the linkage site with L¹,

** marks the linkage site with L²,

P is O or NH,

L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a bond,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

5 or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

10 R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

15 R²² is hydrogen or (C₁-C₄)-alkyl,

or

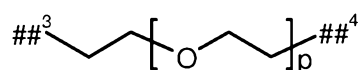
R²¹ and R²² together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R²³ is (C₁-C₄)-alkyl,

20 R²⁴ is hydrogen or (C₁-C₄)-alkyl,

R²⁷ is hydrogen or (C₁-C₄)-alkyl,

L² is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

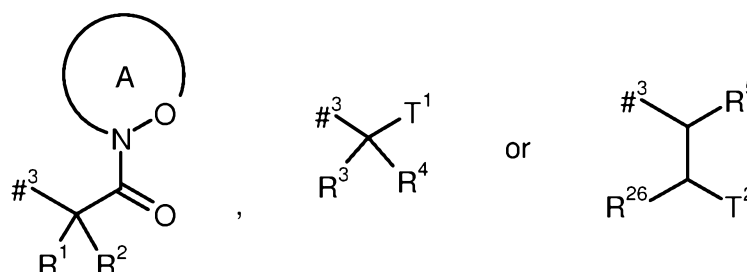
$\#^3$ marks the linkage site with the group B,

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

where (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,
5 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

10 D is a group of the formula



where

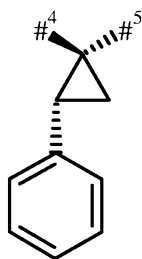
$\#^3$ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

15 R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

20 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

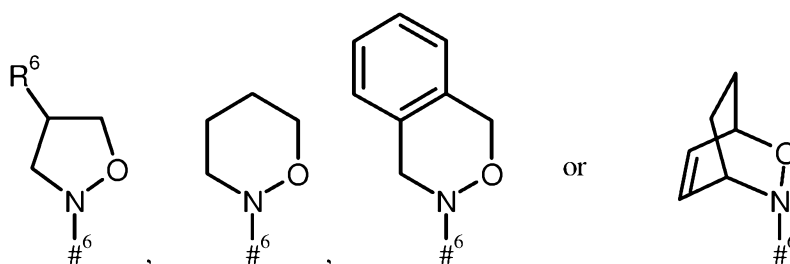


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

10 #⁶ marks the linkage site with the carbonyl group,

R⁶ is hydrogen, hydroxy or benzyloxy,

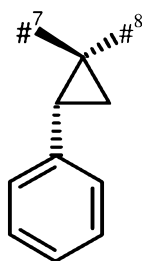
R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenyl-ethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

15

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

- 5 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

- 10 R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

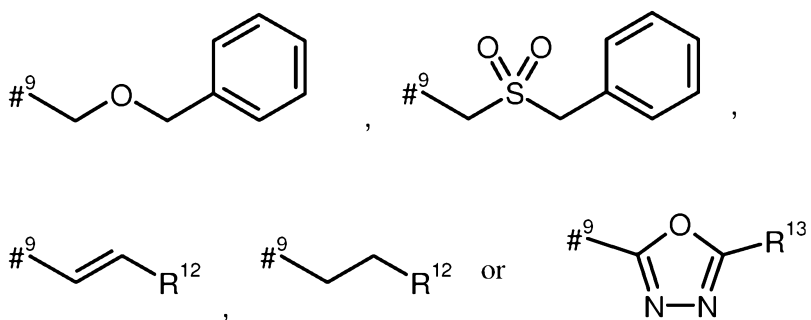
or

R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

- 15 R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



in which

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

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

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

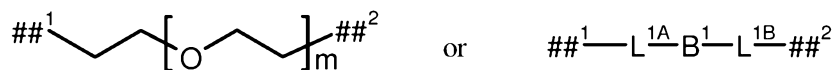
R^{35} is methyl or hydroxy,

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

Preferred subject matter of the present invention are compounds of the formula (XXXa) as indicated above, 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 ($\text{C}_2\text{-C}_6$)-alkanediyl, a group of the formula



where

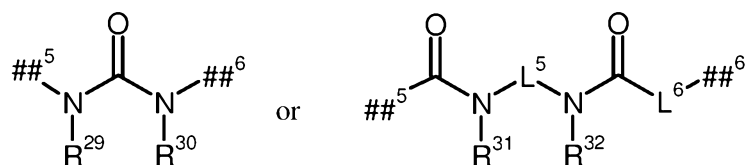
m is a number 2 or 3,

##^1 marks the linkage site with the group G,

##^2 marks the linkage site with the group B,

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

B^1 is a group of the formula



in which

5 $##^5$ 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,

10 R^{30} is hydrogen,

R^{31} is hydrogen or methyl,

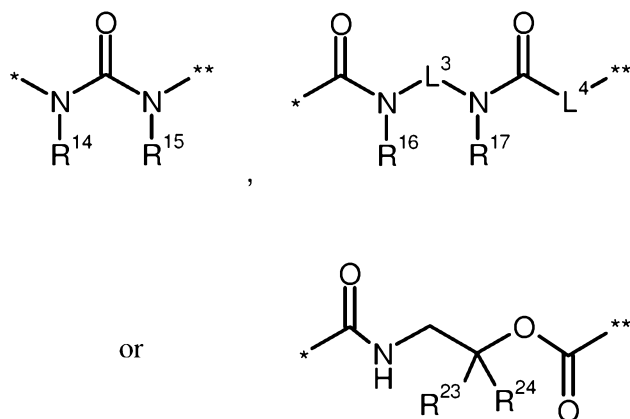
R^{32} is hydrogen or methyl,

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

and

15 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,

5 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,

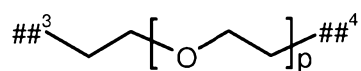
10 or

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,

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



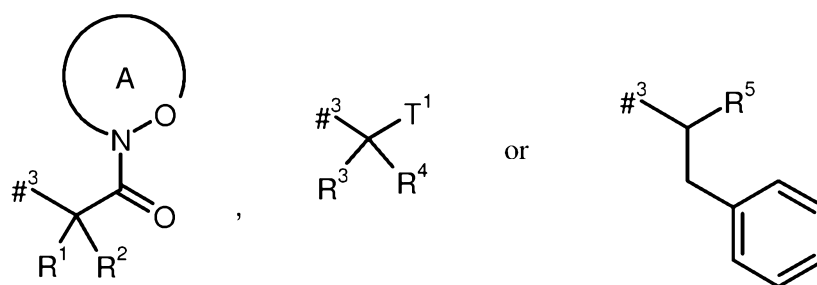
where

p is a number 2 or 3,

$##^3$ marks the linkage site with the group B,

20 $##^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

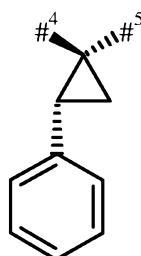
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

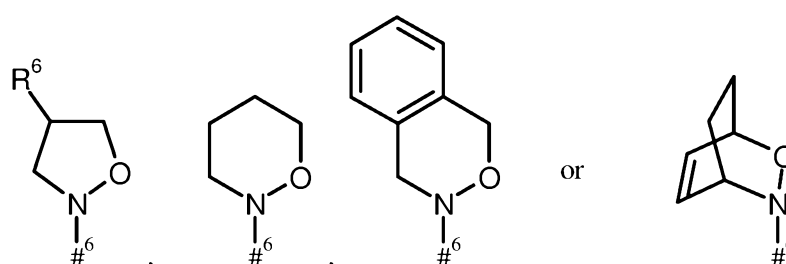


10 in which

#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



15

in which

#⁶ marks the linkage site with the carbonyl group,

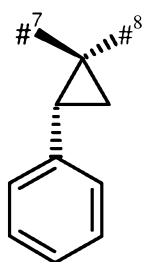
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

5 R⁴ is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10 in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

15 in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

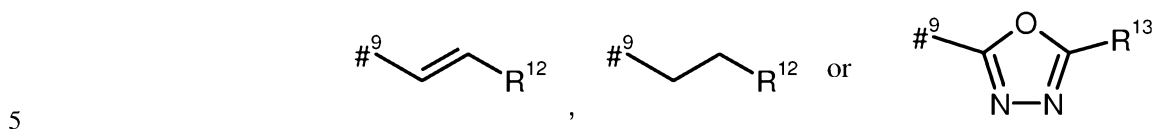
20 or

R⁸ and R⁹ 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 $-\text{CHCH}_2\text{phenyl}$,

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

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

R^{35} is methyl or hydroxy,

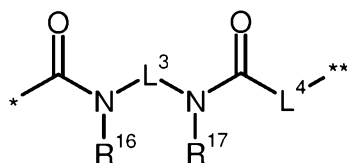
and also their salts, solvates and solvates of the salts.

Preferred subject matter of the present invention are compounds of the formula (XXXa) as indicated above, in which

15 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 $(\text{C}_2\text{-C}_6)$ -alkanediyl,

B is a bond or a group of the formula



20 where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

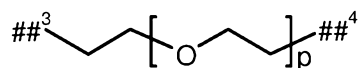
L^3 is a bond,

L^4 is a bond,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

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



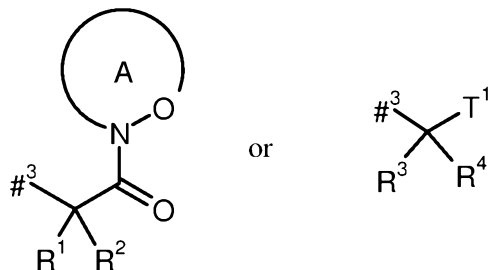
where

p is a number 2 or 3,

$##^3$ marks the linkage site with the group B,

10 $##^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

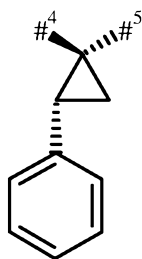
$##^3$ marks the linkage site with the nitrogen atom,

15 R^1 is hydrogen,

R^2 is benzyl or 1*H*-indol-3-ylmethyl,

or

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

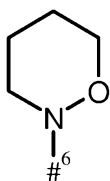


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



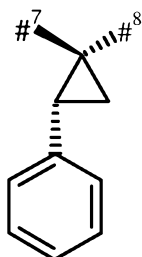
in which

#⁶ marks the linkage site with the carbonyl group,

- 10 R³ is hydrogen,
R⁴ is benzyl or 1*H*-indol-3-ylmethyl,

or

- R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

5 R⁷ is hydrogen,

R⁸ is hydrogen,

R⁹ is hydrogen,

R³⁵ is methyl,

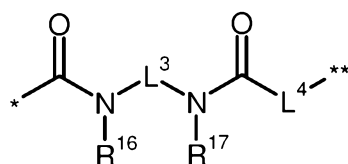
and also their salts, solvates and solvates of the salts.

10 Preferred subject matter of the present invention are compounds of the formula (XXXa) as indicated above, 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,

L¹ is a bond or linear (C₂-C₆)-alkanediyl,

15 B is a bond or a group of the formula



where

* marks the linkage site with L¹,

** marks the linkage site with L²,

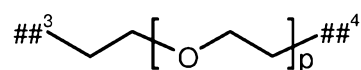
20 L³ is a bond,

L⁴ is a bond,

R¹⁶ 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



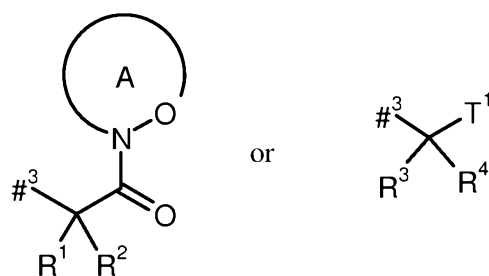
where

5 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



10 where

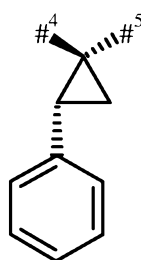
$#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

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



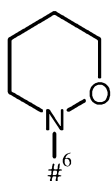
in which

#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

5



in which

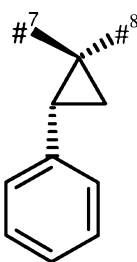
#⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

10 R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R^7 is hydrogen,

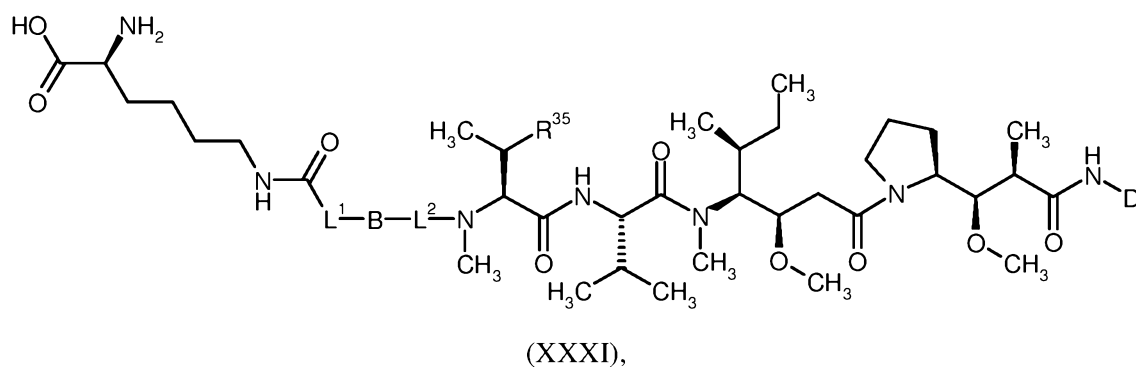
R^8 is hydrogen,

R^9 is hydrogen,

R^{35} is methyl,

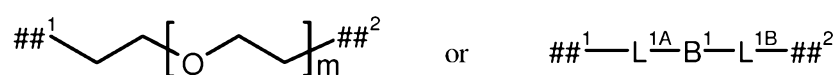
5 and also their salts, solvates and solvates of the salts.

The present invention additionally provides compounds of the formula (XXXI)



in which

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



where

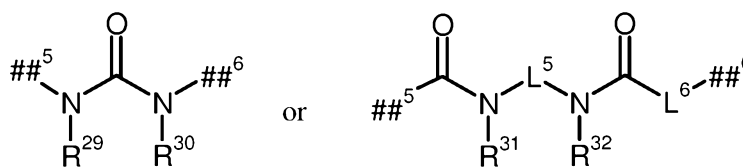
m is a number from 2 to 6,

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

15 $\# \#^2$ 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},

5 L⁵ is a bond or (C₂-C₄)-alkanediyl,

L⁶ is a bond,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

10 R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

R³² is hydrogen or (C₁-C₄)-alkyl,

or

15 R³¹ and R³² together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

and

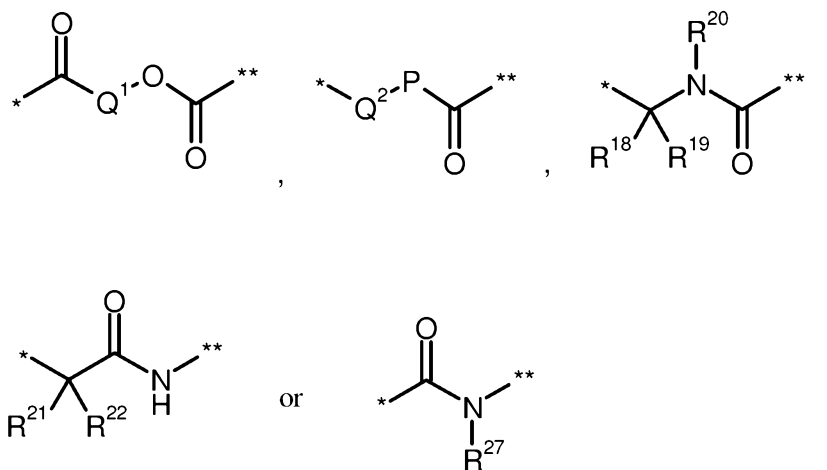
20 where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula

5



where

* marks the linkage site with L¹,

** marks the linkage site with L²,

10 P is O or NH,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

15 R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidiny ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

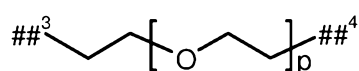
R^{22} is hydrogen or (C₁-C₄)-alkyl,

or

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

5 R^{27} is hydrogen or (C₁-C₄)-alkyl,

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

10 $##^3$ marks the linkage site with the group B,

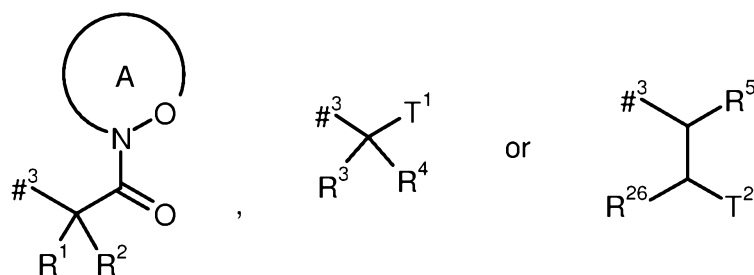
$##^4$ marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

and

15 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

D is a group of the formula



20 in which

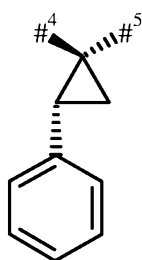
$\#^3$ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

5 or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

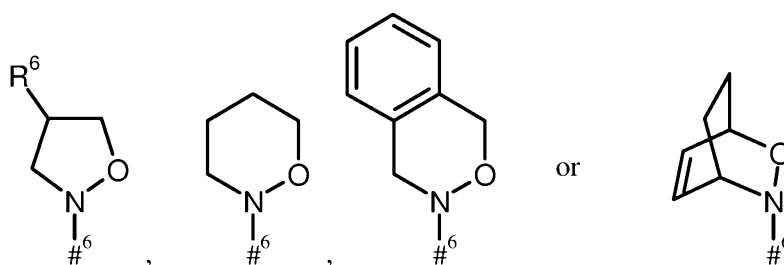


in which

10 #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



15 in which

#⁶ marks the linkage site with the carbonyl group,

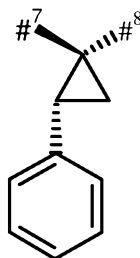
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

5 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

10 #⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

15 R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

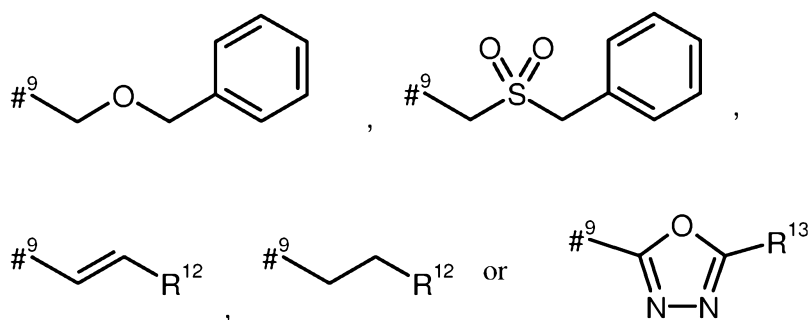
or

20 R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4-to 7-membered heterocycle,

R¹⁰ is benzoyl,

R¹¹ 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 $-\text{CHC}(\text{R}^{26})\text{-T}^2$,

5 R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $-\text{S}(\text{O})_2\text{OH}$,

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

R^{26} is hydrogen or hydroxy,

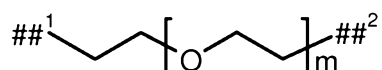
T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

10 R^{35} is methyl or hydroxy,

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

Preferred subject matter of the present invention are compounds of the formula (XXXI) as indicated above, in which

L^1 is a bond, linear $(\text{C}_2\text{-C}_6)$ -alkanediyl or a group of the formula



15

where

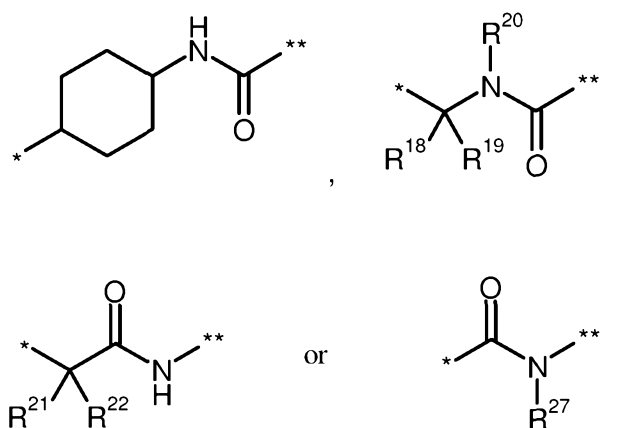
m is a number 2 or 3,

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

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

20 where $(\text{C}_2\text{-C}_6)$ -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 ,

5 ** 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 (C₁-C₄)-alkyl,

or

10 R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidiny ring,

R^{21} is hydrogen or methyl,

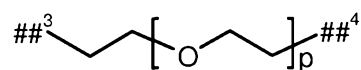
R^{22} is hydrogen or methyl,

or

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

15 R^{27} is hydrogen or methyl,

L^2 is linear (C₂-C₆)-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,

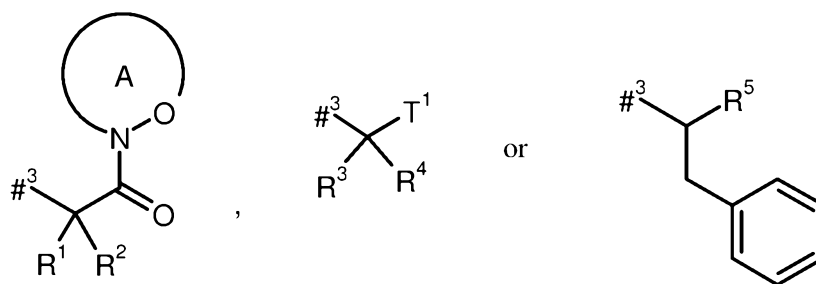
$\#^4$ marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-alkanediyl may be substituted by 1 or 2 methyl substituents,

5 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



10

in which

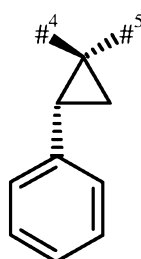
$\#^3$ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

15 or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

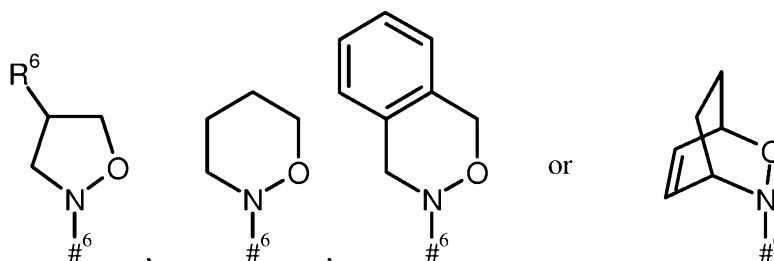
#⁴ marks the linkage site with the adjacent nitrogen atom,

#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

5



in which

#⁶ marks the linkage site with the carbonyl group,

R⁶ is hydrogen, hydroxy or benzyloxy,

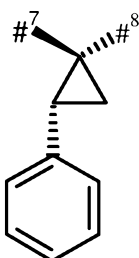
10

R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropan-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

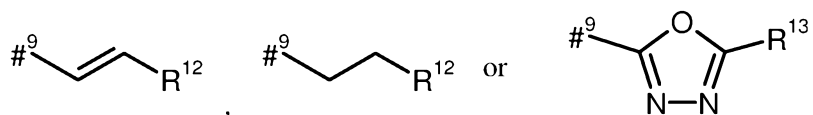
or

R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



in which

#⁹ marks the linkage site with -CHCH₂phenyl,

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula -S(O)₂OH,

R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R³⁵ is methyl or hydroxy,

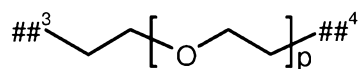
and also their salts, solvates and solvates of the salts.

Preferred subject matter of the present invention are compounds of the formula (XXXI) as indicated above, in which

L¹ is a bond,

B is a bond,

L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



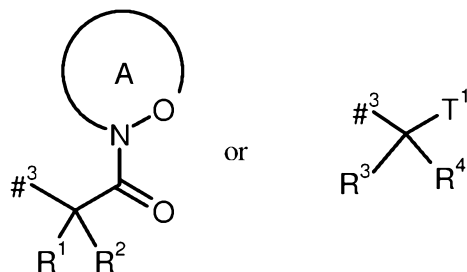
5 where

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 the group of the formula



10

where

##³ marks the linkage site with the nitrogen atom,

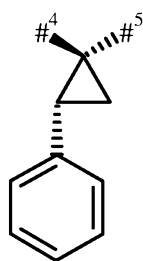
R¹ is hydrogen,

R² is benzyl or 1*H*-indol-3-ylmethyl,

15

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

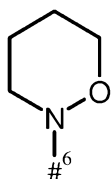


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

5 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,

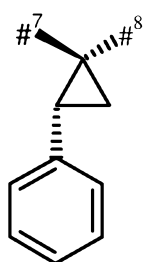
10 R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl or 1*H*-indol-3-ylmethyl,

or

15 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

5 in which

R⁷ is hydrogen,

R⁸ is hydrogen,

R⁹ is hydrogen,

R³⁵ is methyl,

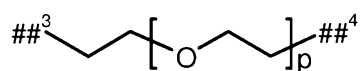
10 and also their salts, solvates and solvates of the salts.

Preferred subject matter of the present invention are compounds of the formula (XXXI) as indicated above, in which

L¹ is a bond,

B is a bond,

15 L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



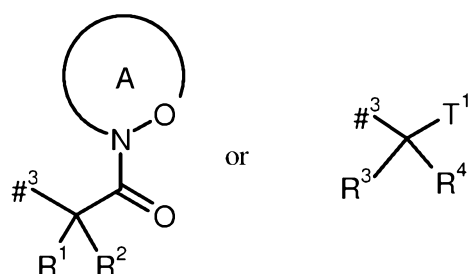
where

p is a number 2 or 3,

##³ marks the linkage site with the group B,

20 ##⁴ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

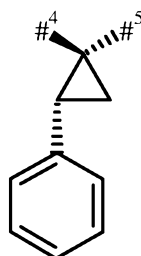
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

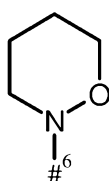


10 in which

#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



15

in which

#⁶ marks the linkage site with the carbonyl group,

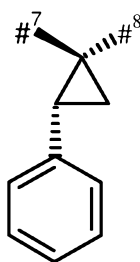
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

5 or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

10 #⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R⁷ is hydrogen,

15 R⁸ is hydrogen,

R⁹ is hydrogen,

R³⁵ is methyl,

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

Preferred subject matter of the present invention are compounds of the formulae (XXXa) and
20 (XXXI) selected from the following group:

N-[6-(3-[(*2R*)-2-amino-2-carboxyethyl]sulphonyl)-2,5-dioxopyrrolidin-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(*3R,4S,5S*)-1-{(*2S*)-2-[(*1R,2R*)-3-[(*1S*)-1-carboxy-2-(1*H*-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.

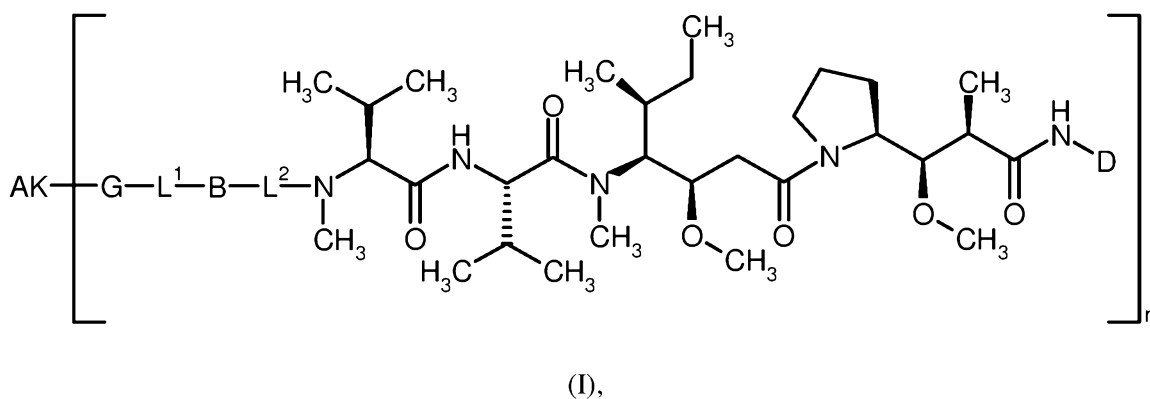
5 *N*-[6-(3-[(*2R*)-2-amino-2-carboxyethyl]sulphanyl)-2,5-dioxopyrrolidin-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(*3R,4S,5S*)-1-[(*2S*)-2-[(*1R,2R*)-3-[(*2S*)-3-(*1H*-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide,

N-(6-{[(5S)-5-amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-
10 { (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-
 15 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.

The present invention additionally provides binder-drug conjugates of the general formula (I)



20 in which

n is a number from 1 to 50.

AK is a binder,

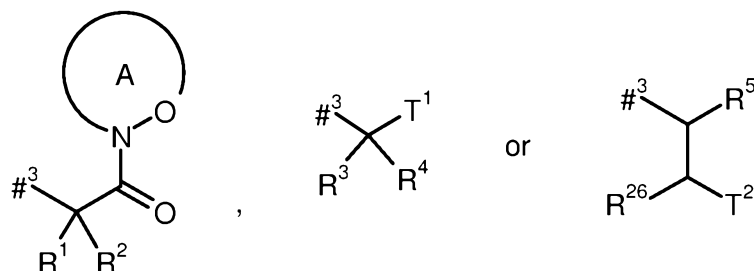
the group $\S\text{-G-L}^1\text{-B-L}^2\text{-}\S$ is a linker,

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



5 where

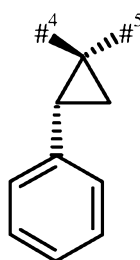
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

10 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

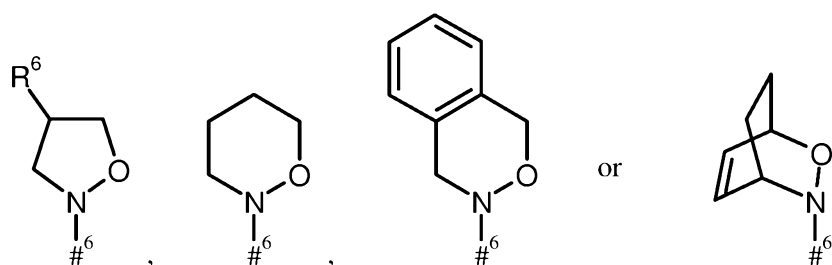


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

15 #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,

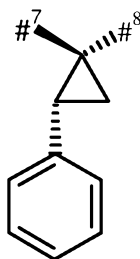
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen,

R⁴ 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

15 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

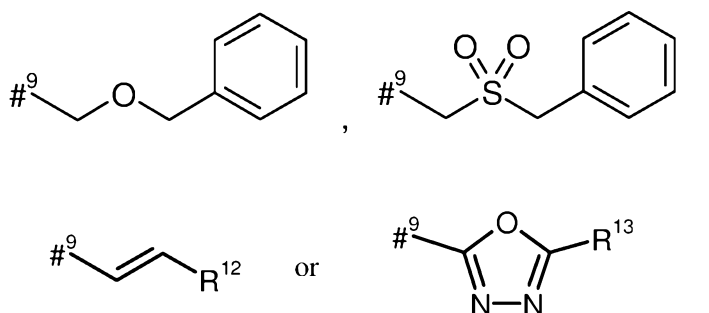
or

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

5 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



10 in which

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

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

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

15 R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

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

Preferred subject matter of the invention are binder-drug conjugates of the general formula (I), in which

20 n is a number from 1 to 50,

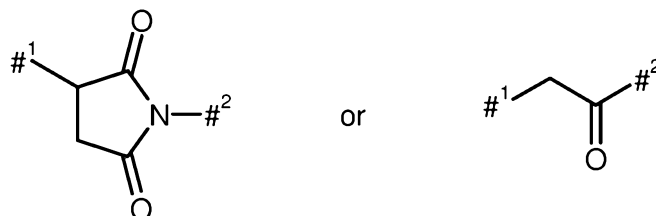
AK is AK_1 or AK_2

where

AK₁ is a binder which is bonded via a sulphur atom of the binder to the group G,

AK₂ is a binder which is bonded via a nitrogen atom of the binder to the group G,

G when AK = AK₁, is a group of the formula



where

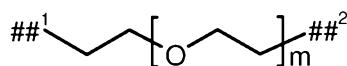
#¹ marks the linkage site with the sulphur atom of the binder,

#² marks the linkage site with the group L¹,

or

10 when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl or is a group of the formula



where

m is a number from 2 to 6,

15 ##¹ marks the linkage site with the group G,

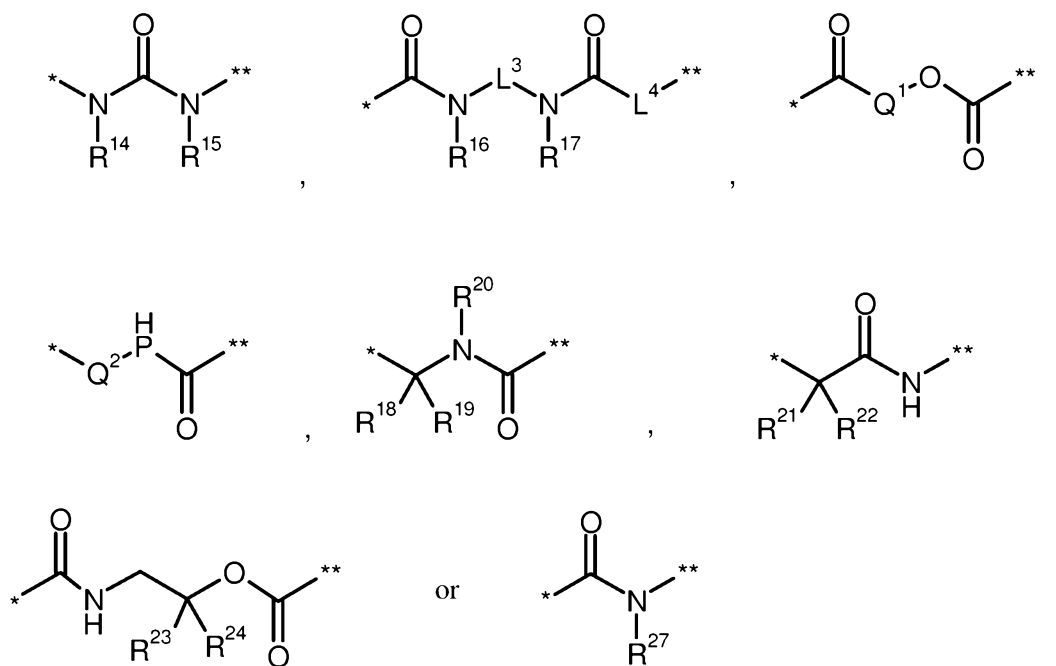
##² marks the linkage site with the group B,

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 methyl substituents,

and

20 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



where

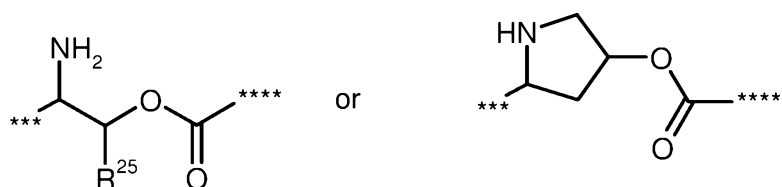
* marks the linkage site with L^1 ,

5 ** marks the linkage site with L^2 ,

P is O or NH,

L^3 is a bond or (C₂-C₄)-alkanediyl,

L^4 is a bond or a group of the formula



10 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 (C₁-C₄)-alkyl,

R^{15} is hydrogen or (C₁-C₄)-alkyl,

or

5 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 (C₁-C₄)-alkyl,

R^{17} is hydrogen or (C₁-C₄)-alkyl,

or

10 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 (C₁-C₄)-alkyl,

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

15 R^{20} is hydrogen or (C₁-C₄)-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 (C₁-C₄)-alkyl,

R^{22} is hydrogen or (C₁-C₄)-alkyl,

20 or

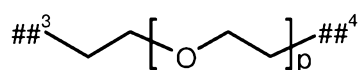
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R^{23} is (C₁-C₄)-alkyl,

R^{24} is hydrogen or (C₁-C₄)-alkyl,

25 R^{27} is hydrogen or (C₁-C₄)-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,

5 ##^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

10 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 above,

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

Preferred subject matter of the invention are binder-drug conjugates of the general formula (I),

15 in which

n is a number from 1 to 50,

AK is AK_1 or AK_2

where

20 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 above,

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

Preferred subject matter of the present invention are binder-drug conjugates of the general formula (I), in which

n is a number from 1 to 20,

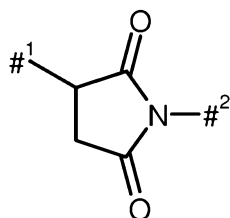
AK is AK_1 or AK_2

5 where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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 C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

10 G when $AK = AK_1$, is a group of the formula



in which

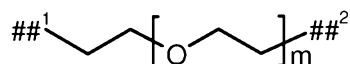
#¹ marks the linkage site with the cysteine residue of the binder,

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

15 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

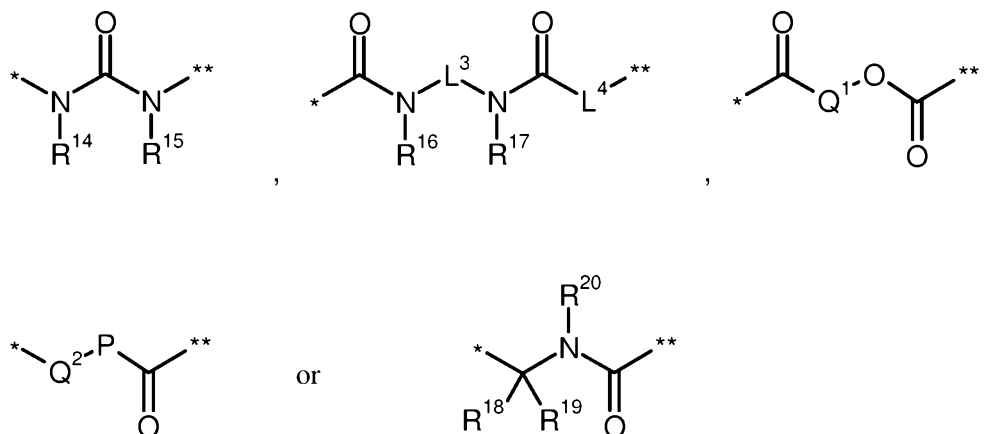
20 m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



5 where

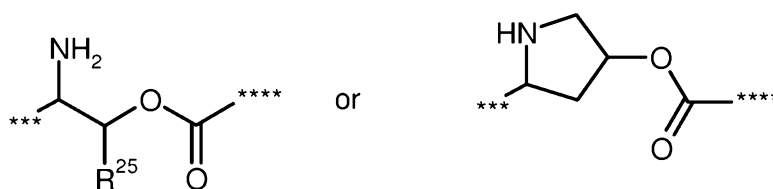
* marks the linkage site with L¹,

** marks the linkage site with L²,

P is O or NH,

L³ is a bond or ethane-1,2-diyl,

10 L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

15 R²⁵ is methyl,

Q¹ is a 4- to 6-membered carbocycle or piperidine-1,4-diyl,

Q^2 is cyclopentyl or cyclohexyl,

R^{14} is hydrogen,

R^{15} is hydrogen,

R^{16} is hydrogen or methyl,

5 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,

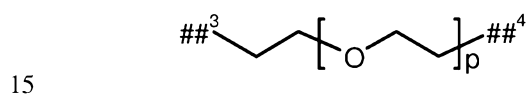
10 R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

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,

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



where

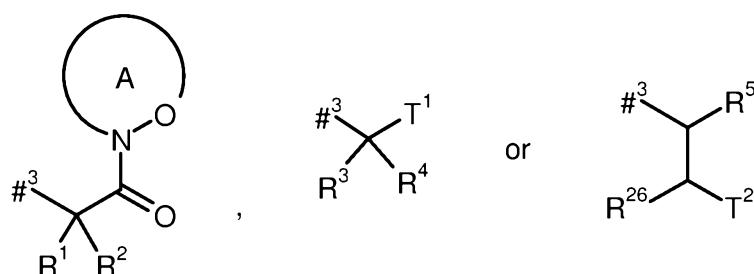
p is a number from 2 to 6,

$##^3$ marks the linkage site with the group B,

$##^4$ marks the linkage site with the nitrogen atom,

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

D is a group of the formula



where

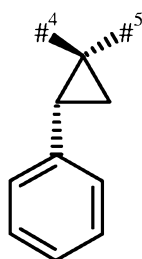
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

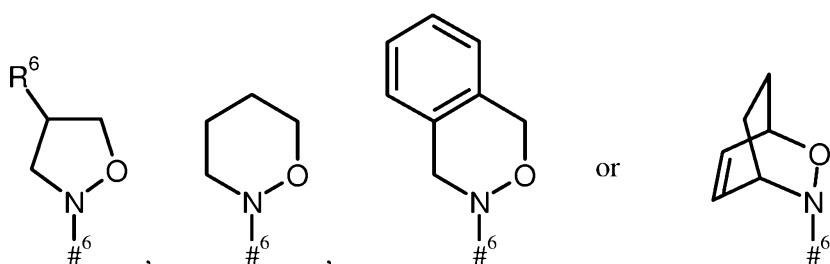


10 in which

#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



15

in which

#⁶ marks the linkage site with the carbonyl group,

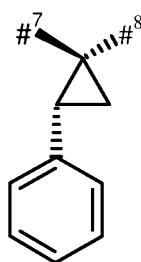
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

5 R⁴ is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10 in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

15 in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

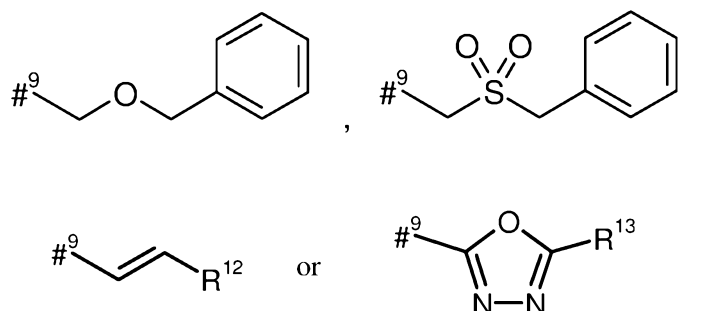
20 or

R⁸ and R⁹ 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



5

in which

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

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

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

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

Particularly preferred subject matter of the present invention are binder-drug conjugates of the
15 general formula (I), in which

n is a number from 1 to 10,

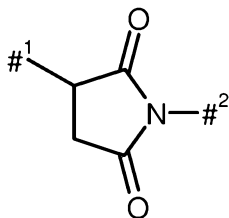
AK is AK_1 or AK_2

where

20 AK_1 is an antibody which comprises the six CDR sequences of an antibody listed in Table 2, the variable light and variable heavy chain of an antibody listed in Table 2 or the light and heavy chain of an antibody listed in Table 2, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK₂ is an antibody which comprises the six CDR sequences of an antibody listed in Table 2, the variable light and variable heavy chain of an antibody listed in Table 2 or the light and heavy chain of an antibody listed in Table 2, and is bonded via the NH side group of a lysine residue of the binder to the group G,

5 G when AK = AK₁, is a group of the formula



in which

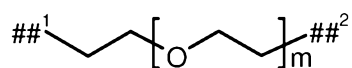
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

10 or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl or is a group of the formula



where

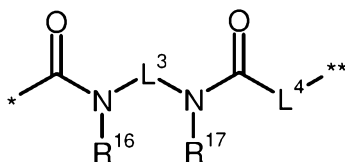
15 m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



20

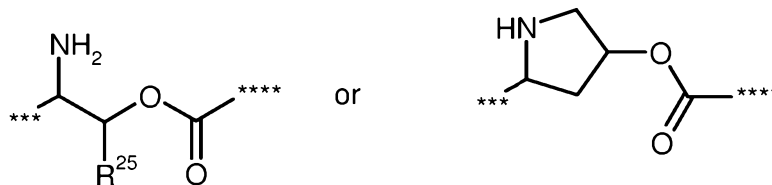
where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

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

5 L^4 is a bond or a group of the formula



where

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2 ,

10 R^{25} is methyl,

R^{16} is hydrogen or methyl,

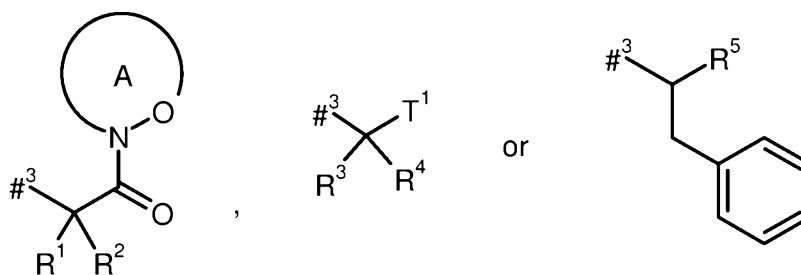
R^{17} is hydrogen or methyl,

or

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

15 L^2 is linear (C_2 - C_6)-alkanediyl,

D is a group of the formula



where

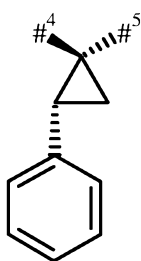
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

- 5 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

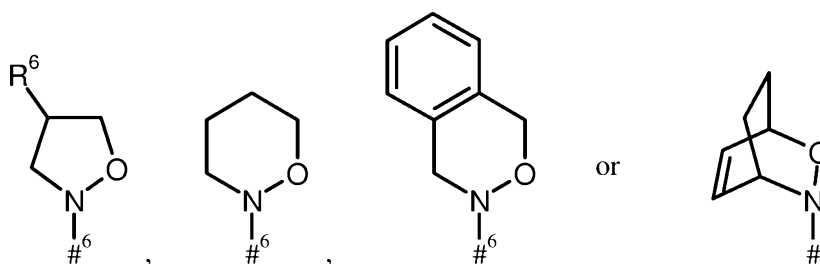


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

- 10 #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

- 15 #⁶ marks the linkage site with the carbonyl group,

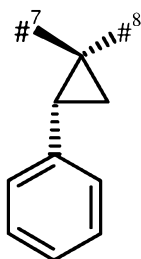
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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



5 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

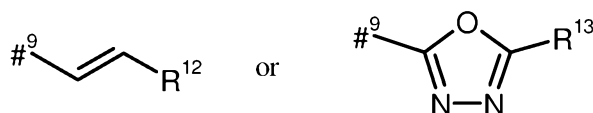
10 R^7 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or adamantylmethyl,

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,

15 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 $-S(O)_2OH$,

20

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

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

Particularly preferred subject matter of the present invention are binder-drug conjugates of the general formula (I), in which

5 n is a number from 1 to 10,

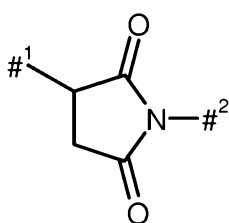
AK is AK_1 or AK_2

where

10 AK_1 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10 or D02-6, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

15 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



20 in which

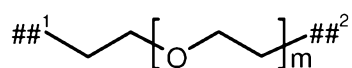
$\#^1$ marks the linkage site with the cysteine residue of the binder,

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

or

when $AK = AK_2$, is carbonyl,

L^1 is a bond, linear (C₂-C₆)-alkanediyl or is a group of the formula



where

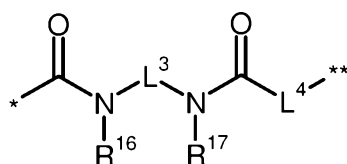
m is a number 2 or 3,

5 ##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



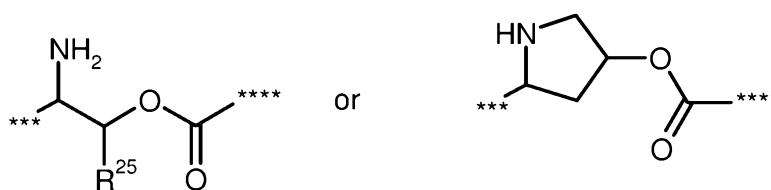
10 where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



15

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is methyl,

R^{16} is hydrogen or methyl,

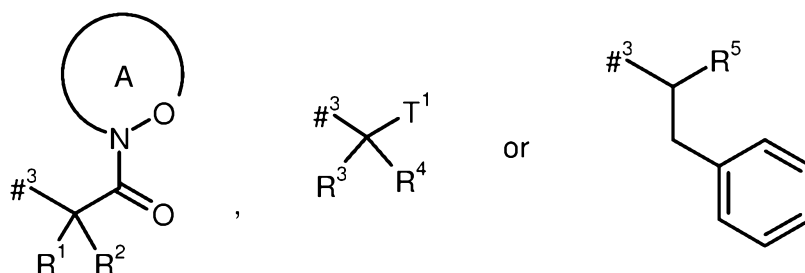
R^{17} is hydrogen or methyl,

or

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

5 L^2 is linear (C_2 - C_6)-alkanediyl,

D is a group of the formula



where

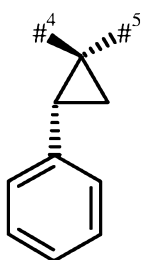
$\#^3$ marks the linkage site with the nitrogen atom,

10 R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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



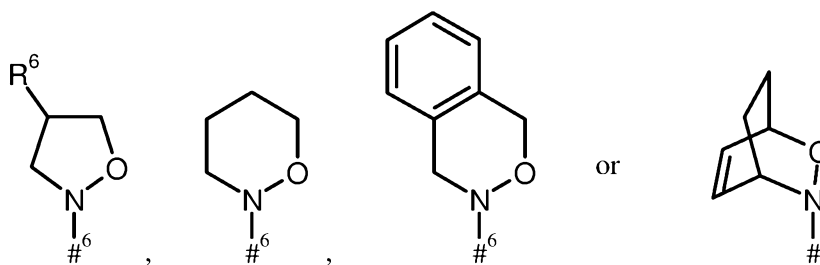
15

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

5 $\#^6$ marks the linkage site with the carbonyl group,

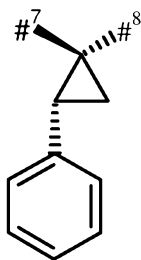
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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



in which

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

15 $\#^8$ marks the linkage site with the group T,

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

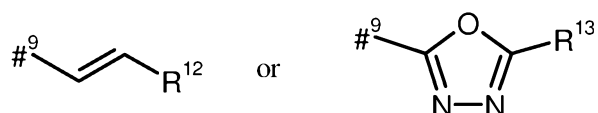
R^7 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or adamantylmethyl,

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,

5 R^5 is hydrogen or a group of the formula



in which

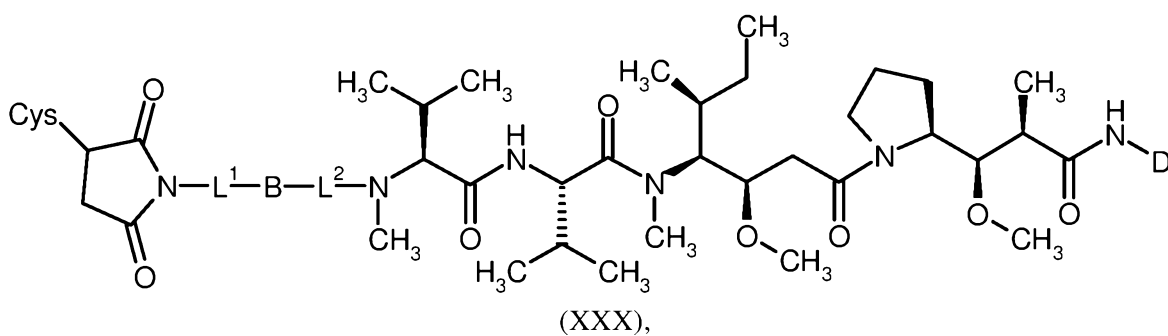
$\#^9$ marks the linkage site with $\text{---CHC}(R^{26})\text{phenyl}$,

10 R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $\text{---S(O)}_2\text{OH}$,

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

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

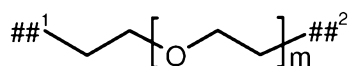
The present invention additionally provides compounds of the formula (XXX)



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 $(C_1\text{---}C_{10})$ -alkanediyl or is a group of the formula



in which

m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

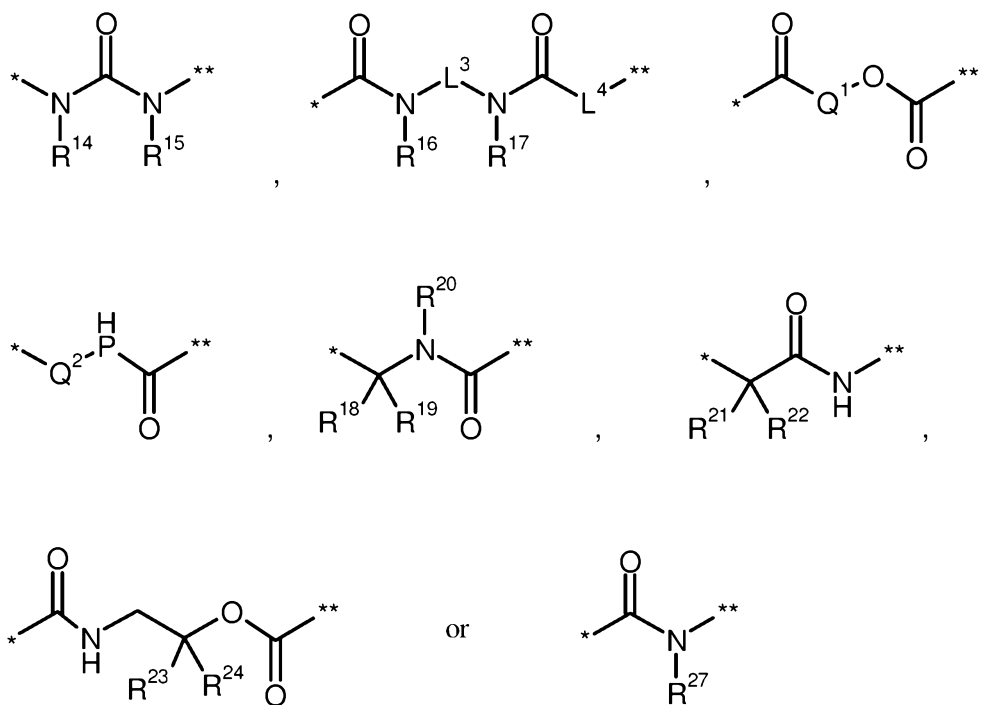
##² marks the linkage site with the group B,

5 where (C₁-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

10 B is a bond or a group of the formula



where

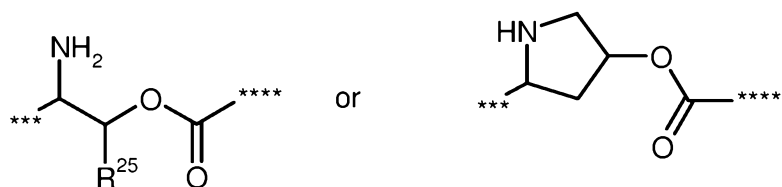
* marks the linkage site with L¹,

** marks the linkage site with L²,

15 P is O or NH,

L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

5 **** marks the linkage site with L²,

R²⁵ is hydrogen or methyl

Q¹ is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

10 R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

15 R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

20 R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-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 (C₁-C₄)-alkyl,

R^{22} is hydrogen or (C₁-C₄)-alkyl,

5 or

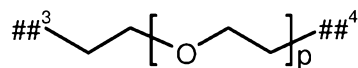
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R^{23} is (C₁-C₄)-alkyl,

R^{24} is hydrogen or (C₁-C₄)-alkyl,

10 R^{27} is hydrogen or (C₁-C₄)-alkyl,

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

15 ##^3 marks the linkage site with the group B,

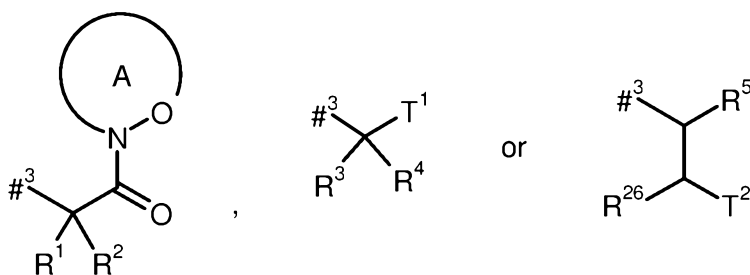
##^4 marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents,

and

20 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

D is a group of the formula



in which

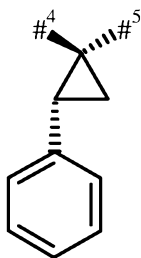
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



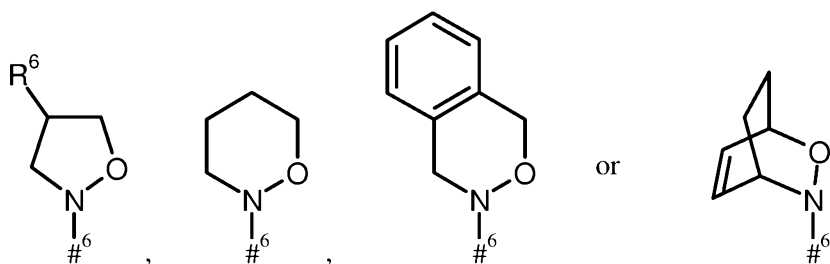
10

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



15

in which

#⁶ marks the linkage site with the carbonyl group,

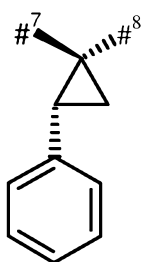
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

5 R⁴ is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10 in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

15 in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

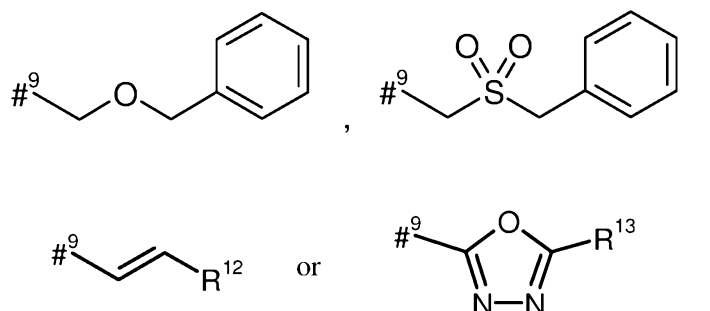
20 or

R⁸ and R⁹ 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



5

in which

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

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

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

R^{26} is hydrogen or hydroxy,

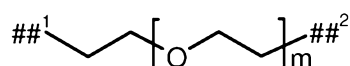
T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

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

Particularly preferred in the context of the present invention in addition are also compounds of the
15 formula (XXX), 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 or is a group of the formula



20

in which

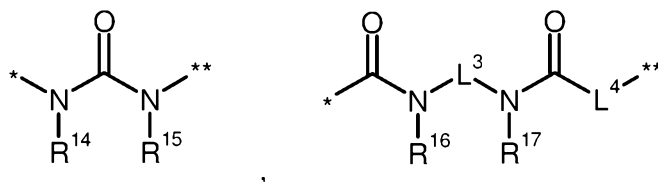
m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

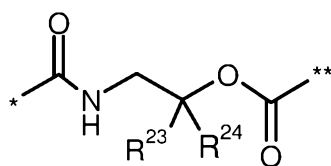
##² marks the linkage site with the group B,

where (C₂-C₆)-alkandiyl may be substituted by 1 or 2 methyl substituents,

5 B is a bond or a group of the formula



or



where

* marks the linkage site with L¹,

** marks the linkage site with L²,

10 L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond,

R¹⁴ is hydrogen,

R¹⁵ is hydrogen,

R¹⁶ is hydrogen or methyl,

15 R¹⁷ is hydrogen or methyl,

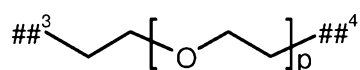
or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

R²³ is methyl,

R²⁴ is hydrogen or methyl,

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



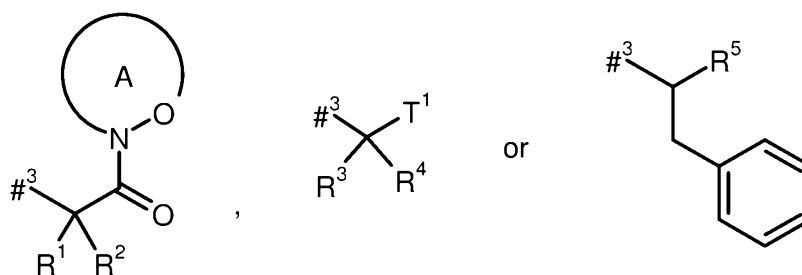
where

p is a number 2 or 3,

5 $##^3$ 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

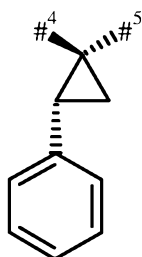
10 $##^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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

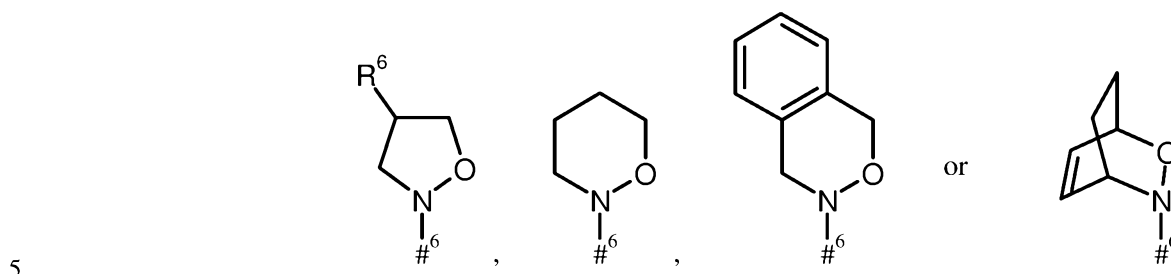


in which

#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,

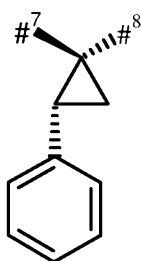
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

10 R⁴ is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R^7 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or adamantylmethyl,

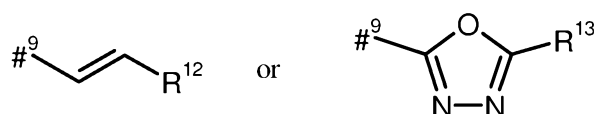
R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

5 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



10 in which

$\#^9$ marks the linkage site with $-\text{CHC}(\text{R}^{26})\text{phenyl}$,

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

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

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

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 $n = 2-8$.

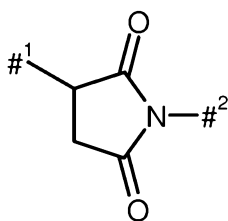
Preferred in the context of the present invention are also compounds of the formula (Ia), in which

AK is AK_1

20 where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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 L¹,

5 and

n, L¹, B, L², D and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

AK is AK₂

10 where

AK₂ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

G is carbonyl,

and

15 n, L¹, B, L², D and R³⁵ have the definitions indicated above,

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

Preference in the context of the present invention is also given to compounds of the formula (Ia), in which

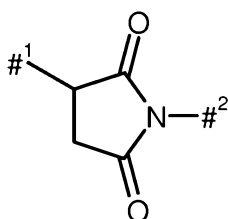
AK is AK₁

20 where

AK₁ is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10 or D02-6, the variable light and variable heavy chain of the antibody

B01-3, B01-10 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10 or D02-6, and which is attached via the sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula



5

where

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

#² marks the linkage site with the group L¹,

and

10 n, L¹, B, L², D and R³⁵ have the definitions indicated above,

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

Preference in the context of the present invention is also given to compounds of the formula (Ia), in which

AK is AK₂

15 where

AK₂ 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 which is bonded via the NH side group of a lysine residue of the binder to the group G,

20

G is carbonyl,

and

n, L¹, B, L², D and R³⁵ have the definitions indicated above,

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

Preference in the context of the present invention is also given to compounds of the general formula (Ia), in which

AK is AK_2

where

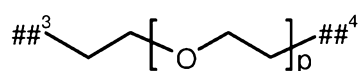
- 5 AK_2 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10, M31-B01 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6, and which is bonded via the NH side group of a lysine residue of the binder to the group G,

- 10 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



- 15 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,

n, D and R^{35} have the definitions indicated above,

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

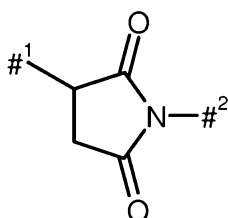
Preference in the context of the present invention is also given to compounds of the general formula (Ia), in which

AK is AK_1

where

AK₁ is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10 or D02-6, and which is attached via the sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula

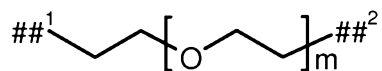


where

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

#² marks the linkage site with the group L¹,

L¹ is a bond, linear (C₃-C₅)-alkanediyl or a group of the formula



where

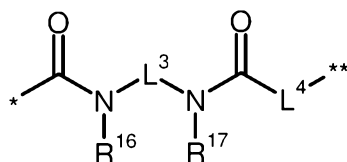
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



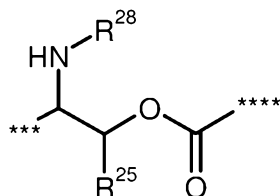
where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



5

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is methyl,

10 R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

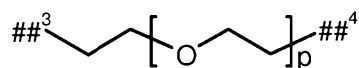
R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

15 L² is linear (C₃-C₅)-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,

20 ##⁴ marks the linkage site with the nitrogen atom,

and

n, D and R³⁵ have the definitions indicated above,

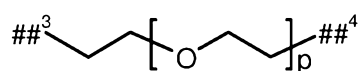
and also their salts, solvates and solvates of the salts.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

5 L¹ is a bond,

B is a bond,

L² is linear (C₃-C₆)-alkanediyl or is a group of the formula



where

10 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,

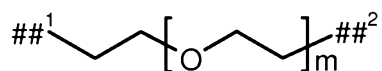
and

n, AK, Cys, G, D and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

L¹ is linear (C₁-C₁₀)-alkanediyl or a group of the formula



where

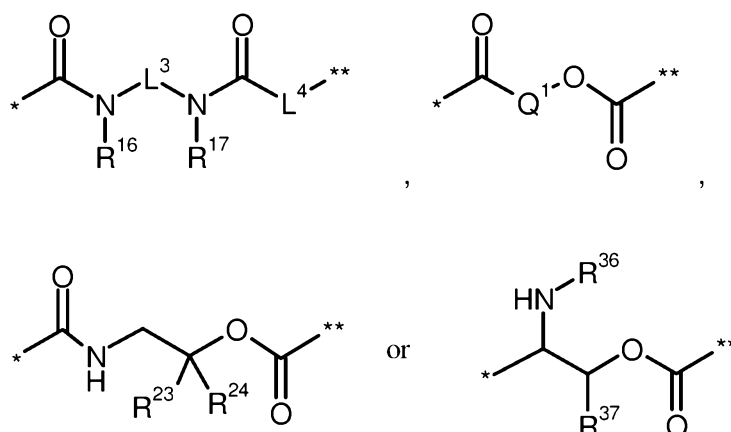
20 m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxyl and benzyl,

B is a bond or a group of the formula



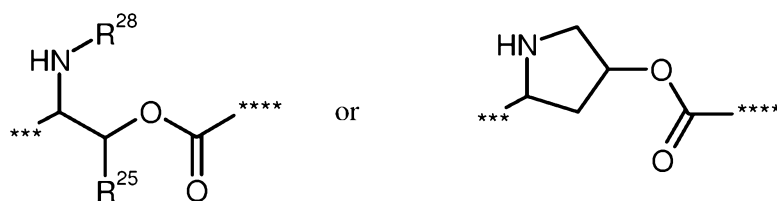
5 where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a group of the formula



10

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is hydrogen or methyl,

15 R²⁸ is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

Q¹ is a 4- to 7-membered heterocycle,

R^{16} is hydrogen or (C₁-C₄)-alkyl,

R^{17} is hydrogen or (C₁-C₄)-alkyl,

or

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

R^{23} is (C₁-C₄)-alkyl,

R^{24} is hydrogen or (C₁-C₄)-alkyl,

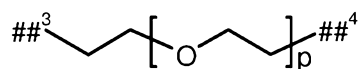
R^{36} is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R^{37} is hydrogen or methyl,

10 or

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

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



where

15 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 (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxyl and benzyl,

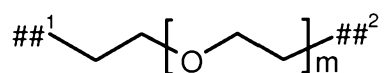
20 and

n , AK, G, D and R^{35} have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

L^1 is linear (C_2 - C_6)-alkanediyl or a group of the formula



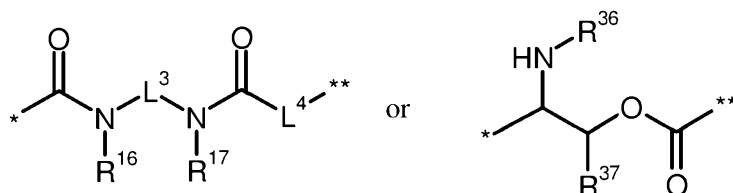
where

m is a number 2 or 3,

5 $\# \#^1$ marks the linkage site with the group G,

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

B is a bond or a group of the formula



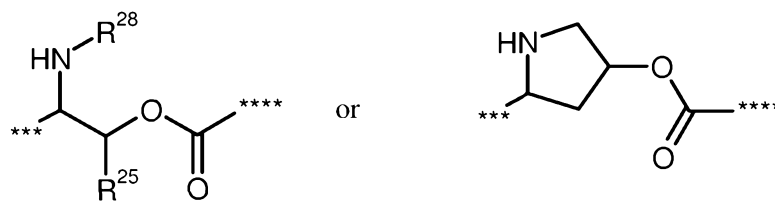
where

10 $*$ 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 group of the formula



15 where

$***$ 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,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

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

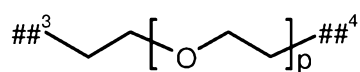
R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

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,

10 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,

15 ##^4 marks the linkage site with the nitrogen atom,

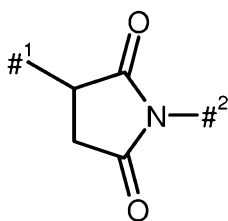
and

n , AK, G, D and R^{35} have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia) and
 20 (XXXa), in which

G is a group of the formula

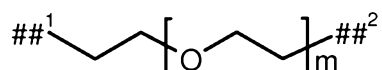


in which

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

#² marks the linkage site with the group L¹,

5 L¹ is linear (C₃-C₅)-alkanediyl or a group of the formula



in which

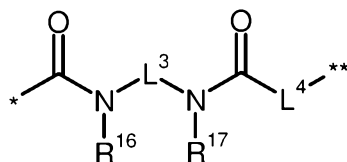
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

10 ##² marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



where

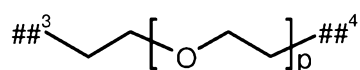
15 * marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond,

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



where

p is a number 2 or 3,

5 $##^3$ marks the linkage site with the group B,

$##^4$ marks the linkage site with the nitrogen atom,

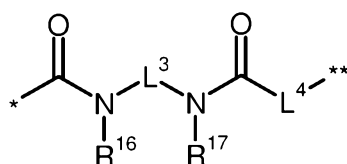
and

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.

10 Preferred in the context of the present invention are also compounds of the formula (Ia) and (XXXa), in which

B is a bond or a group of the formula



where

15 * marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

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

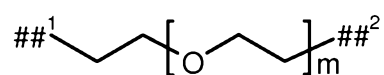
L^4 is a bond,

n , AK, Cys, G, L^1 , L^2 , D, R^{16} , R^{17} and R^{35} have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

L^1 is a bond, linear (C₃-C₅)-alkanediyl or a group of the formula



where

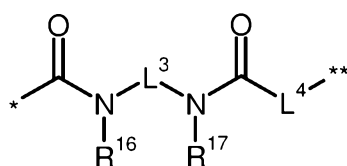
m is a number 2 or 3,

5 $##^1$ marks the linkage site with the group G,

$##^2$ marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



10 where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

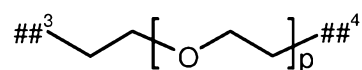
L^3 is a bond,

L^4 is a bond

15 R^{16} is hydrogen,

R^{17} is hydrogen,

L^2 is linear (C₃-C₆)-alkanediyl or is a group of the formula



where

20 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,

n, AK, Cys, G, D and R³⁵ have the definitions indicated above,

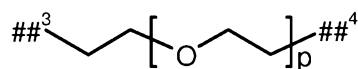
and also their salts, solvates and solvates of the salts.

- 5 Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

L¹ is a bond,

B is a bond,

L² is linear (C₃-C₆)-alkanediyl or is a group of the formula



10

where

p is a number 2 or 3,

##³ marks the linkage site with the group B,

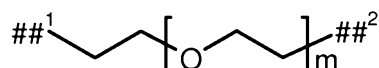
##⁴ marks the linkage site with the nitrogen atom,

- 15 n, AK, Cys, G, D and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

L¹ is linear (C₃-C₅)-alkanediyl or a group of the formula



20

where

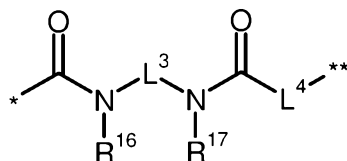
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a group of the formula



5 where

* marks the linkage site with L¹,

** marks the linkage site with L²,

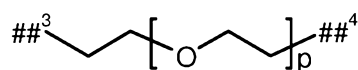
L³ is a bond,

L⁴ is a bond,

10 R¹⁶ is hydrogen,

R¹⁷ is hydrogen,

L² is linear (C₃-C₆)-alkanediyl or is a group of the formula



where

15 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,

n, AK, Cys, G, D and R³⁵ have the definitions indicated above,

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

20 Preferred in the context of the present invention are also compounds of the formula (Ia), in which

n is a number from 2 to 8, preferably 2 to 5,

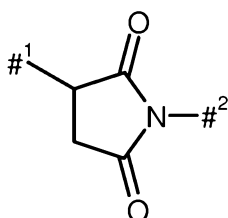
AK is AK_1 or AK_2

where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

5 AK_2 is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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

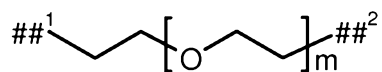
10 $\#^1$ marks the linkage site with the cysteine residue of the binder,

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

or

when $AK = AK_2$, is carbonyl,

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



15

where

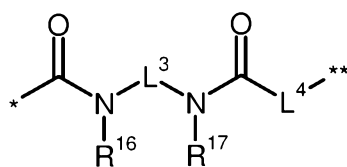
m is a number 2 or 3,

$##^1$ marks the linkage site with the group G,

$##^2$ marks the linkage site with the group B,

20 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 ,

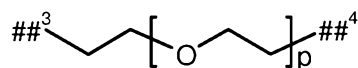
5 L^3 is a bond,

L^4 is a bond,

R^{16} is hydrogen,

R^{17} is hydrogen,

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



10

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,

15 and

D and R^{35} have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

n is a number from 2 to 8, preferably 2 to 5,

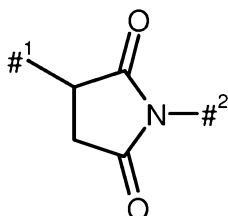
20 AK is AK_1 or AK_2 ,

where

AK₁ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK₂ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

5 G when AK = AK₁, 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 L¹,

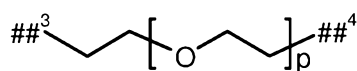
10 or

when AK = AK₂, is carbonyl,

L¹ is a bond,

B is a bond,

L² is linear (C₃-C₆)-alkanediyl or is a group of the formula



15

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,

20 D and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

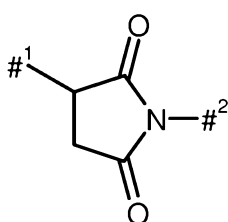
n is a number from 2 to 8, preferably 2 to 5,

AK is AK₁,

where

5 AK₁ is an antibody or an antigen-binding antibody fragment which binds to C4.4a 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

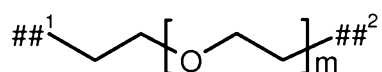


where

10 #¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

L¹ is linear (C₃-C₅)-alkanediyl or a group of the formula



where

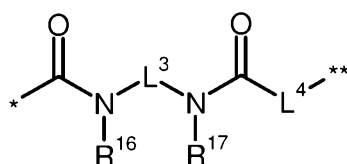
15 m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a group of the formula



where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

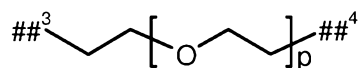
5 L^3 is a bond,

L^4 is a bond,

R^{16} is hydrogen,

R^{17} is hydrogen,

L^2 is linear (C₃-C₆)-alkanediyl or is a group of the formula



10

where

p is a number 2 or 3,

##³ marks the linkage site with the group B,

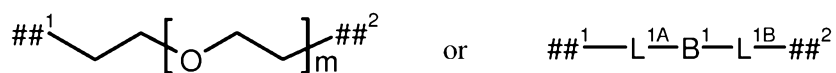
##⁴ marks the linkage site with the nitrogen atom,

15 D and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

L^1 is a bond, linear (C₃-C₅)-alkanediyl, a group of the formula



20

where

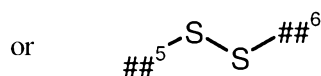
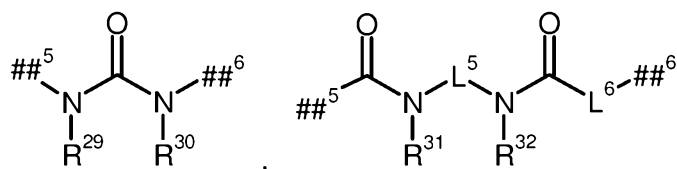
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₃-C₆)-alkanediyl,

5 B¹ is a group of the formula



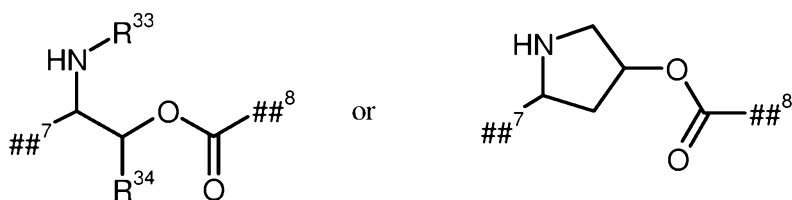
in which

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

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

10 L⁵ is a bond or ethane-1,2-diyl,

L⁶ is a bond or a group of the formula



in which

##⁷ marks the linkage site with the carbonyl group,

15 ##⁸ marks the linkage site with L^{1B},

R³³ is hydrogen, (C₁-C₄)-alkylcarbonyl or tert-butyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R^{29} is hydrogen or methyl,

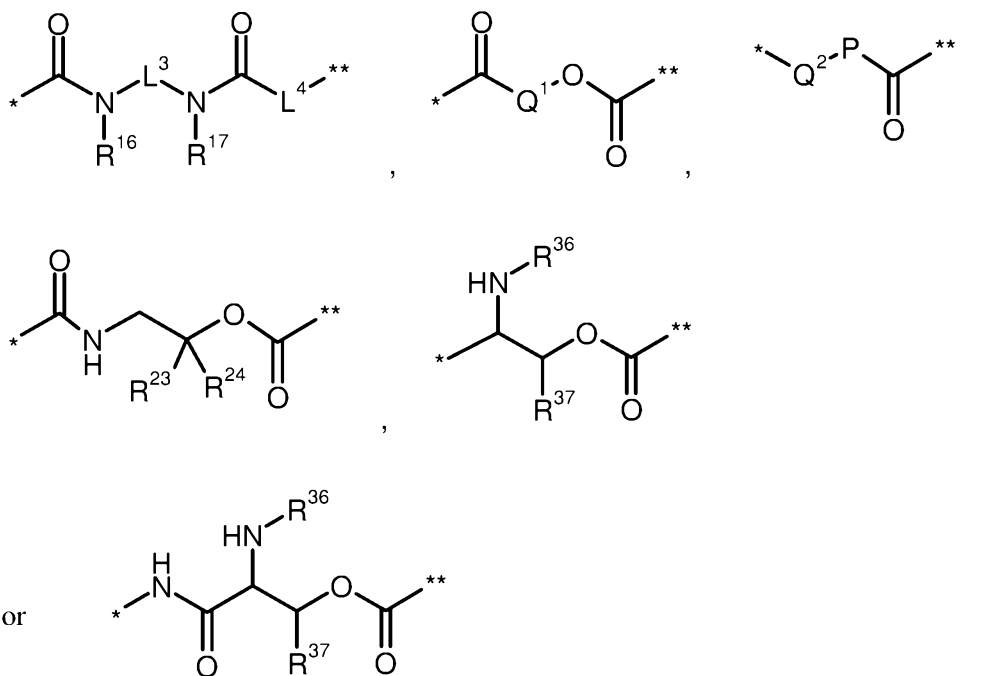
R^{30} is hydrogen or methyl,

R^{31} is hydrogen or methyl,

R^{32} is hydrogen or methyl,

5 L^{1B} is linear (C_3 - C_6)-alkanediyl,

B is a bond or a group of the formula



where

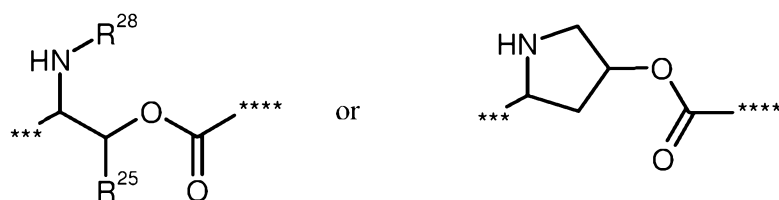
10 * marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

P is O,

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

L^4 is a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

5 R²⁵ is hydrogen or methyl,

R²⁸ is hydrogen, (C₁-C₄)-alkylcarbonyl or tert-butyloxycarbonyl,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R¹⁶ is hydrogen or methyl,

10 R¹⁷ is hydrogen or methyl,

R²³ is (C₁-C₄)-alkyl,

R²⁴ is hydrogen or (C₁-C₄)-alkyl,

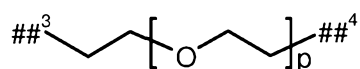
R³⁶ is hydrogen, (C₁-C₄)-alkylcarbonyl or tert-butyloxycarbonyl,

R³⁷ is hydrogen or methyl,

15 or

R³⁶ and R³⁷ together with the atoms to which they are bonded form a pyrrolidine ring,

L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



where

20 p is a number 2 or 3,

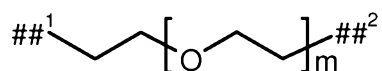
##³ marks the linkage site with the group B,

##⁴ marks the linkage site with the nitrogen atom,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), in which

5 L¹ is linear (C₃-C₅)-alkanediyl or a group of the formula



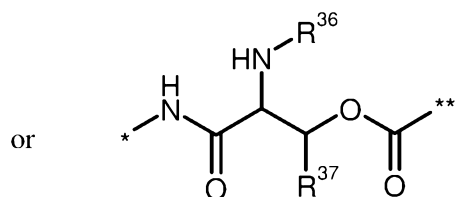
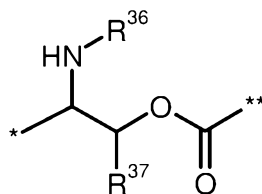
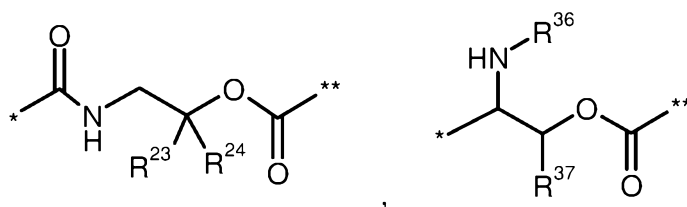
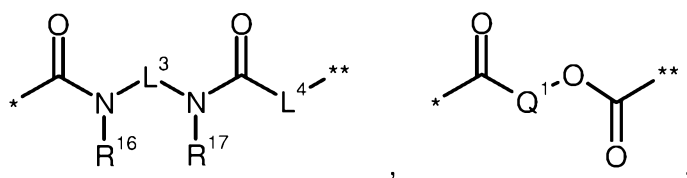
where

m is a number 2 or 3,

##¹ marks the linkage site with the group G,

10 ##² marks the linkage site with the group B,

B is a group of the formula



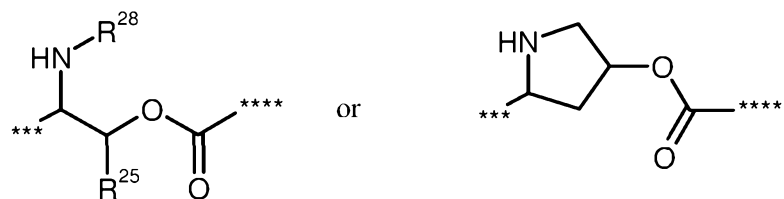
where

15 * marks the linkage site with L¹,

** marks the linkage site with L^2 ,

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

L^4 is a group of the formula



in which

5 *** 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,

10 R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

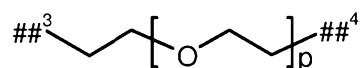
R^{23} is methyl,

R^{24} is hydrogen,

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

15 R^{37} is hydrogen or methyl,

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



where

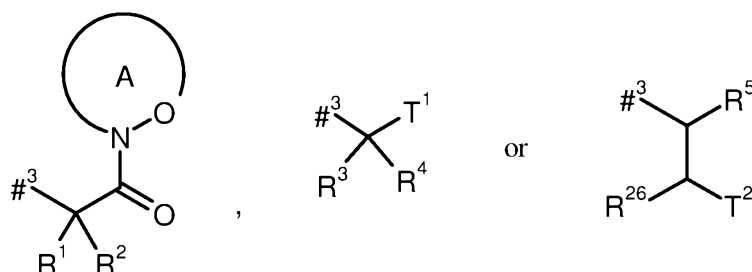
p is a number 2 or 3,

20 ##³ marks the linkage site with the group B,

##⁴ marks the linkage site with the nitrogen atom,
and also their salts, solvates and solvates of the salts.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

5 D is a group of the formula



where

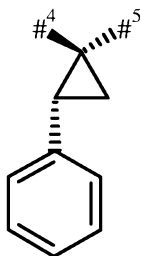
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

10 R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

15 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

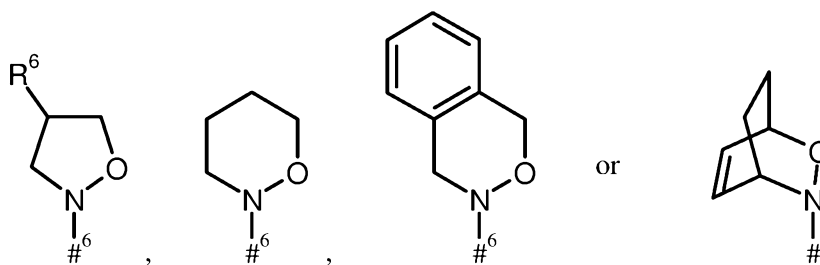


in which

#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

5 #⁶ marks the linkage site with the carbonyl group,

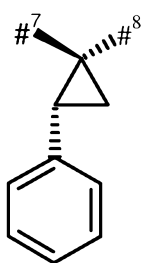
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen or methyl,

10 R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15 in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

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

R^8 is hydrogen or methyl,

5 R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

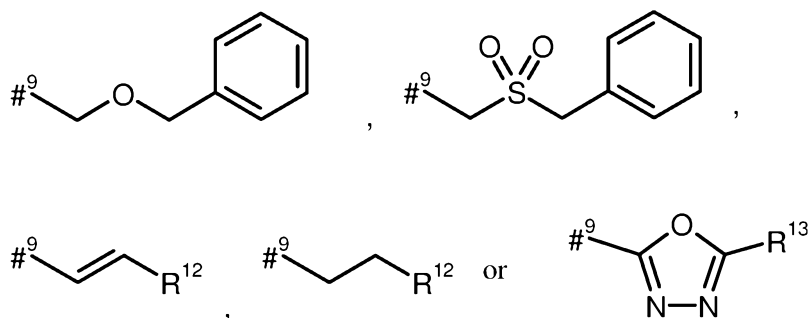
or

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,

10 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



15 in which

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

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

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

20 R^{26} is hydrogen,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

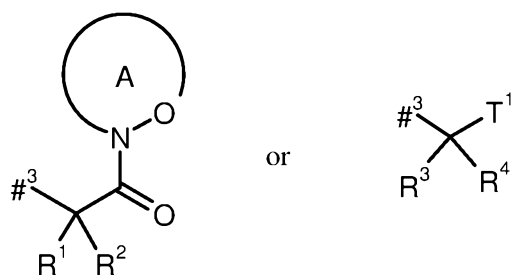
and

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.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa)
5 and (XXXI), in which

D is a group of the formula



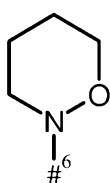
where

#³ marks the linkage site with the nitrogen atom,

10 R¹ is hydrogen,

R² is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

the ring A with the N-O moiety present therein is a heterocycle of formula



in which

15 #⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

R⁴ is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R^7 is hydrogen,

R^8 is hydrogen,

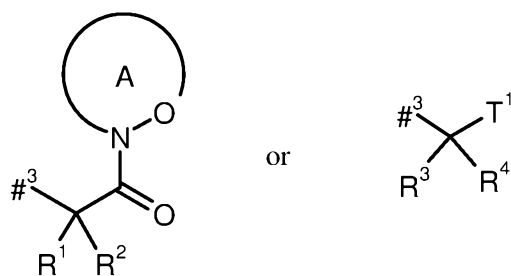
R^9 is hydrogen,

n, AK, Cys, G, L^1 , B, L^2 , D and R^{35} have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

D is a group of the formula



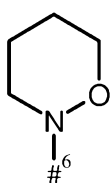
10 where

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

R^1 is hydrogen,

R^2 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

the ring A with the N-O moiety present therein is a heterocycle of the formula



15

in which

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

R^3 is hydrogen,

R^4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

T¹ is a group of the formula -C(=O)-NR⁸R⁹,

in which

R⁸ is hydrogen,

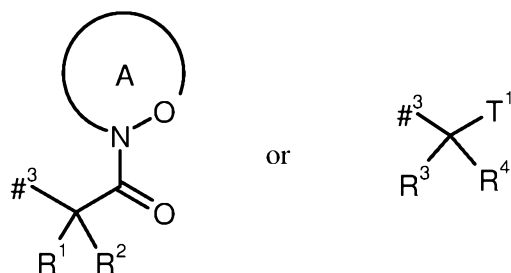
R⁹ is hydrogen,

5 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.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

D is a group of the formula



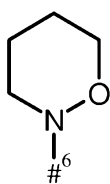
where

#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

15 the ring A with the N-O moiety present therein is a heterocycle of the formula



in which

#⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

R^4 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

T^1 is a group of the formula $-C(=O)-NR^8R^9$,

in which

R^8 is hydrogen,

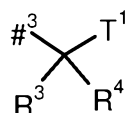
5 R^9 is hydrogen,

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.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

10 D is a group of the formula



where

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

R^3 is hydrogen,

15 R^4 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

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,

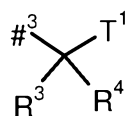
20 R^9 is hydrogen,

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.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

D is a group of the formula



5 where

#³ marks the linkage site with the nitrogen atom,

R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

T¹ is a group of the formula -C(=O)-NR⁸R⁹,

10 in which

R⁸ is hydrogen,

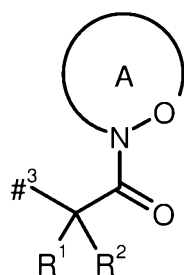
R⁹ is hydrogen,

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.

15 Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

D is a group of the formula



where

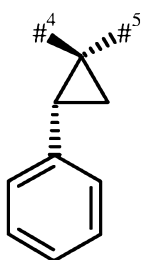
20 #³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

5 or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

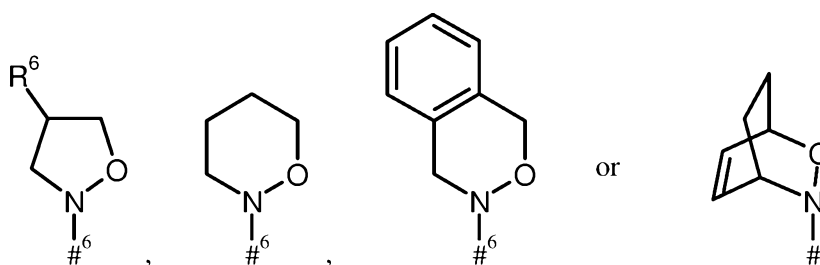


in which

10 #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



15 in which

#⁶ marks the linkage site with the carbonyl group,

R⁶ is hydrogen, hydroxy or benzyloxy,

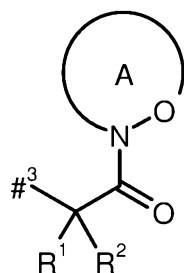
and

n, AK, Cys, G, L¹, B, L² and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

D is a group of the formula



5

where

#³ marks the linkage site with the nitrogen atom,

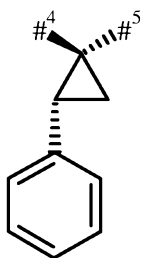
R¹ is hydrogen,

R² is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

10

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



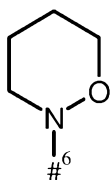
in which

15

#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,

and

5 n, AK, Cys, G, L¹, B, L² and R³⁵ have the definitions indicated above,

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

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

R³⁵ is hydroxyl,

10 and

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.

Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

15 R³⁵ is methyl,

and

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.

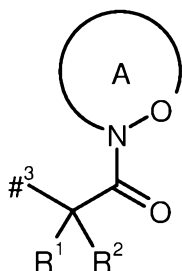
20 Particularly preferred in the context of the present invention are, furthermore, also compounds of the formula (XXXa), in which

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.

Preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

D is a group of the formula



5 where

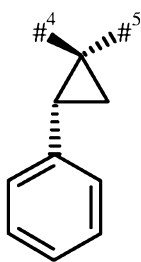
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

10 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

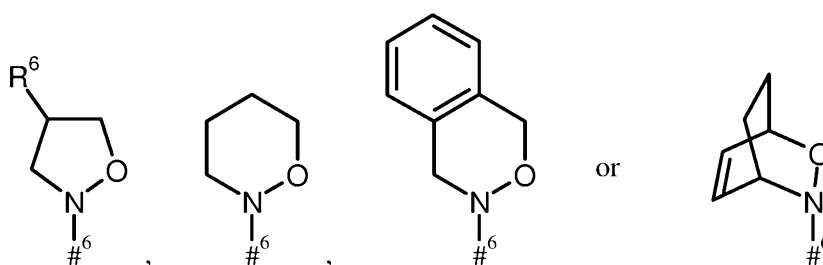


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

15 #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,

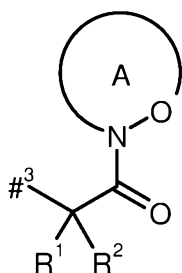
R⁶ is hydrogen, hydroxy or benzyloxy,

5 n, AK, Cys, G, L¹, L² and B have the definitions indicated above,

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

Particularly preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

D is a group of the formula



10

where

#³ marks the linkage site with the nitrogen atom,

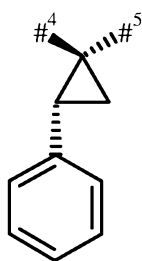
R¹ is hydrogen,

R² is benzyl or 1*H*-indol-3-ylmethyl,

15

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

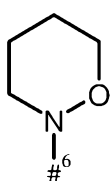


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

5 the ring A with the N-O moiety present therein is a heterocycle of the formula



in which

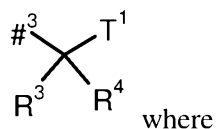
#⁶ marks the linkage site with the carbonyl group,

n, AK, Cys, G, L¹, L² and B have the definitions indicated above,

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

A further particularly preferred subject of the present invention are compounds of the formula (I), in which

D is a group of the formula



15 T¹ is -C(=O)-OH or -C(=O)-NH₂ and

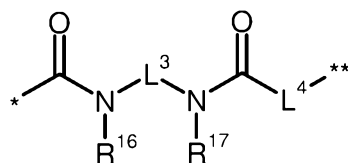
n, AK, G, L¹, B, L², #³, R³ and R⁴ have the definitions indicated above.

Preferred in the context of the present invention are also compounds of the formula (I), in which

n = 1-20, more preferably n = 1-10 and very preferably n = 2-8.

Preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

B is a bond or a group of the formula



5 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,

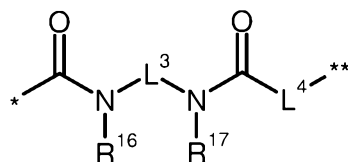
L^4 is a bond,

10 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.

Particularly preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

B is a bond or a group of the formula



15

where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

L^3 and L^4 is a bond,

20 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.

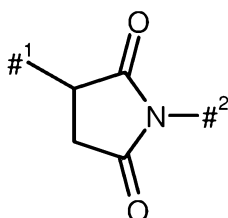
Preferred in the context of the present invention are also binder-drug conjugates of the general formula (I), in which

AK is AK₁,

where

- 5 AK₁ is a binder which is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula

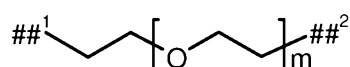


where

- 10 #¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl or is a group of the formula



where

- 15 m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

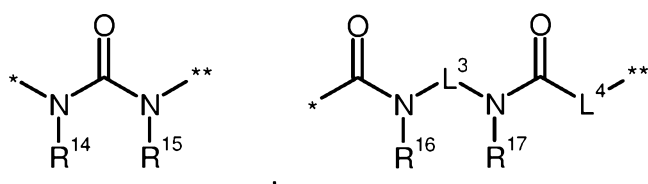
##² marks the linkage site with the group B,

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 methyl substituents,

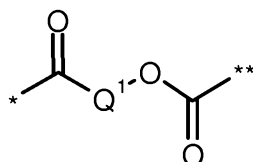
and

- 20 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



or



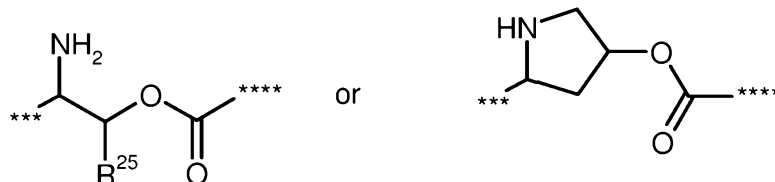
where

* marks the linkage site with L^1 ,

5 ** marks the linkage site with L^2 ,

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

L^4 is a bond or a group of the formula



in which

10 **** 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,

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

15 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,

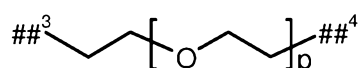
R^{16} is hydrogen or (C₁-C₄)-alkyl,

R^{17} is hydrogen or (C₁-C₄)-alkyl,

5 or

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

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



10 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 (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 methyl substituents,

15 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

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

20 Preferred in the context of the present invention are also binder-drug conjugates of the general formula (I), in which

AK is AK₂,

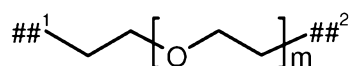
where

AK₂ is a binder which is bonded via the NH side group of a lysine residue of the binder to the group G,

25

G is carbonyl,

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl or is a group of the formula



where

5 m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

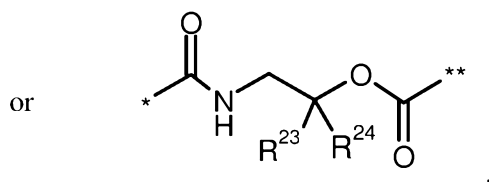
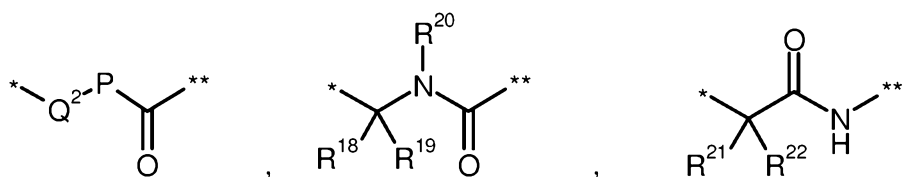
##² marks the linkage site with the group B,

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 methyl substituents,

and

10 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



15 where

* marks the linkage site with L¹,

** marks the linkage site with L²,

P is O or NH,

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,

5 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,

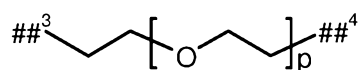
10 or

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,

15 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,

20 $##^4$ 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

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

- 5 Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

n is a number from 2 to 8,

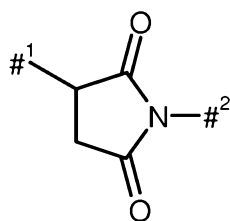
AK is AK₁ or AK₂,

where

- 10 AK₁ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

- AK₂ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the
15 binder to the group G,

G when AK = AK₁, is a group of the formula



in which

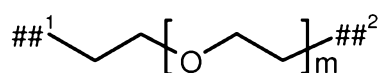
#¹ marks the linkage site with the cysteine residue of the binder,

- 20 #² marks the linkage site with the group L¹,

or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl or is a group of the formula



where

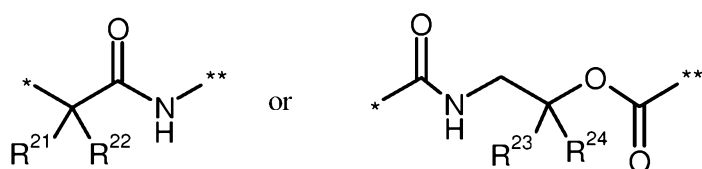
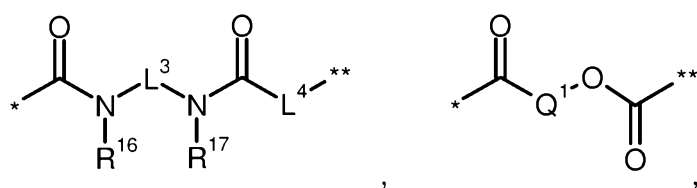
m is a number 2 or 3,

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

5 $\# \#^2$ marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



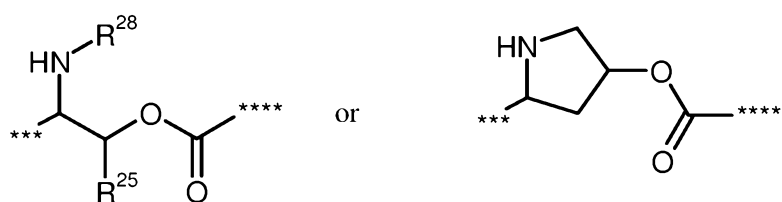
where

10 * marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



15 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,

5 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,

10 R^{21} is hydrogen or methyl,

R^{22} is hydrogen or methyl,

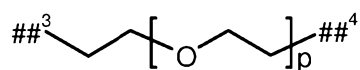
or

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

R^{23} is methyl,

15 R^{24} is hydrogen,

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



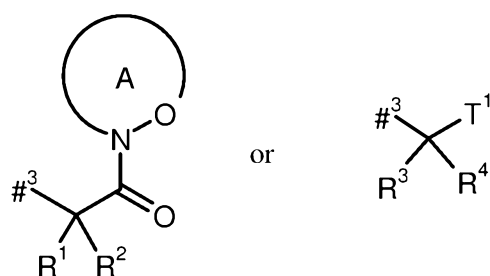
where

p is a number from 2 to 6,

20 $##^3$ marks the linkage site with the group B,

$##^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



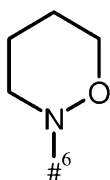
where

#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

the ring A with the N-O moiety present therein is



in which

#⁶ marks the linkage site with the carbonyl group,

10 R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

T¹ is a group of the formula -C(=O)-NR⁸R⁹,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, or ethyl,

15 R³⁵ is methyl,

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

Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

n is a number from 2 to 8, preferably 2 to 5,

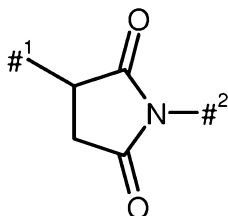
AK is AK₁,

where

AK₁ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

5

G is a group of the formula



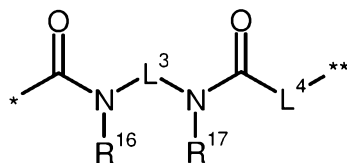
where

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

10 #² marks the linkage site with the group L¹,

L¹ is pentane-1,5-diyl,

B is a group of the formula



where

15 * marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond,

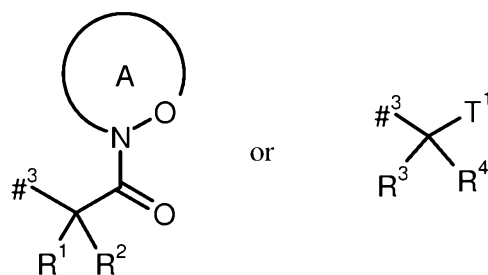
L⁴ is a bond,

R¹⁶ is hydrogen,

20 R¹⁷ is hydrogen,

L^2 is propane-1,3-diyl,

D is a group of the formula



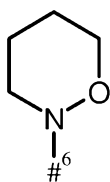
where

5 $\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

the ring A with the N-O moiety present therein is



10 in which

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

R^3 is hydrogen,

R^4 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

T^1 is a group of the formula $-C(=O)-NR^8R^9$,

15 R^8 is hydrogen,

R^9 is hydrogen,

R^{35} is methyl,

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

Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

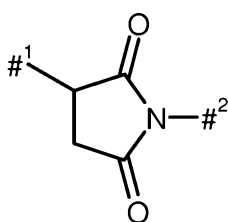
n is a number from 2 to 8, preferably 2 to 5,

AK is AK₁,

5 where

AK₁ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a 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



10

where

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

#² marks the linkage site with the group L¹,

L¹ is a bond,

15 B is a bond,

L² is hexane-1,6-diyl,

and D has the definition indicated above,

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

Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

20

n is a number from 2 to 8, preferably 2 to 5,

AK is AK₂,

where

AK₂ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

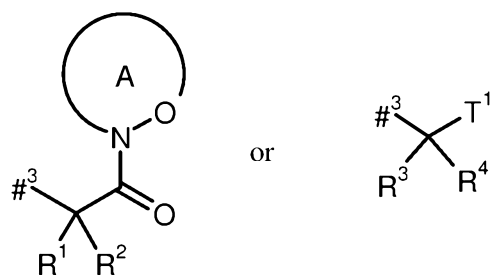
5 G is carbonyl,

L¹ is a bond,

B is a bond,

L² is pentane-1,5-diyl,

D is a group of the formula



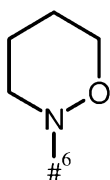
where

#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

15 the ring A with the N-O moiety present therein is



in which

#⁶ marks the linkage site with the carbonyl group,

R³ is hydrogen,

R^4 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

T^1 is a group of the formula $-C(=O)-NR^8R^9$,

R^8 is hydrogen,

R^9 is hydrogen,

5 R^{35} is methyl,

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

Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

n is a number from 2 to 8, preferably 2 to 5,

10 AK is AK_2 ,

where

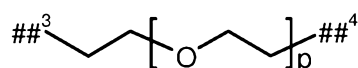
AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

15 G is carbonyl,

L^1 is a bond,

B is a bond,

L^2 is a group of the formula



20 where

p is the number 3,

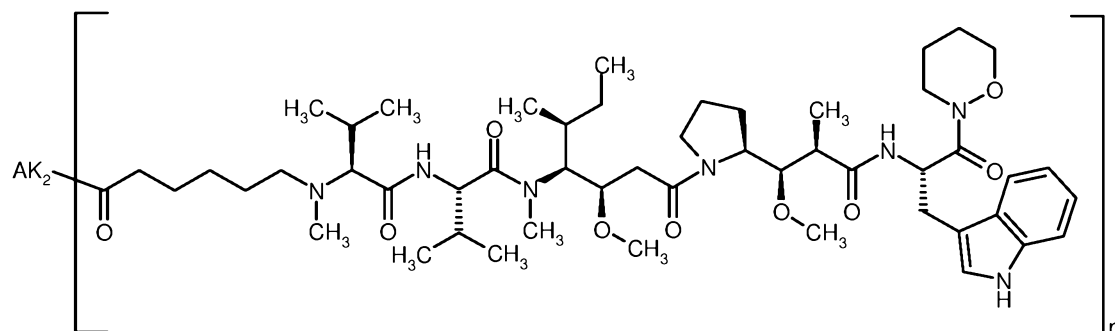
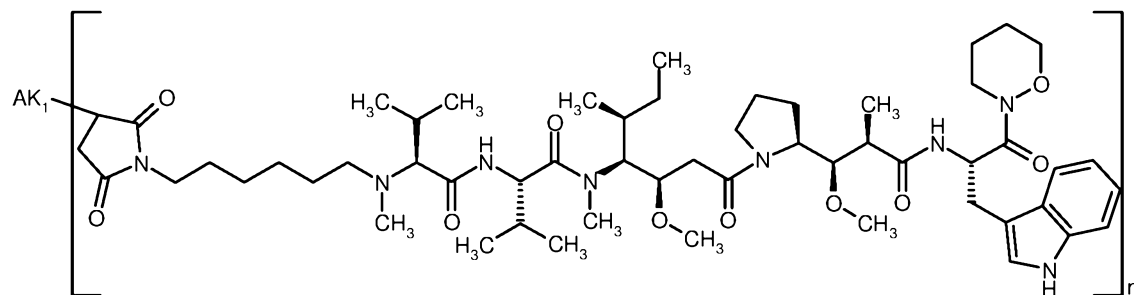
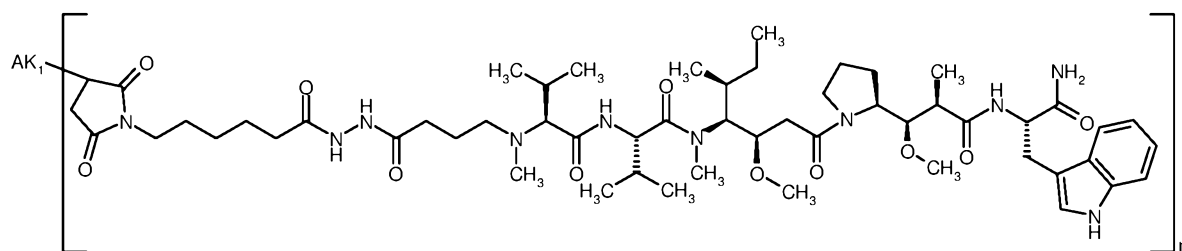
##^3 marks the linkage site with the group B,

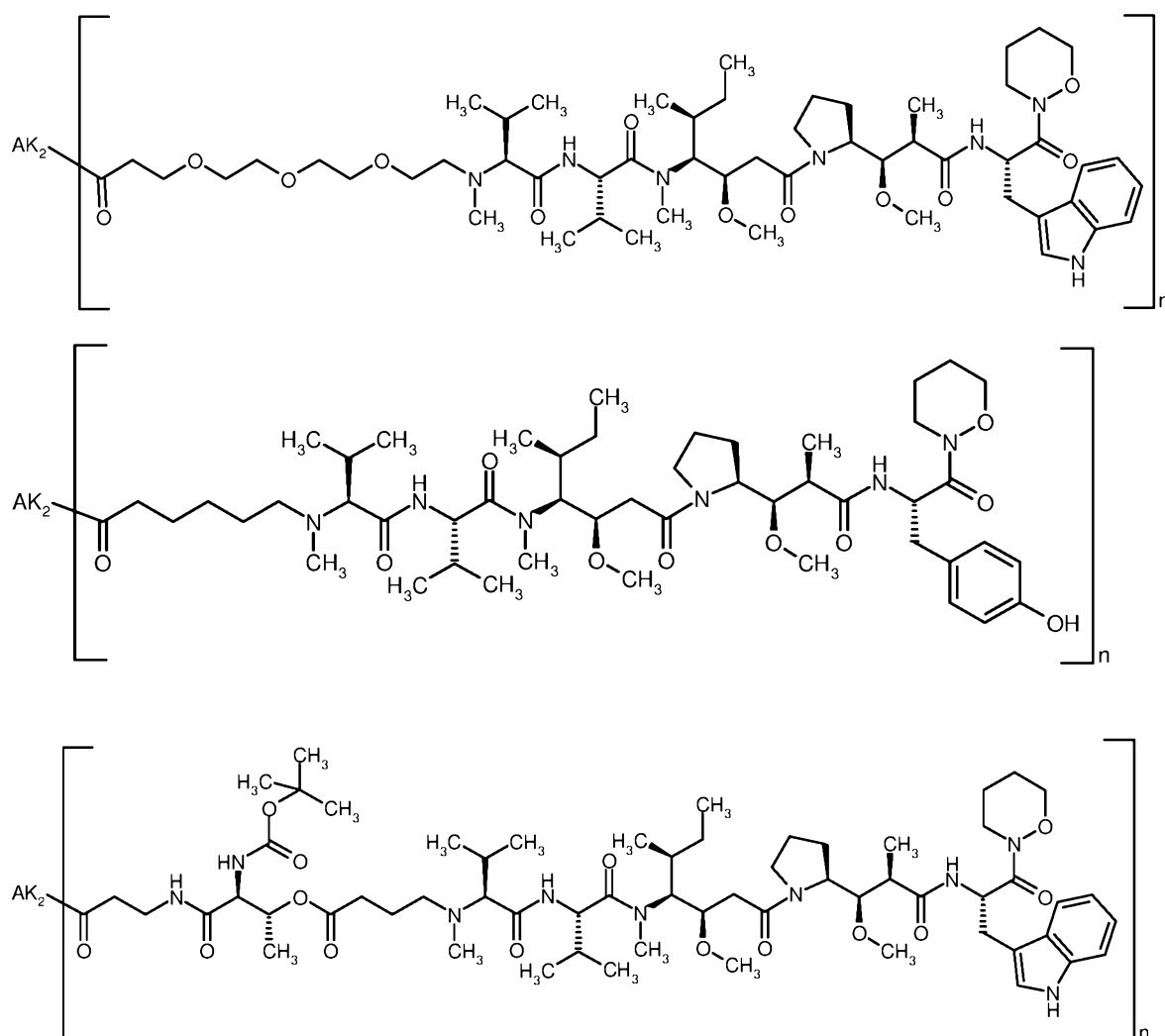
##^4 marks the linkage site with the nitrogen atom,

and D has the meaning indicated above,

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

Particularly preferred in the context of the present invention are also drug-binder conjugates selected from the following compounds:





where in each case

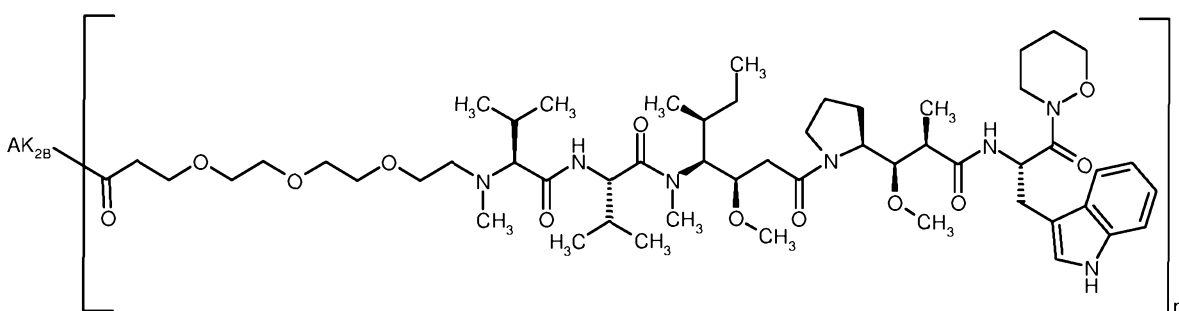
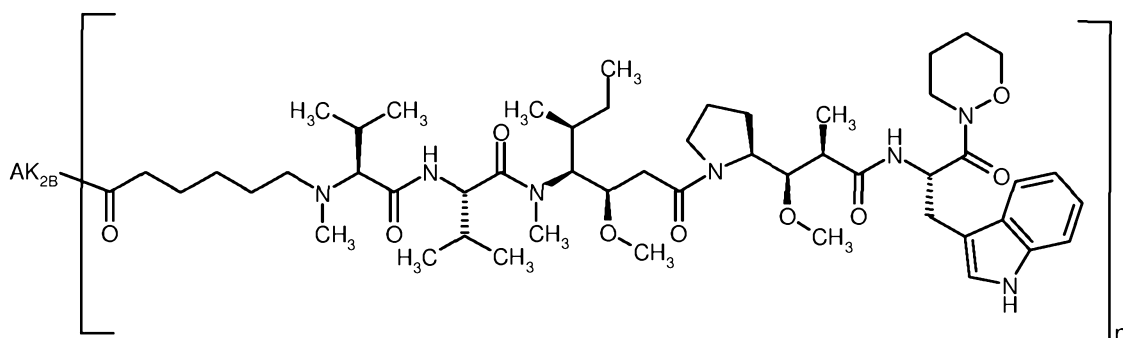
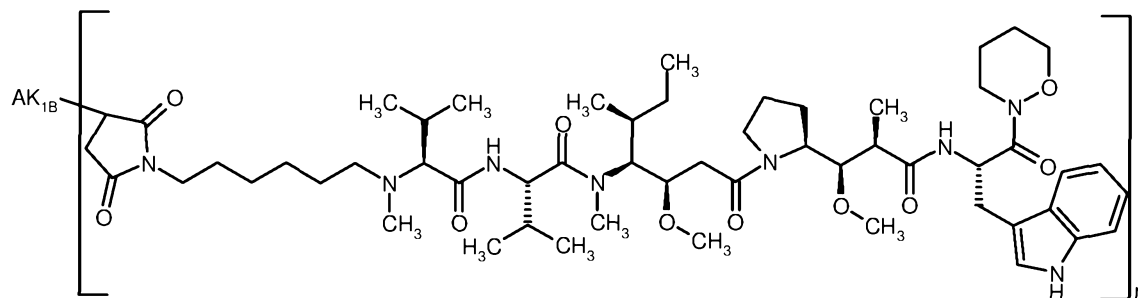
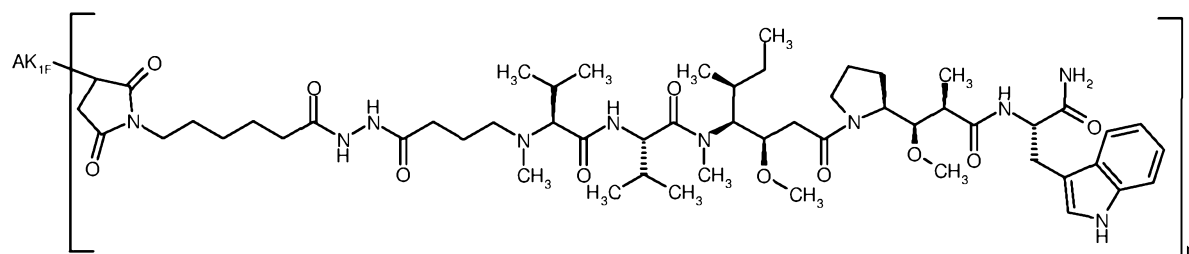
5 n is a number from 2 to 8, preferably 2 to 5,

AK₁ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

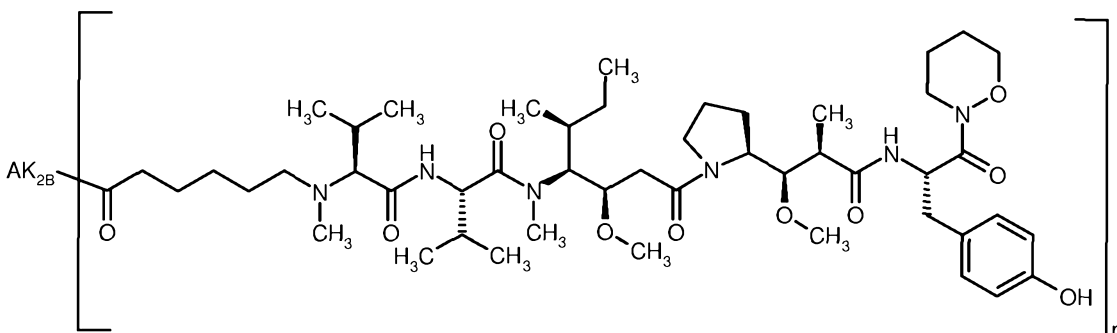
and

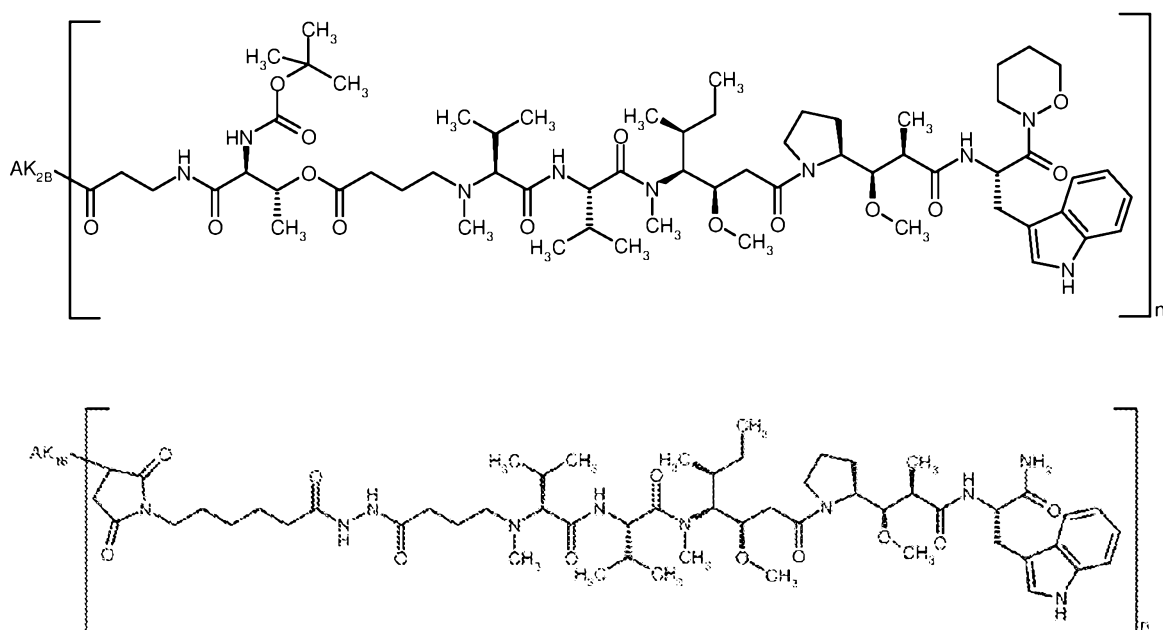
10 AK₂ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G.

More particularly preferred in the context of the present invention are binder-drug conjugates selected from the following compounds:



5





where in each case

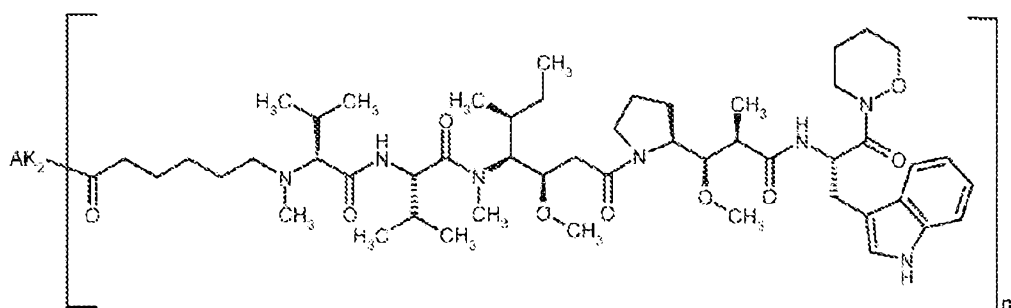
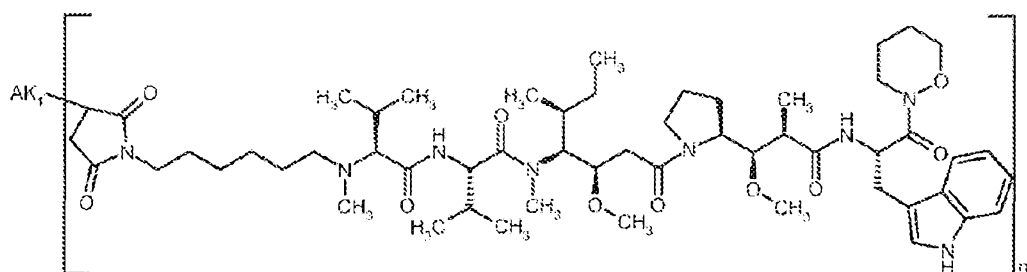
n is a number from 2 to 8, preferably 2 to 5,

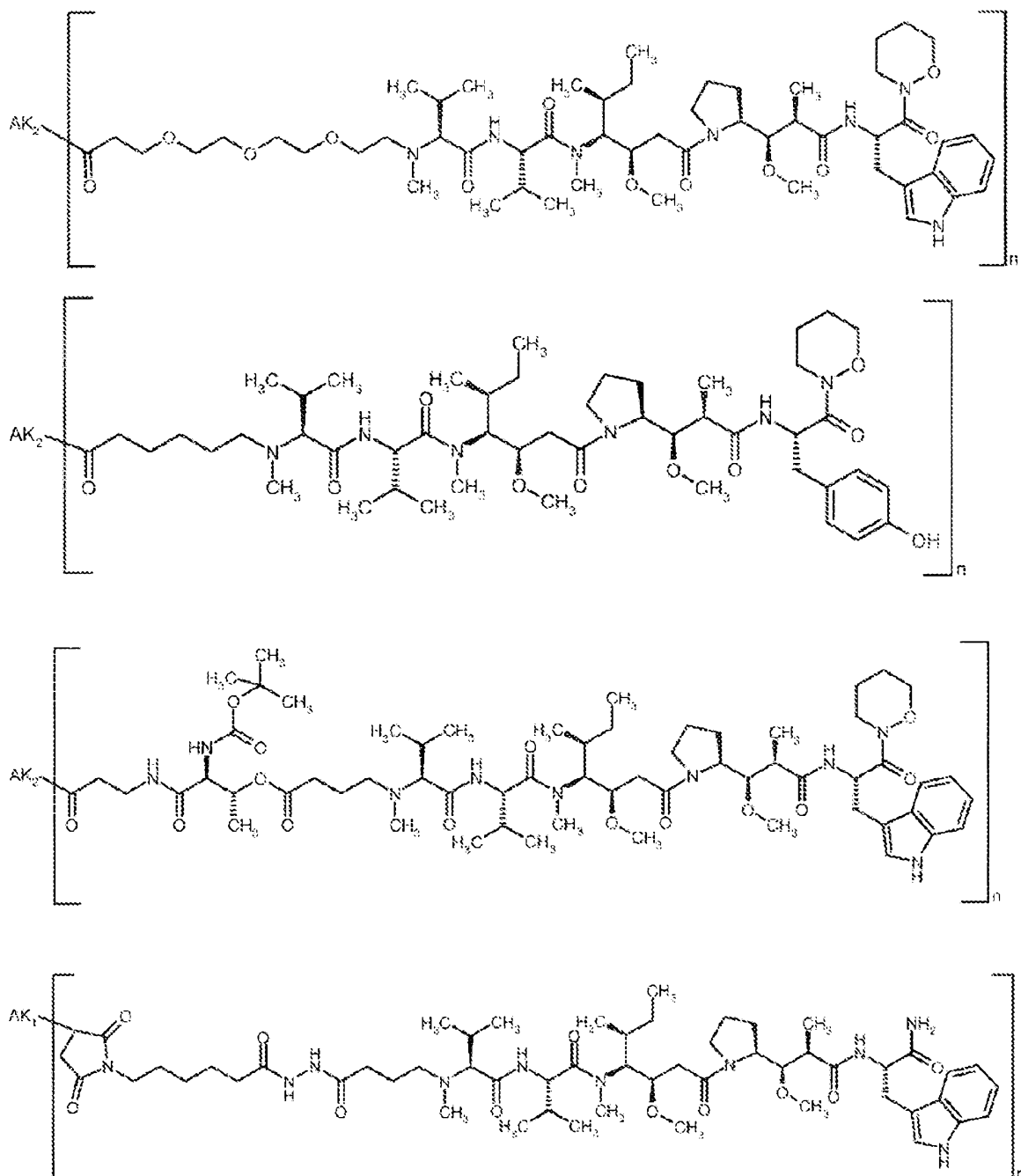
5 and

AK is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a.

In these formulae, AK_{1F}, AK_{1B} and AK_{2B} may be replaced by other human or humanized anti-C4.4a antibodies.

10 Particularly preferred are binder-drug conjugates selected from the following compounds:





where in each case

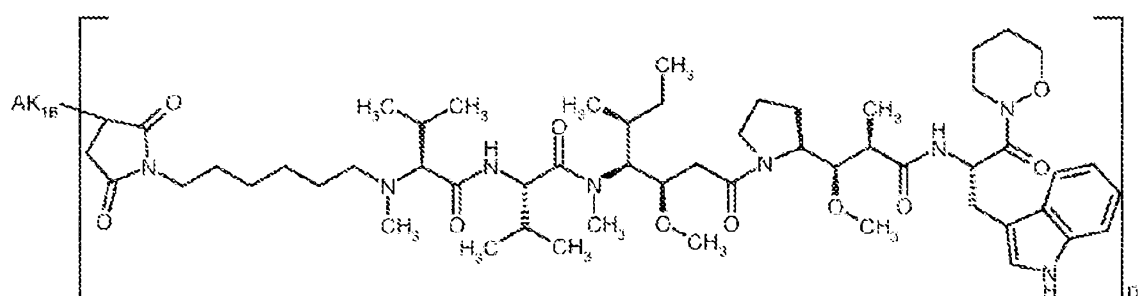
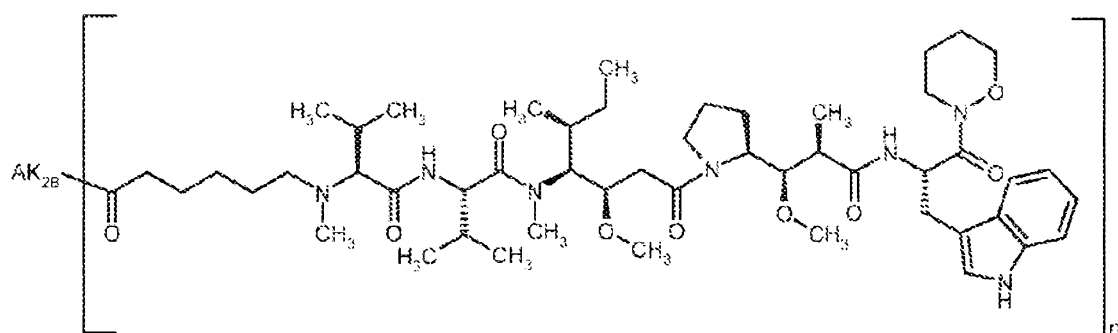
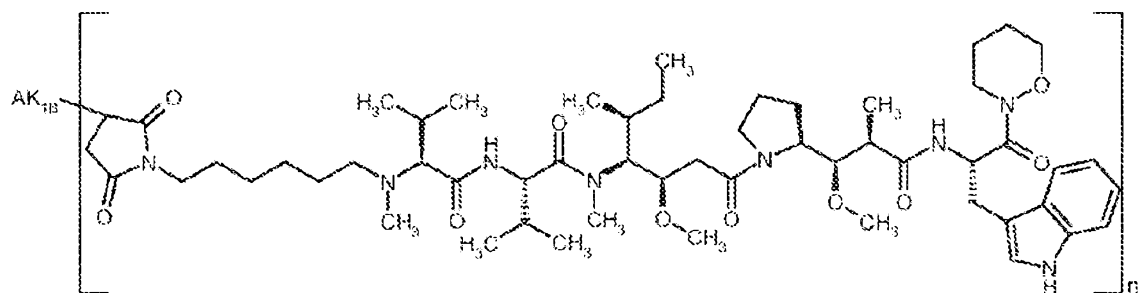
n is a number from 2 to 8, preferably 2 to 5,

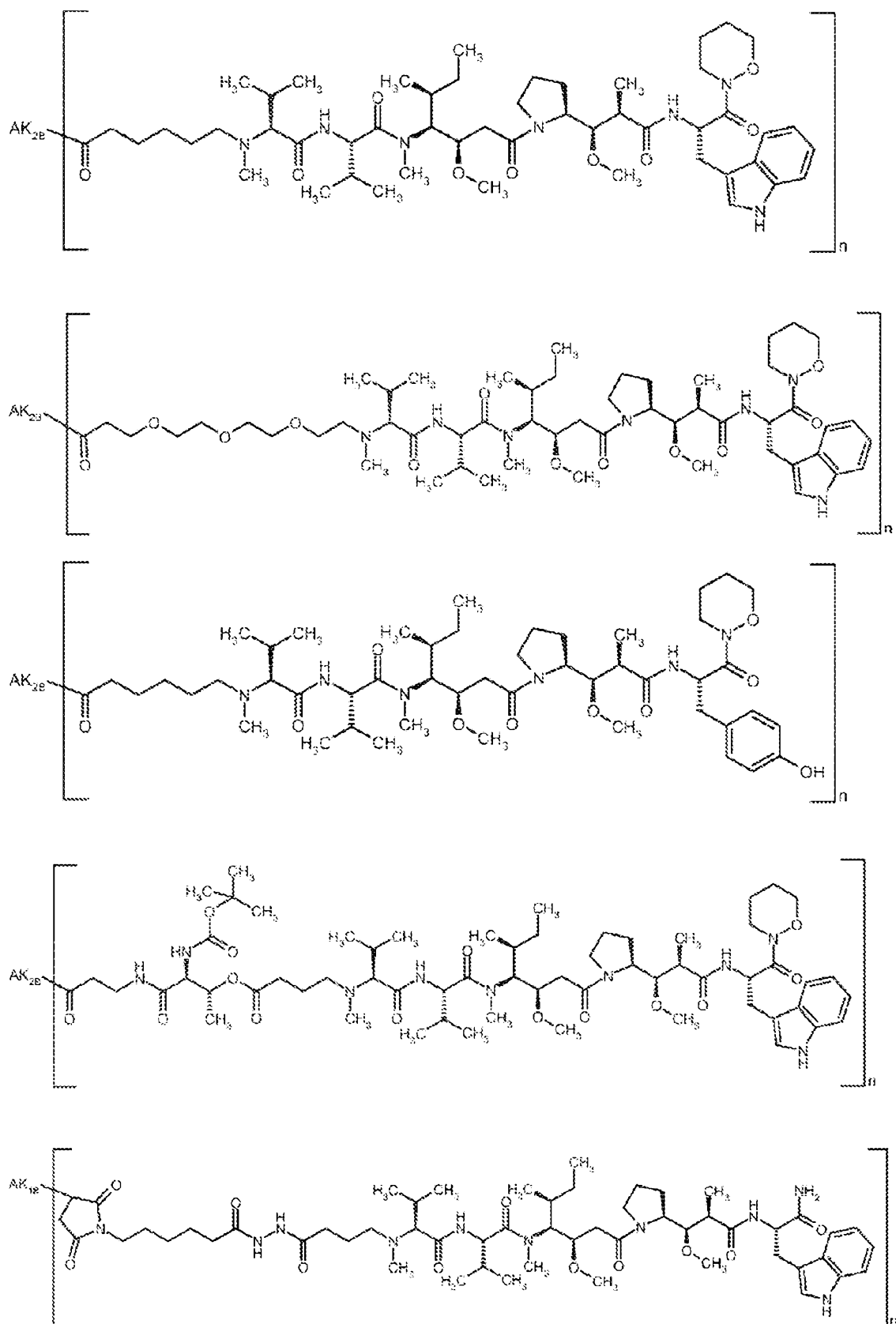
and

- 5 AK₁ is a human or humanized antibody or antigen-binding antibody fragment which binds to C4.4a and is bonded via a cysteine group to the toxophore linker unit, and

AK₂ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via a lysine group to the toxophore linker unit.

Particularly preferred are binder-drug conjugates selected from the following compounds:





where in each case

n is a number from 2 to 8, preferably 2 to 5,

and

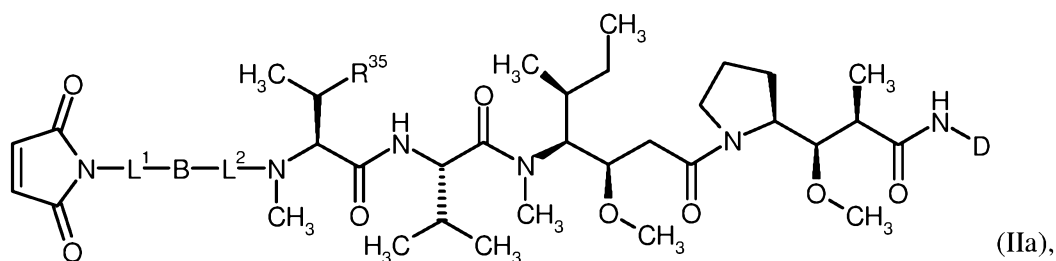
AK_{1B} and AK_{2B} are B01-3.

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.

Especially preferred are combinations of two or more of the abovementioned preference ranges.

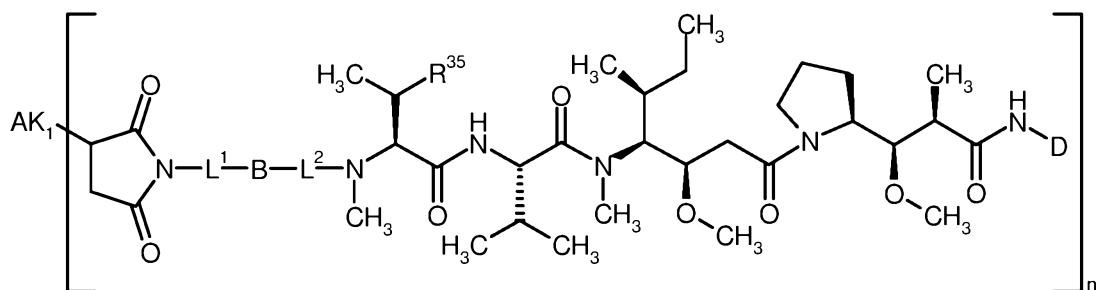
Further provided by the invention is a process for preparing the compounds of the invention of the formula (Ia), characterized in that a solution of the binder (preferably in buffer such as, for example, PBS buffer)

- 10 [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)



in which D, L¹, B, L² and R³⁵ each have the definitions indicated above,

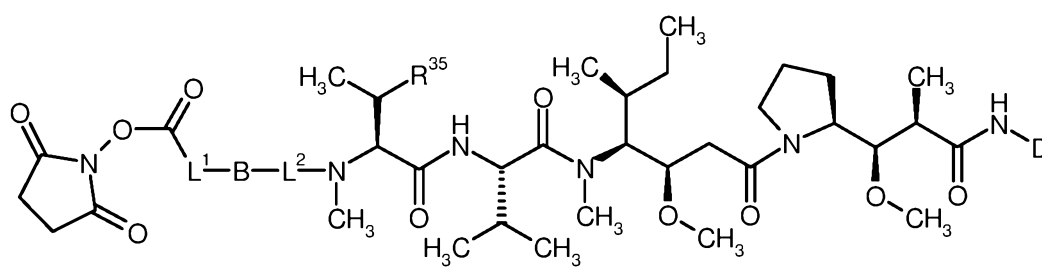
- 15 to give a compound of the formula (I-A)



(Ia-A),

in which n, AK₂, D, L¹, B, L² and R³⁵ each have the definitions indicated above,

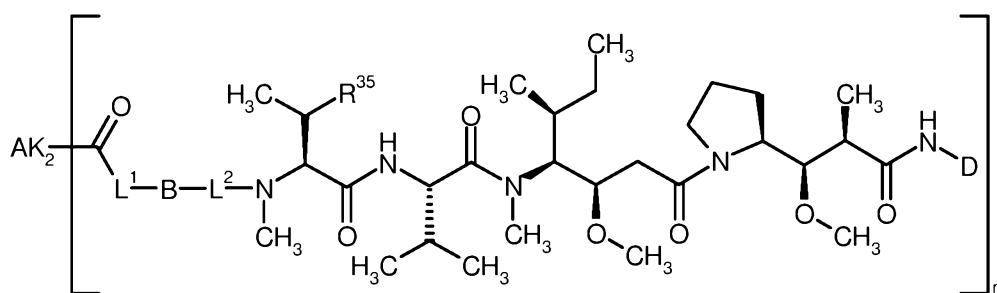
[B] is reacted with a compound of formula (IIIa)



(IIIa),

in which D , L^1 , B , L^2 and R^{35} each have the definitions indicated above,

5 to give a compound of the formula (Ia-B)

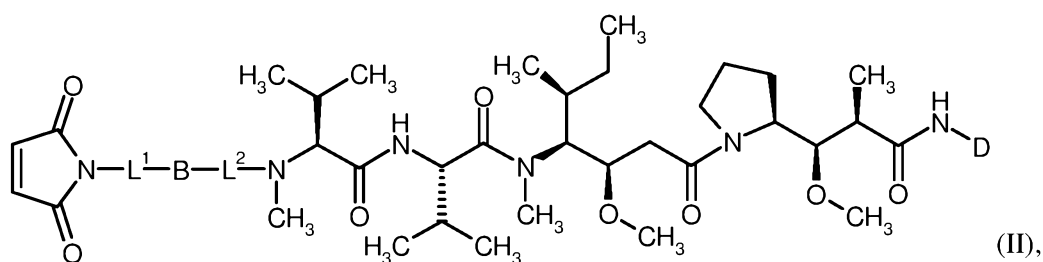


(Ia-B),

in which n , AK_2 , D , L^1 , B , L^2 and R^{35} each have the definitions indicated above.

Further provided by the invention is a process for preparing the compounds of the invention of the
10 formula (I), characterized in that a solution of the binder in PBS buffer

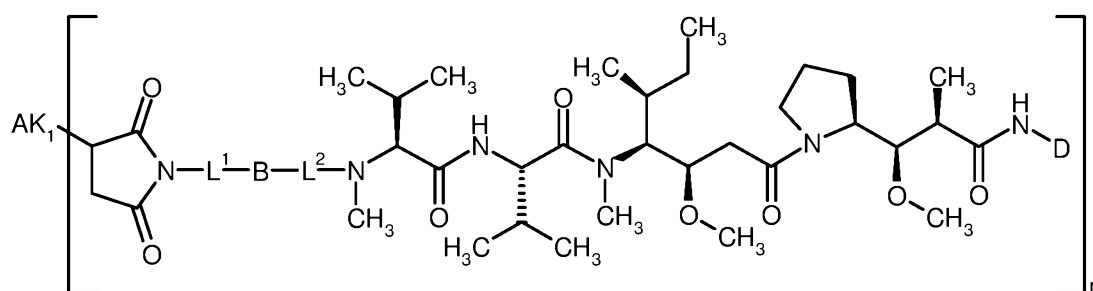
[A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (II)



(II),

15 in which D , L^1 , B and L^2 each have the definitions indicated above,

to give a compound of the formula (I-A)

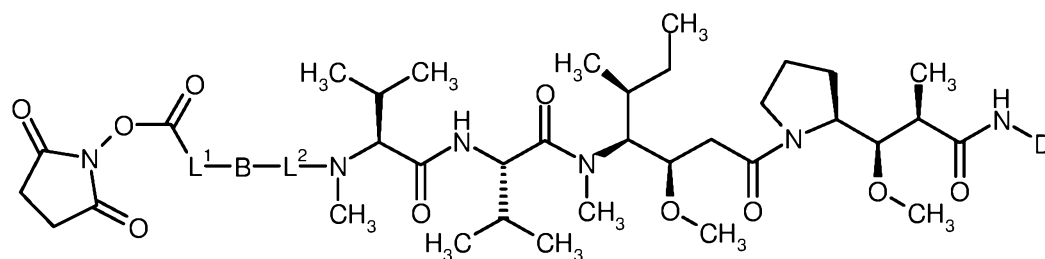


(I-A),

5 in which n , AK_1 , D , L^1 , B and L^2 each have the definitions indicated above,

or

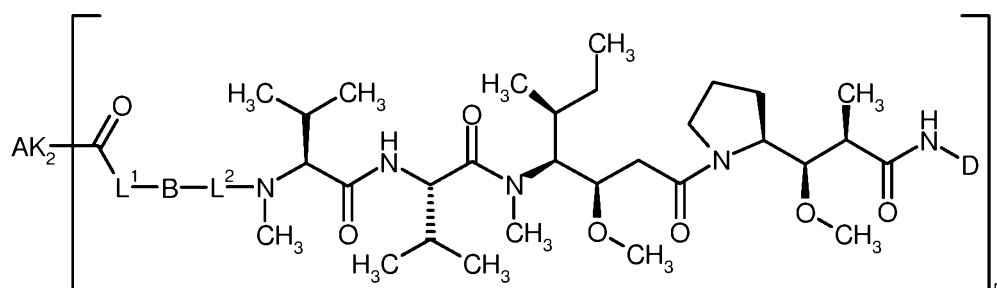
[B] is reacted with a compound of the formula (III)



(III),

10 in which D , L^1 , B and L^2 each have the definitions indicated above,

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 above.

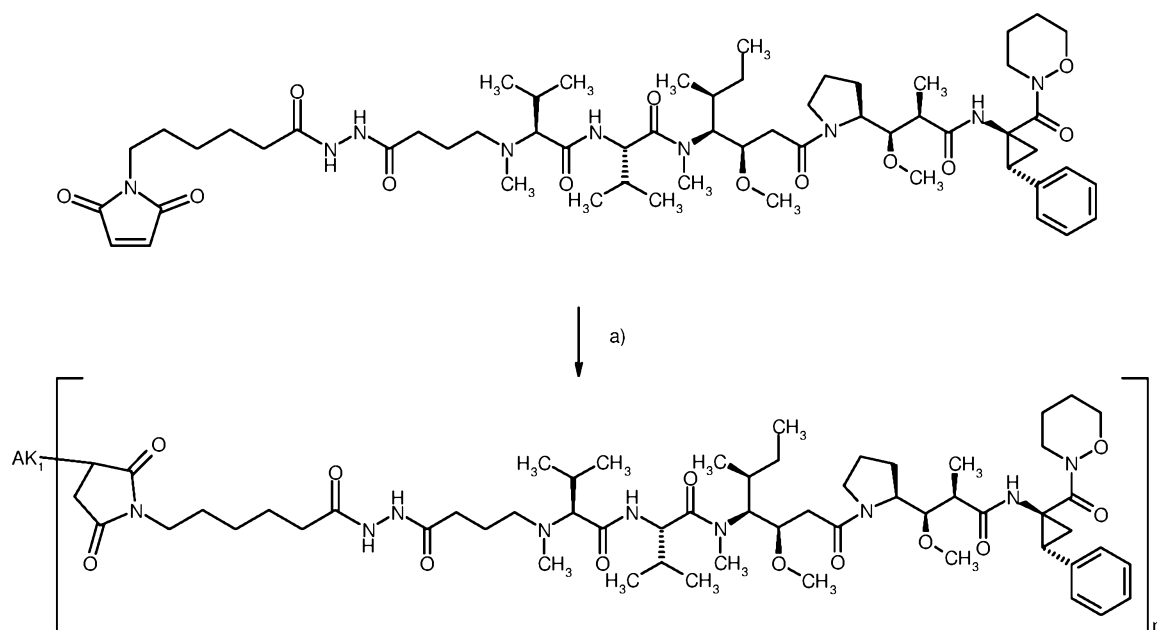
Cysteine coupling:

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
 5 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,
 10 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:

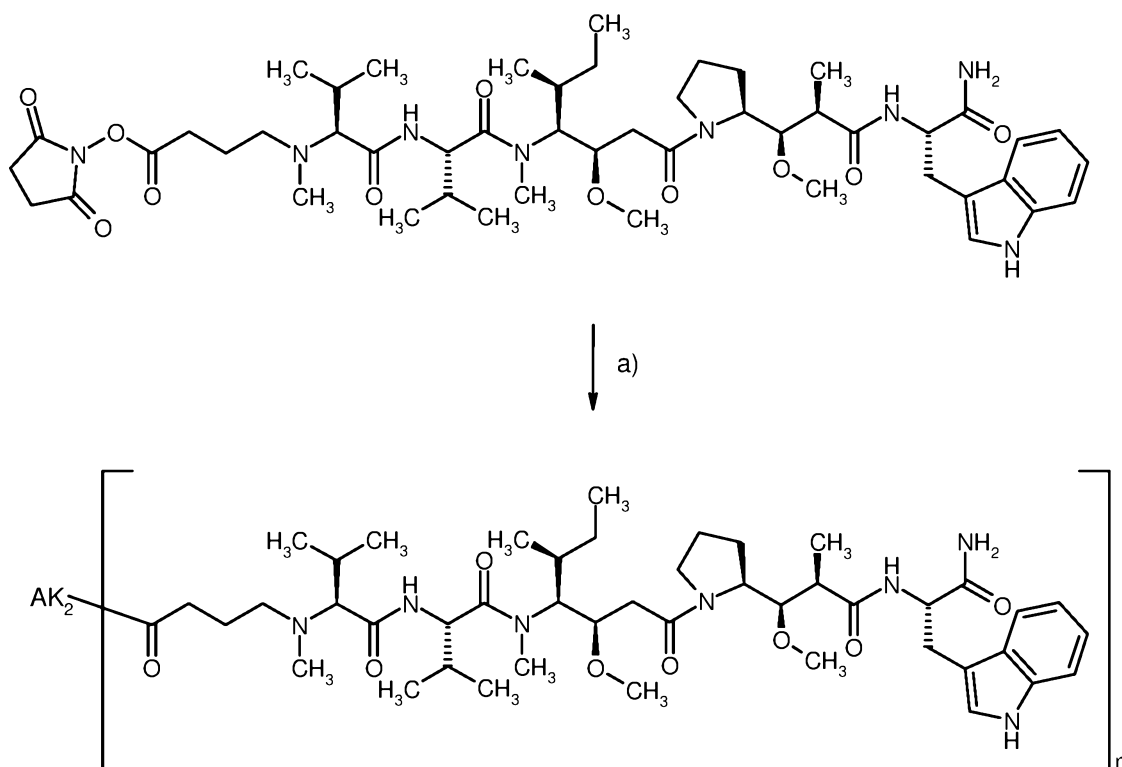
First of all the compounds of the formula (III) or (IIa) or comparable activated carboxyl
 15 components are prepared by conventional methods of peptide chemistry. They are then taken up in inert solvents such as DMSO or DMF, for example, and added to the antibody, which is preferably present in phosphate buffer at a neutral pH. The solution is stirred for 1-16 h at a temperature between 15 and 40°C, preferably RT.

The preparation processes described above are elucidated by way of example using the schemes
 20 below (Scheme 1 and 2):

Scheme 1

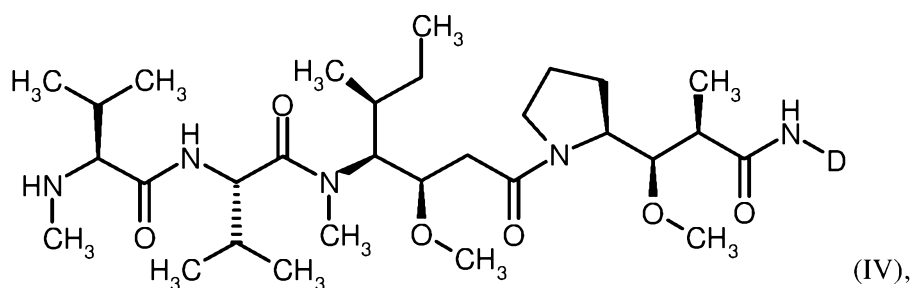
[a): 1. AK (antibody), TCEP, PBS buffer, RT; 2. Addition of the maleimide derivative in DMSO, RT].

Scheme 2



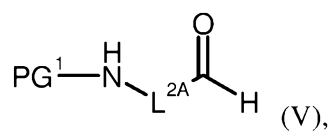
- 5 [a): AK (antibody), PBS buffer, RT admix with activated carboxyl derivative of the linker-drug components].

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)



- 10 in which D has the definition indicated above,

to reductive amination in an inert solvent with a compound of the formula (V)

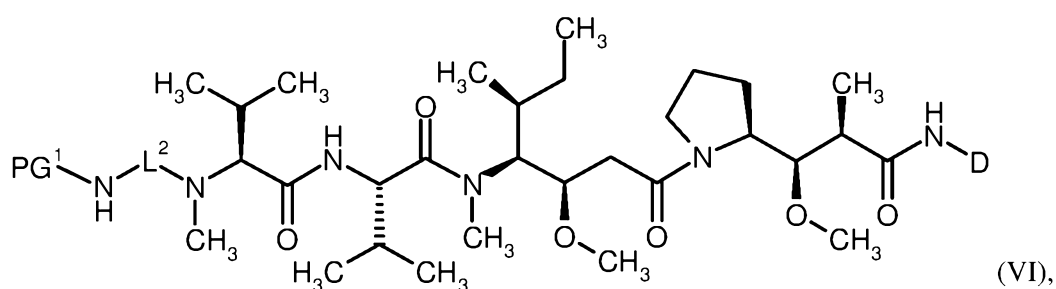


in which

$\text{L}^{2\text{A}}$ has the above-defined definition of L^2 , but is shortened by one carbon atom in the alkyl chain length,

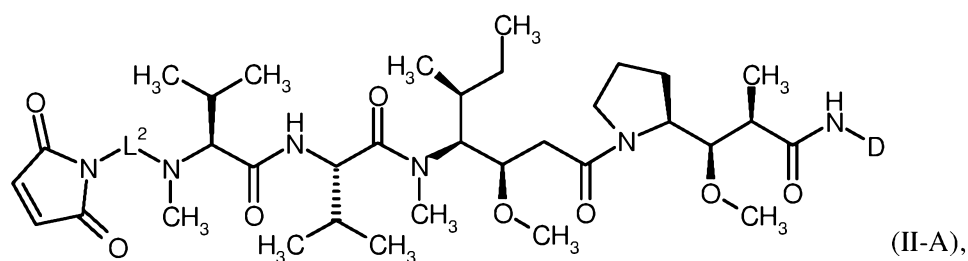
- 5 PG^1 is an amino-protective group such as, for example, (9H-fluoren-9-ylmethoxy)carbonyl, *tert*-butoxycarbonyl or benzyloxycarbonyl,

to give a compound of the formula (VI)



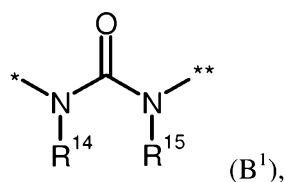
in which D, L^2 and PG^1 have the definition indicated above,

- 10 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)



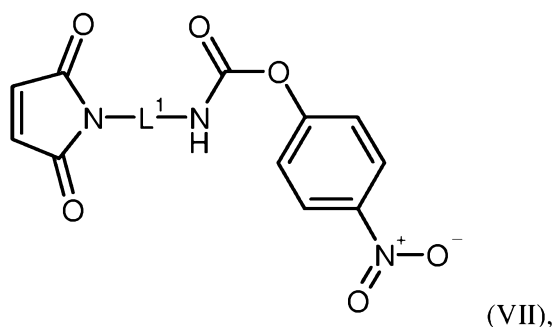
in which D and L^2 each have the definitions indicated above.

- 15 The compounds of the formula (II) in which B is a group of the formula (B^1)



in which *, **, R^{14} and R^{15} each have the conditions indicated above,

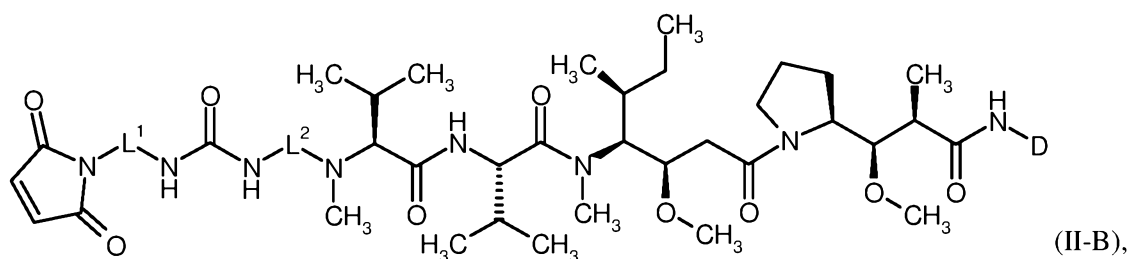
can be prepared by eliminating the protective group PG^1 from a compound of the formula (VI) by methods known to the skilled person, and reacting the deprotected compound in an inert solvent in the presence of a suitable base with a compound of the formula (VII)



5

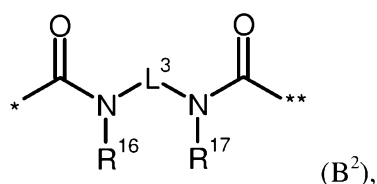
in which L^1 has the definition indicated above,

to give a compound of the formula (II-B)



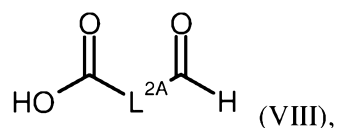
in which D, L^1 and L^2 each have the definitions indicated above.

10 The compounds of the formula (II) in which B is a group of the formula (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)

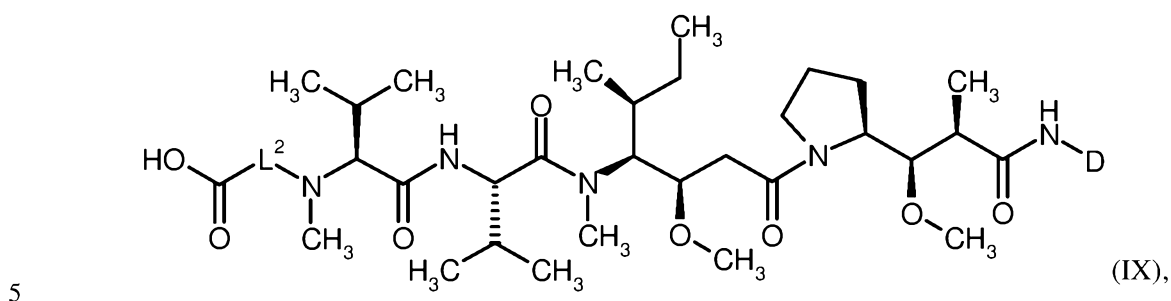


15

in which

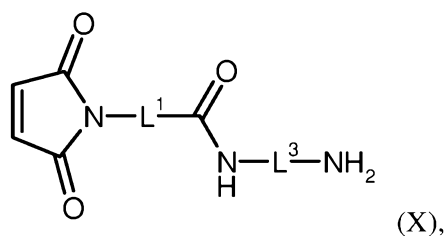
L^{2A} has the above-defined definition of L^2 , but is shortened by one carbon atom in the alkyl chain length,

to give a compound of the formula (IX)



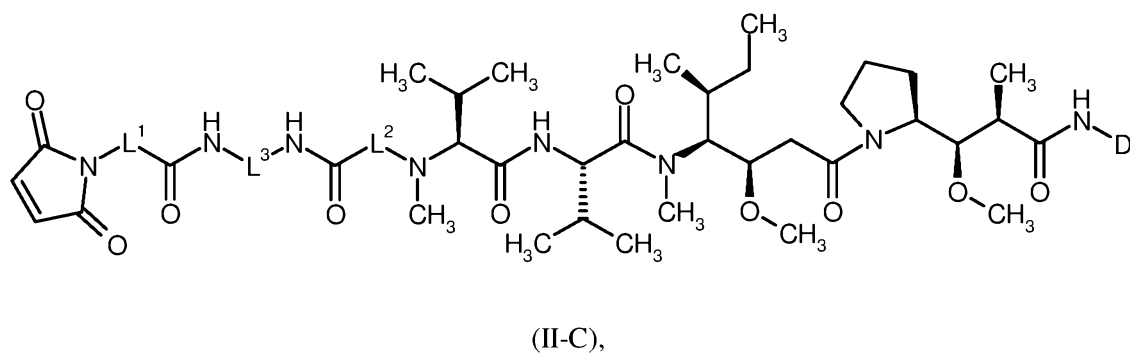
in which D and L^2 have the definitions indicated above,

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)



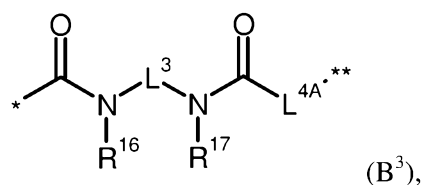
10 in which L^1 and L^3 each have the definitions indicated above,

to give a compound of the formula (II-C)



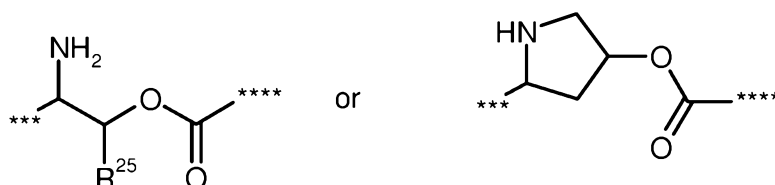
in which D, L^1 , L^2 and L^3 each have the definitions indicated above.

15 Compound of the formula (II), in which B is a group of the formula (B^3)



in which *, **, L³, R¹⁶ and R¹⁷ each have the conditions indicated above and

L^{4A} is a group of the formula



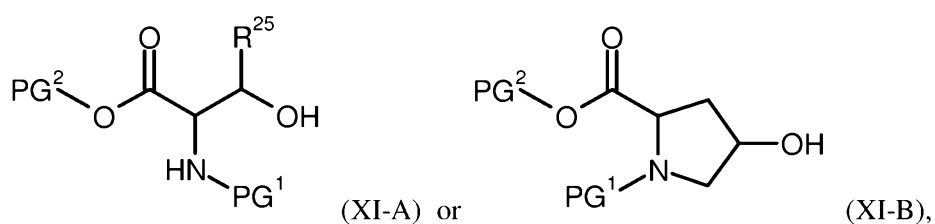
5 in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is hydrogen or methyl,

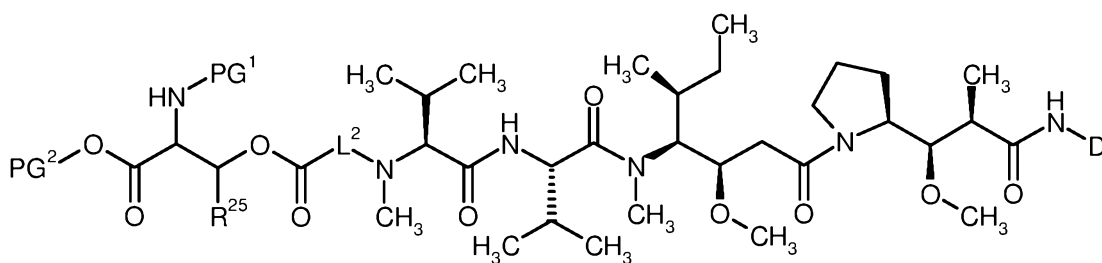
10 can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable base and a suitable coupling reagent with a compound of the formula (XI-A) or (XI-B)



in which R²⁵ and PG¹ each have the definitions indicated above and

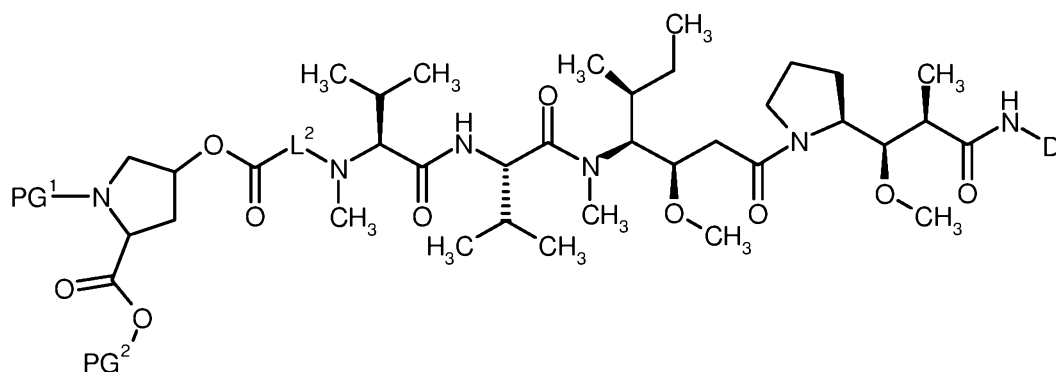
PG² is a suitable carboxyl-protective group, more particularly benzyl,

15 to give a compound (XII-A) or (XII-B)



(XII-A)

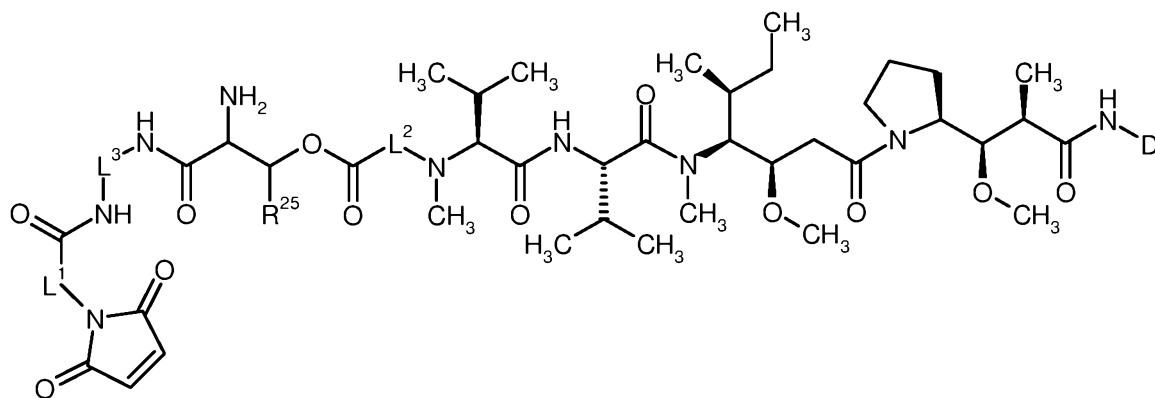
or



(XII-B),

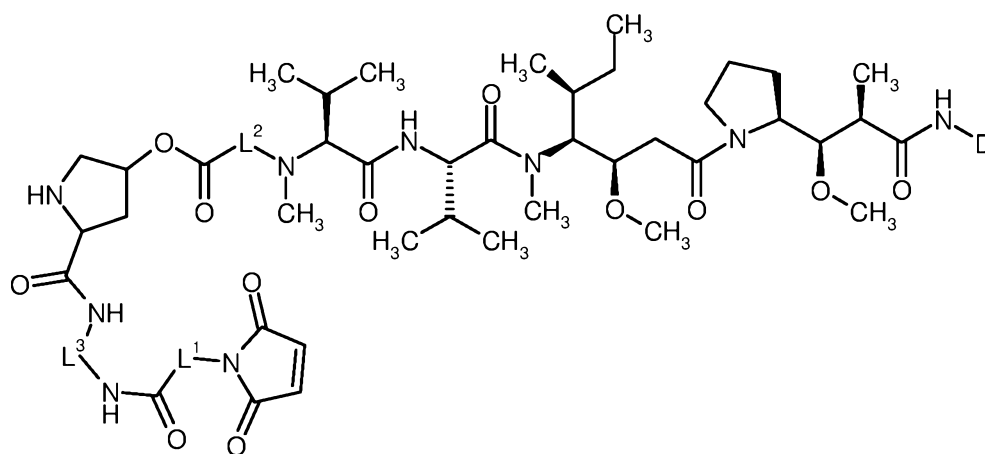
in which D, PG¹, PG² and L² have the definitions indicated above,

eliminating the protective group PG² 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),

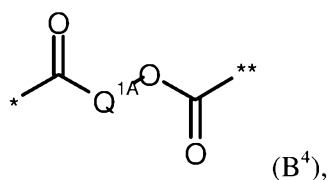
or



(II-D-B),

in which D, L¹, L² and L³ have the definitions indicated above.

Compound of the formula (II), in which B is a group of the formula (B⁴)

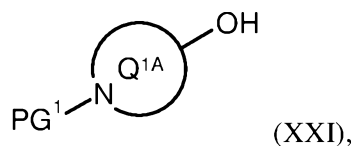


5

in which *, ** each have the conditions indicated above and

Q^{1A} is an N-linked 4- to 7-membered heterocycle,

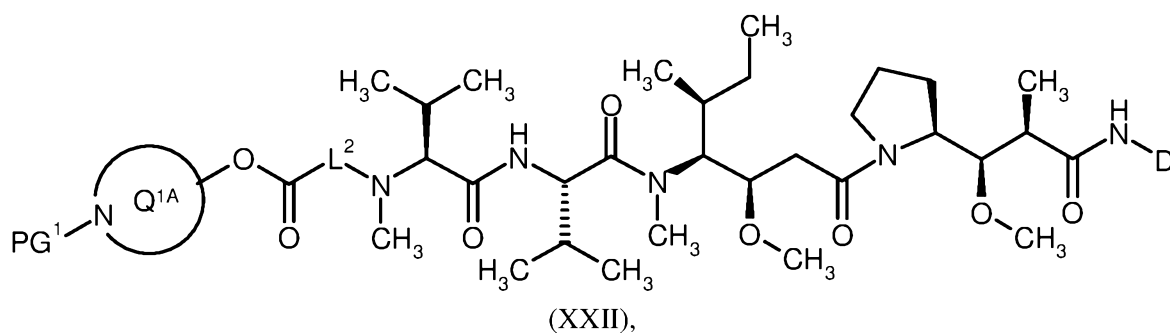
can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable base and a suitable coupling reagent with a compound of the formula (XXI)



10

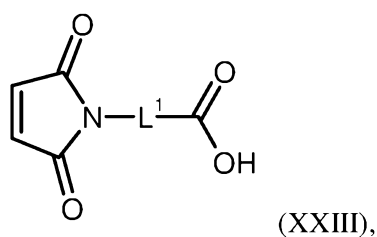
in which PG¹ and Q^{1A} each have the definitions indicated above,

to give a compound of the formula (XXII)



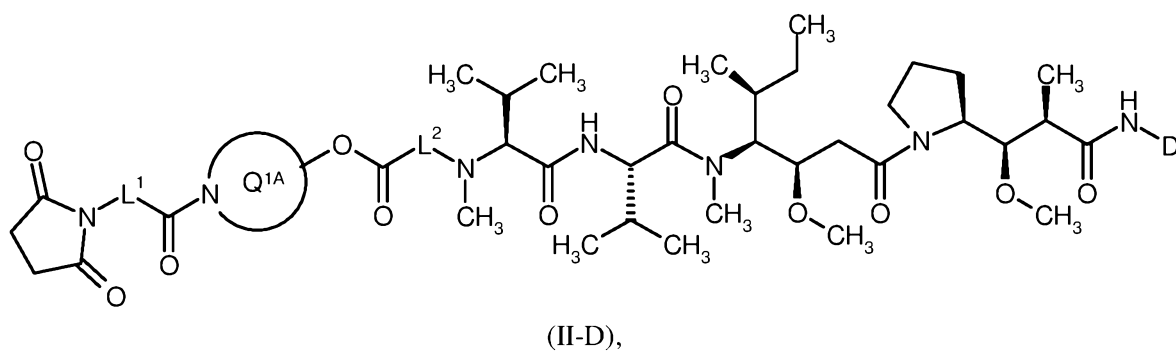
in which PG^1 , Q^{1A} , D and L^2 have the definitions indicated above,

eliminating the protective group PG¹ from this compound, by methods known to the skilled person,
5 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)



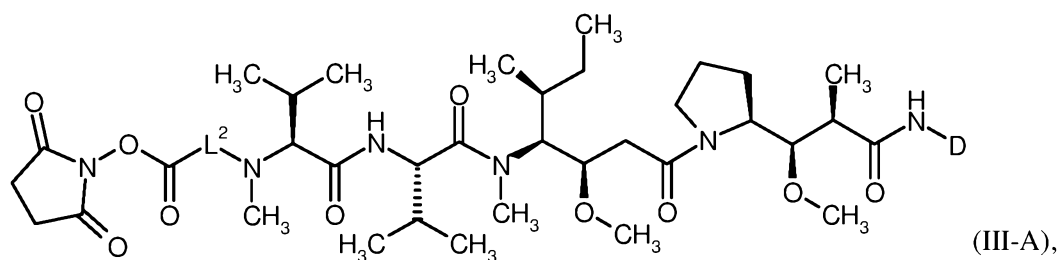
in which L^1 has the definition indicated above,

to give a compound of the formula (II-D)



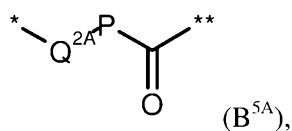
in which Q^{1A} , D , L^1 and L^2 have the definitions indicated above.

The compounds of the formula (III), in which L¹ 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)



in which D and L² each have the definitions indicated above.

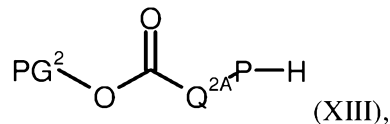
The compounds of the formula (III), in which L¹ is a bond and B is a group of the formula (B^{5A})



- 5 in which *, ** and P each have the definitions indicated above and

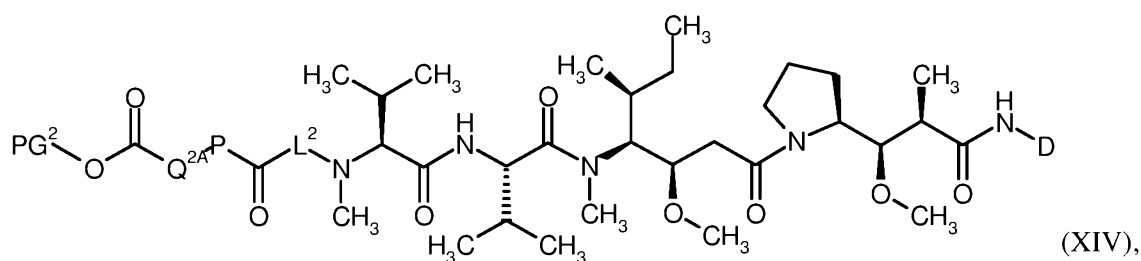
Q^{2A} is a 3- to 7-membered carbocycle,

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)



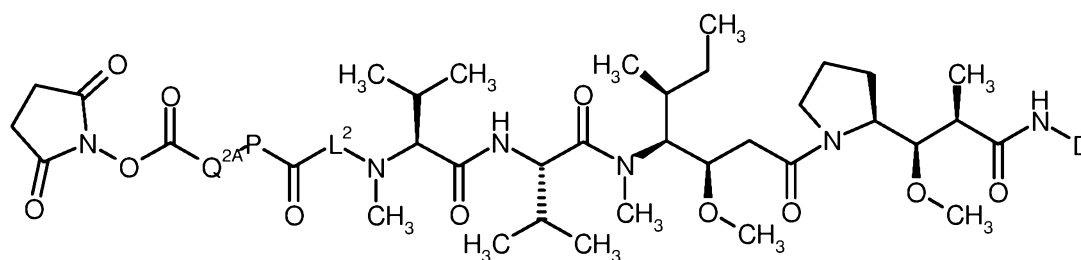
- 10 in which P, Q^{2A} and PG² each have the definitions indicated above,

to give a compound of the formula (XIV)



in which D, P, Q^{2A}, L² and PG² each have the definitions indicated above,

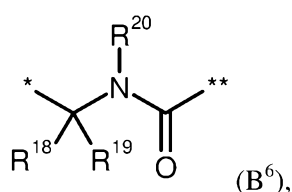
- eliminating the protective group PG² from this compound by methods known to the skilled person,
 15 and subsequently reacting the deprotected compound in an inert solvent in the presence of a suitable base with N-hydroxysuccinimide to give a compound of the formula (III-B)



(III-B),

in which D, P, Q^{2A} and L² each have the definitions indicated above.

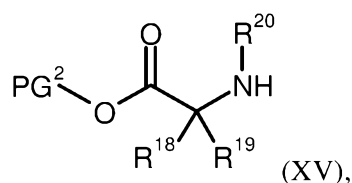
The compounds of the formula (III), in which L¹ is a bond and B is a group of the formula (B⁶)



5

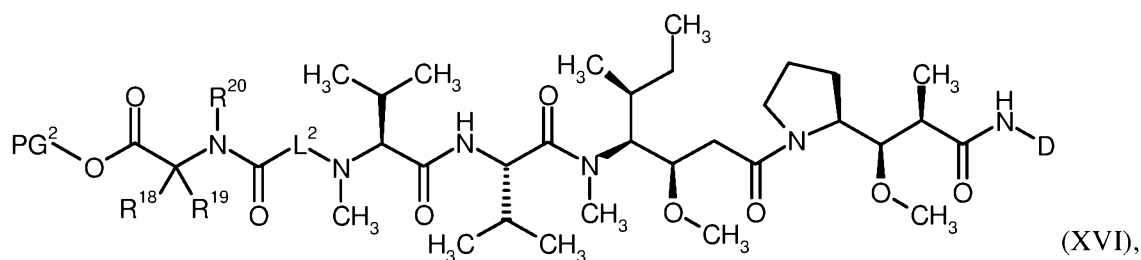
in which *, **, R¹⁸, R¹⁹ and R²⁰ each have the definitions indicated above,

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)



10 in which R¹⁸, R¹⁹, R²⁰ and PG² each have the definitions indicated above,

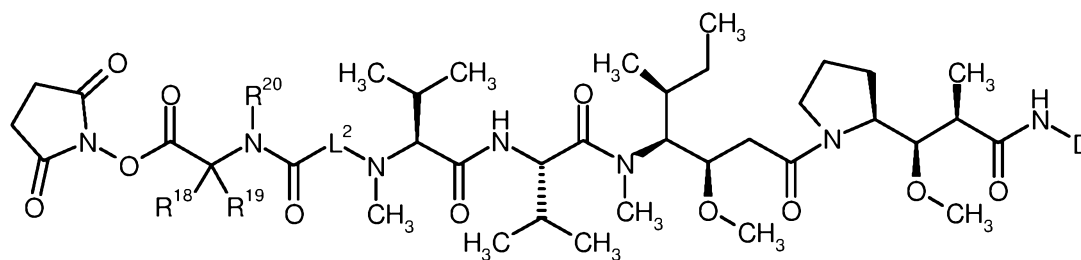
to give a compound of the formula (XVI)



in which D, R¹⁸, R¹⁹, R²⁰, L² and PG² each have the definitions indicated above,

eliminating the protective group PG² from this compound by methods known to the skilled person,
 15 and subsequently reacting the deprotected compound in an inert solvent in the presence of a

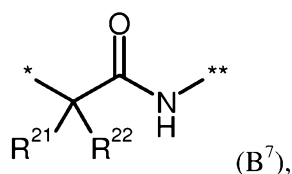
suitable coupling reagent and a suitable base with N-hydroxysuccinimide to give a compound of the formula (III-C)



(III-C),

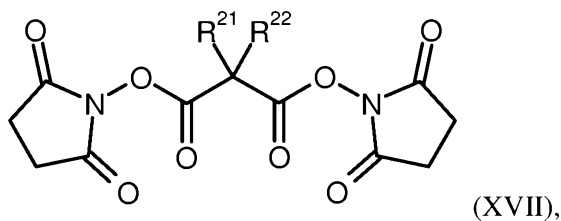
- 5 in which D, R^{18} , R^{19} , R^{20} and L^2 each have the definitions indicated above.

The compounds of the formula (III), in which L^1 is a bond and B is a group of the formula (B⁷)

(B⁷),

in which *, **, R^{21} and R^{22} each have the definitions indicated above,

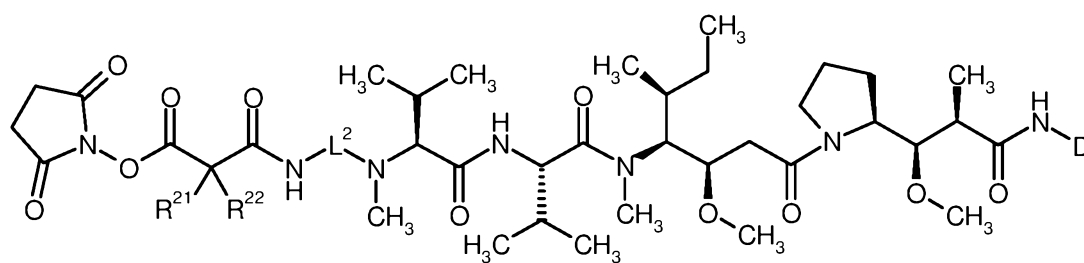
- 10 can be prepared by eliminating the protective group PG¹ from a compound of the formula (VI) by methods known to the skilled person, and reacting the resultant deprotected compound in an inert solvent in the presence of a suitable base with a compound of the formula (XVII)



(XVII),

in which R^{21} and R^{22} each have the definitions indicated above,

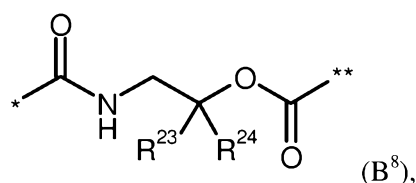
- 15 to give a compound of the formula (III-D)



(III-D),

in which D, R^{21} , R^{22} and L^2 each have the definitions indicated above.

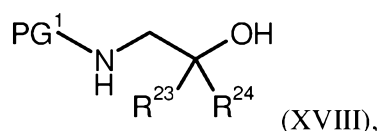
The compounds of the formula (III), in which B is a group of the formula (B⁸)



5

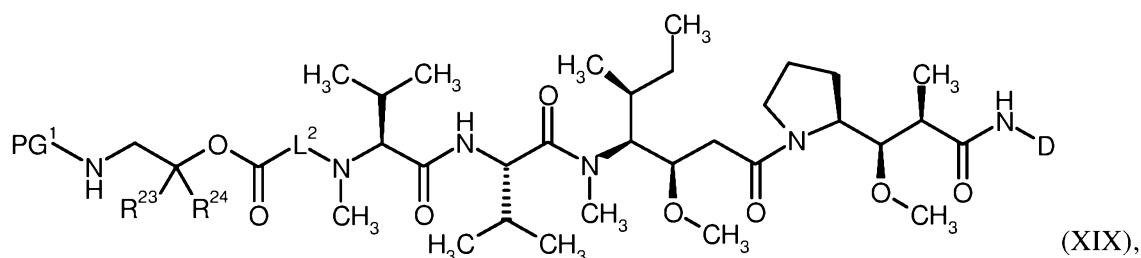
in which *, **, R^{23} and R^{24} each have the definitions indicated above,

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)



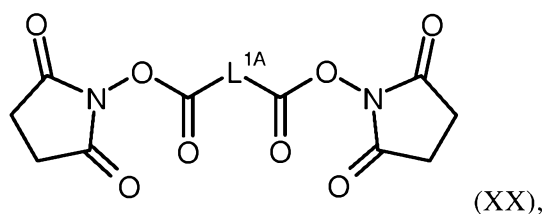
10 in which R^{23} , R^{24} and PG^1 each have the definitions indicated above,

to give a compound of the formula (XIX)



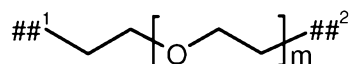
in which D, R^{23} , R^{24} , L^2 and PG^1 each have the definitions indicated above,

eliminating the protective group PG^1 from this compound by methods known to the skilled person,
 15 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)



in which

L^{1A} is linear (C_1-C_{10}) -alkanediyl or is a group of the formula



5 where

m is a number from 2 to 6,

$##^1$ marks the linkage site with the group G,

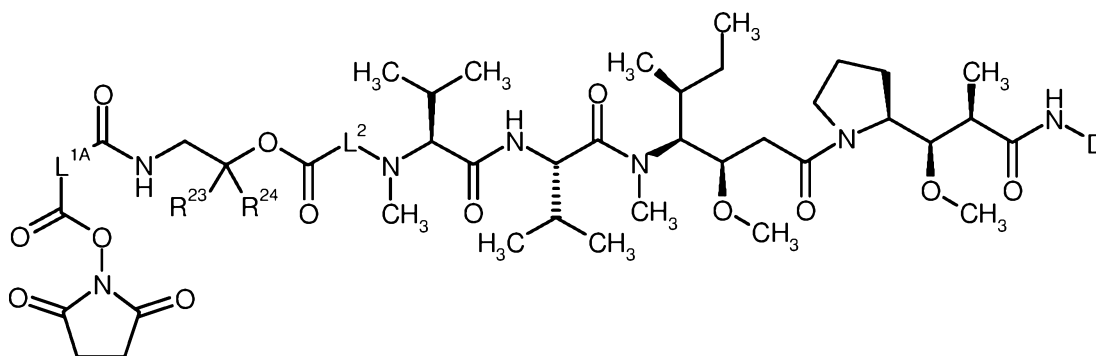
$##^2$ marks the linkage site with the group B,

where (C_1-C_{10}) -alkanediyl may be substituted by 1 to 4 methyl substituents,

10 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,

to give a compound of the formula (III-E)

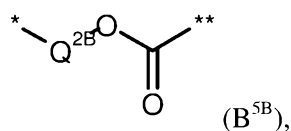


15

(III-E),

in which D, R^{23} , R^{24} , L^{1A} and L^2 each have the definitions indicated above.

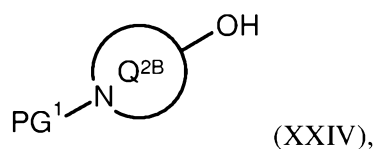
The compounds of the formula (III), in which B is a group of the formula (B^{5B})



in which * and ** each have the definitions indicated above and

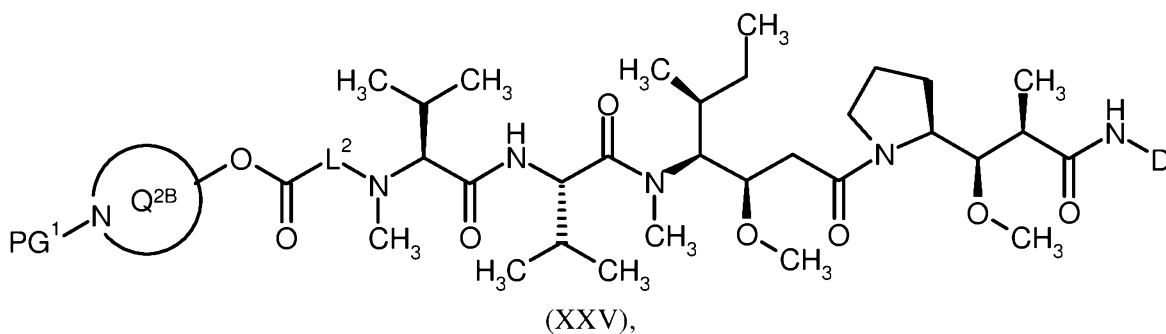
Q^{2B} is an N-linked 4- to 7-membered heterocycle,

- 5 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)



in which PG^1 and Q^{2B} each have the definitions indicated above,

to give a compound of the formula (XXV)



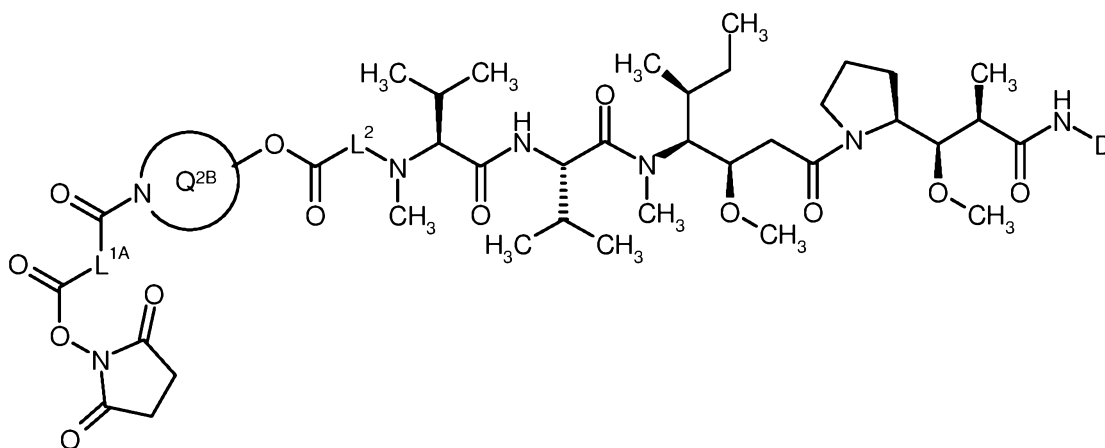
10

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

- 15 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.

The reactions (IV) + (V) $\rightarrow$ (VI) and (IV) + (VIII) $\rightarrow$ (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.

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.

The reactions (IV) + (V) $\rightarrow$ (VI) and (IV) + (VIII) $\rightarrow$ (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.

The above-described coupling reactions (IX) + (X) $\rightarrow$ (II-C), (XII-A) or (XII-B) + (X) $\rightarrow$ (II-D-A) or (II-D-B), (IX) + (XIII) $\rightarrow$ (XIV), (IX) + (XV) $\rightarrow$ (XVI) and (XXII) + (XXIII) $\rightarrow$ (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].

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.

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-(2*H*)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or *O*-(1*H*-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.

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.

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
5 operate under atmospheric pressure.

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-dimethylamino-
10 pyridine at a temperature of +50°C to 100°C under atmospheric pressure.

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
15 [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.

As an amino-protective group PG¹ it is preferred to use *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Z) or (9*H*-fluoren-9-ylmethoxy)carbonyl (Fmoc); for a hydroxyl or carboxyl
20 function it is preferred to use *tert*-butyl or benzyl as protective group PG². 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
25 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 (9*H*-fluoren-9-ylmethoxy)carbonyl group is generally eliminated using a secondary amine base such as diethylamine or piperidine.

30 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.

Suitable bases for the reaction (VI) $\rightarrow$ (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,
5 sodium ethoxide or potassium *tert*-butoxide. It is preferred to use sodium hydrogencarbonate.

The reaction (VI) $\rightarrow$ (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.

10 The reaction (VI) + (VII) $\rightarrow$ (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*-
15 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.

Suitable bases for the reaction (VI) + (VII) $\rightarrow$ (II-B) are, for example, tertiary amine bases such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine, pyridine or
20 4-*N,N*-dimethylaminopyridine. Preference is given to using *N,N*-diisopropylethylamine.

The reaction (VI) + (VII) $\rightarrow$ (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.

The reactions (IX) $\rightarrow$ (III-A), (XIV) $\rightarrow$ (III-B) and (XVI) $\rightarrow$ (III-C) and also (VI) + (XVII) $\rightarrow$ (III-D), (XIX) + (XX) $\rightarrow$ (III-E) and (XXV) + (XX) $\rightarrow$ (III-F) take place in a solvent which is inert
25 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,
30 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.

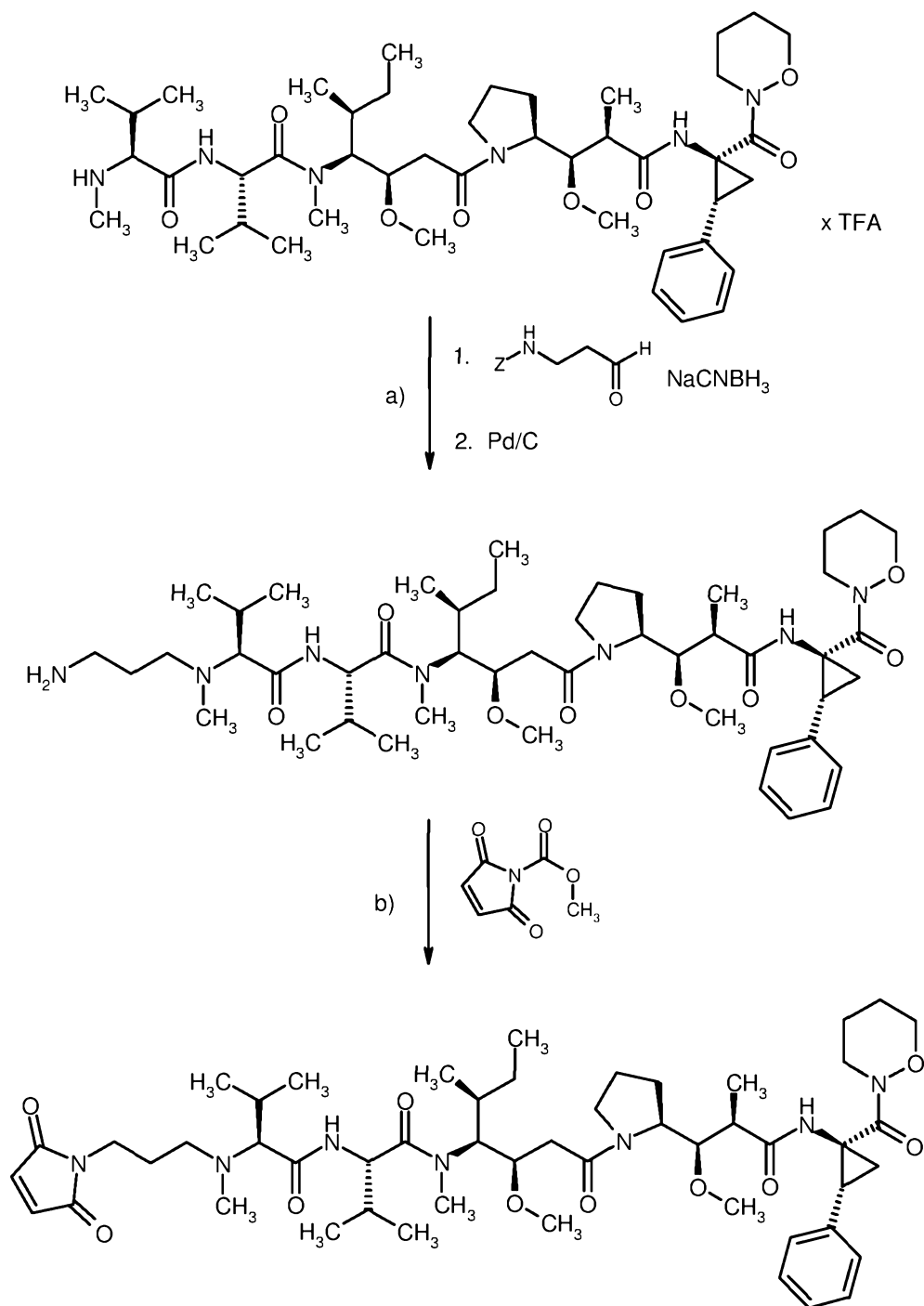
Suitable bases for these reactions are, for example, tertiary amines such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine, pyridine or 4-*N,N*-dimethylaminopyridine. Preference is given to using *N,N*-diisopropylethylamine, optionally with addition of 4-*N,N*-dimethylaminopyridine.

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.

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 R³⁵ 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.

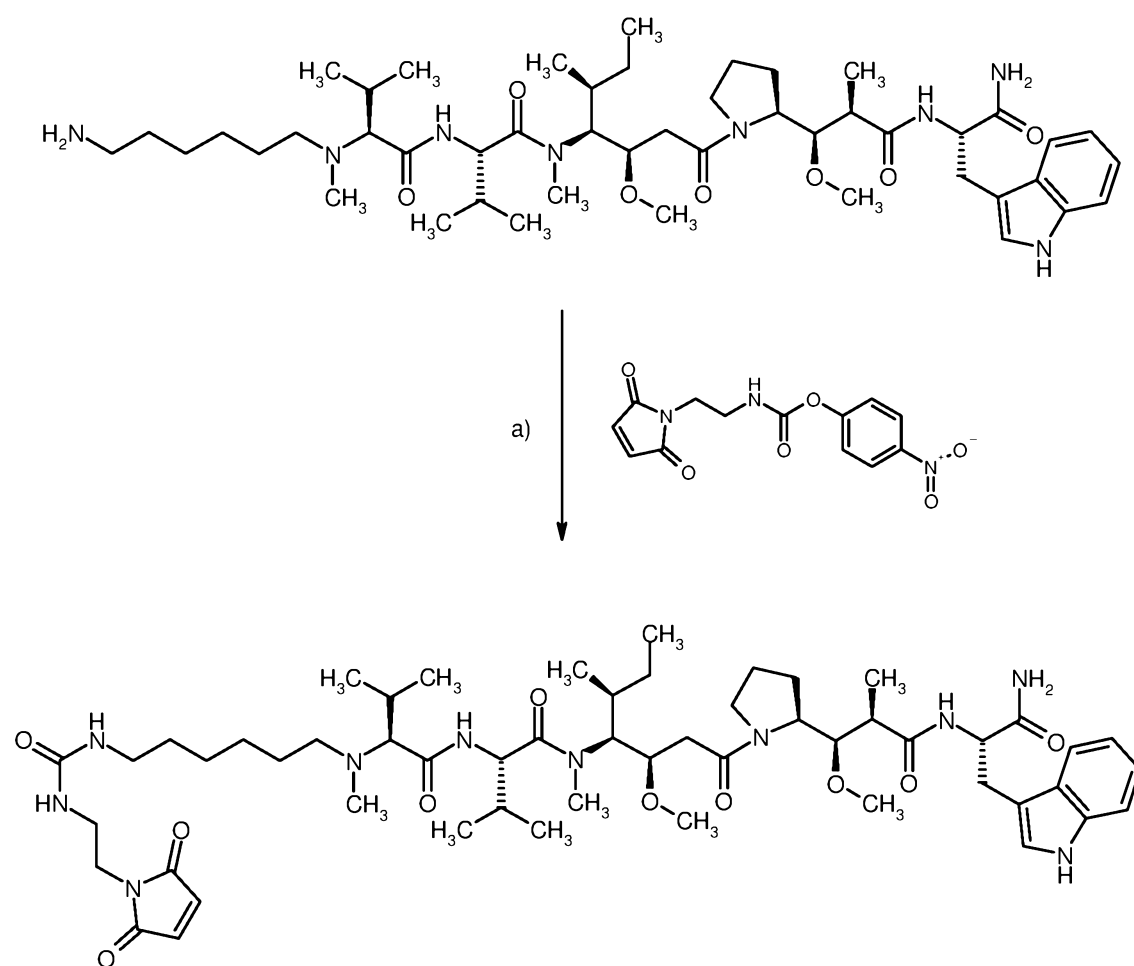
The above-described processes are illustrated by way of example by the following synthesis schemes (Scheme 3 to 13, 18):

Scheme 3



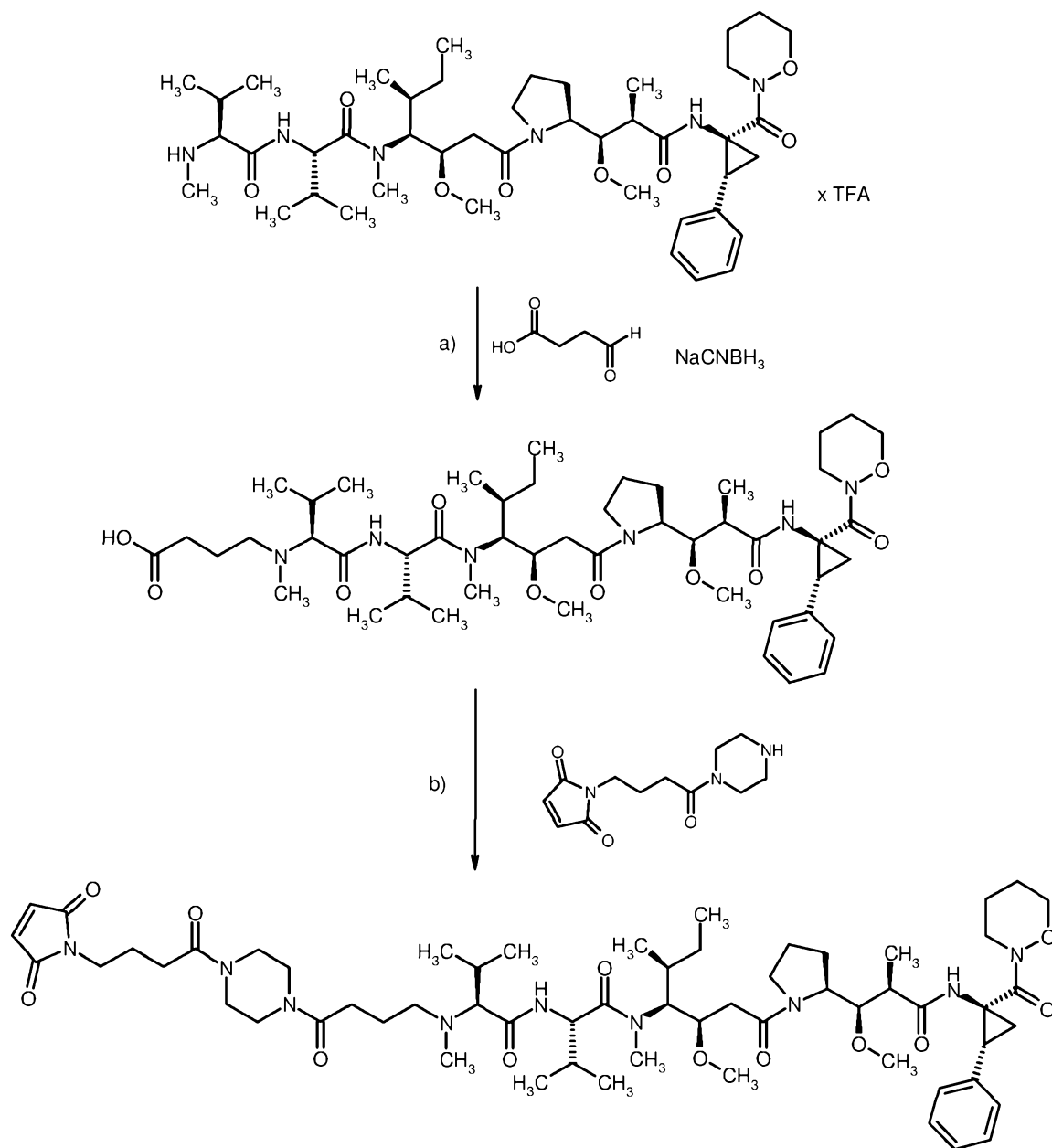
[a): 1. Water/dioxane, 1N HCl, 100°C; 2. H_2 , Pd/C, methanol, RT; b): $NaHCO_3$, H_2O , dioxane, RT].

Scheme 4



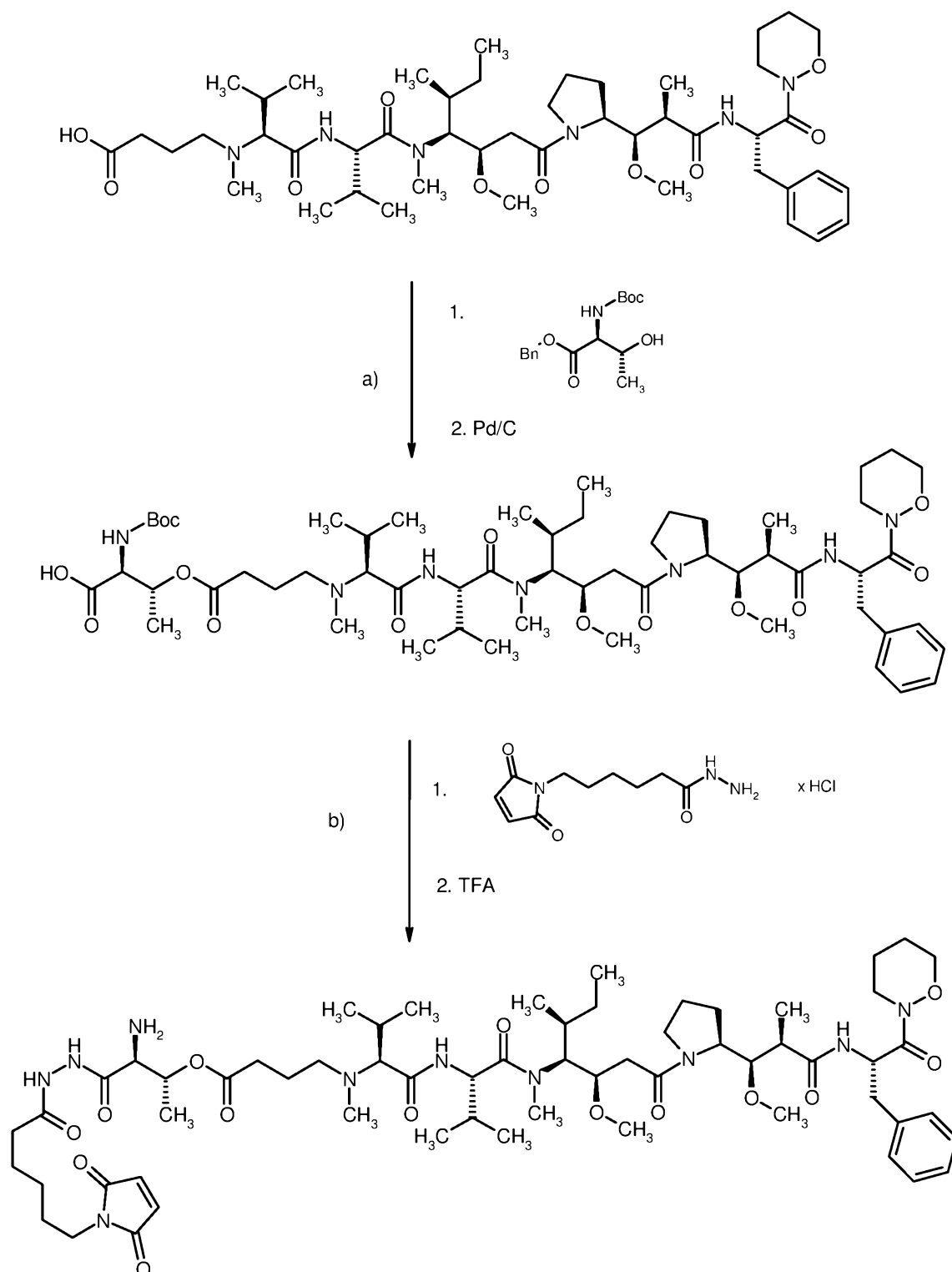
[a): Diisopropylethylamine, DMF, RT].

Scheme 5



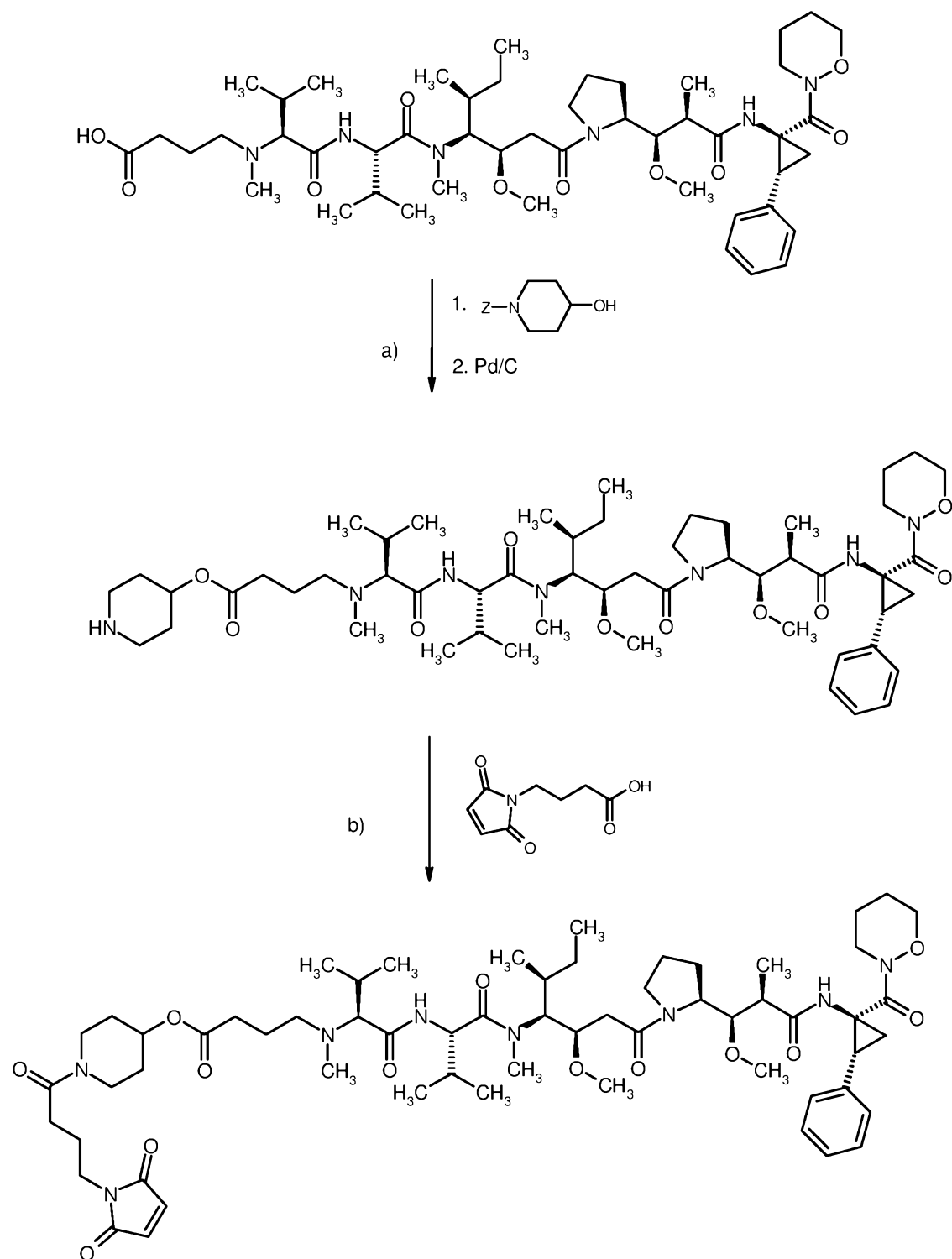
[a): Water/dioxane, 1N HCl, 100°C; b): HATU, diisopropylamine, DMF, RT].

Scheme 6



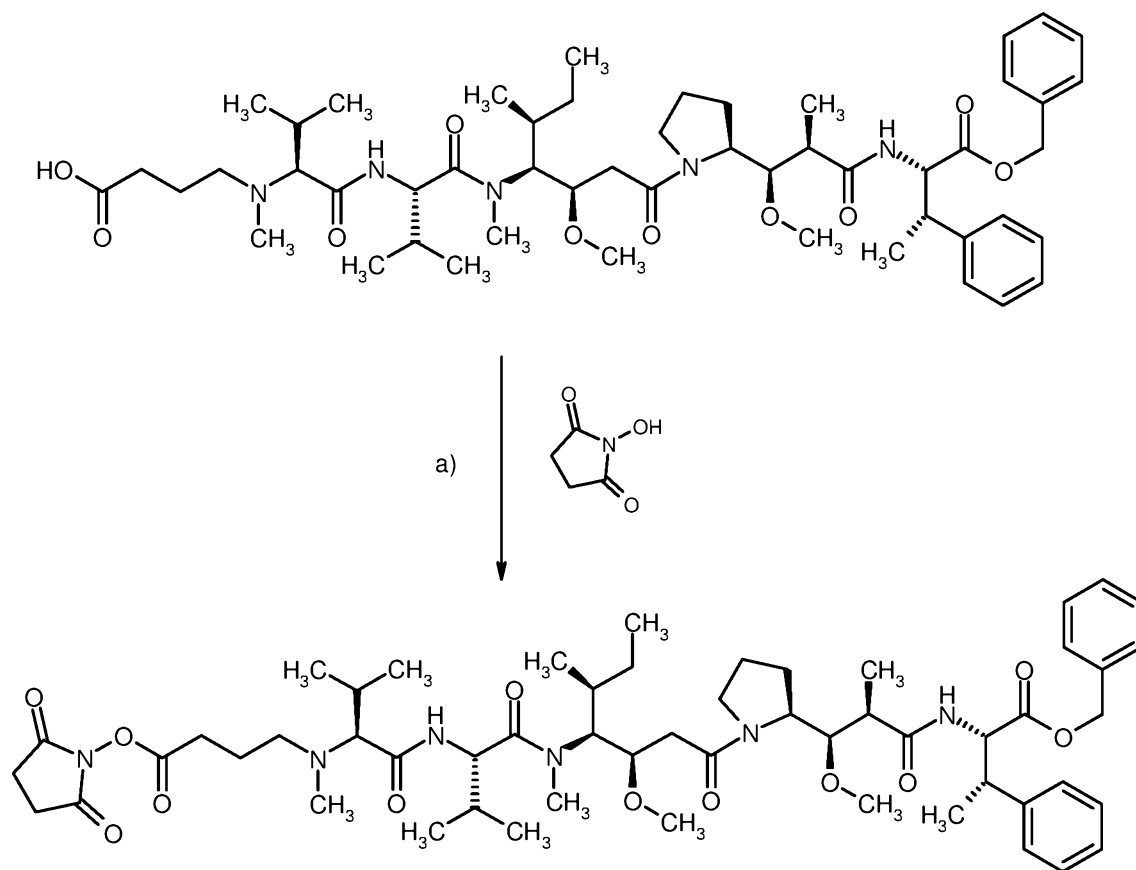
[a): 1. EDCI, DMAP, dichloromethane, RT; 2. H_2 , methanol, RT; b): 1. EDCI, HOBt, diisopropylamine, DMF, RT; 2. dichloromethane, RT].

Scheme 7



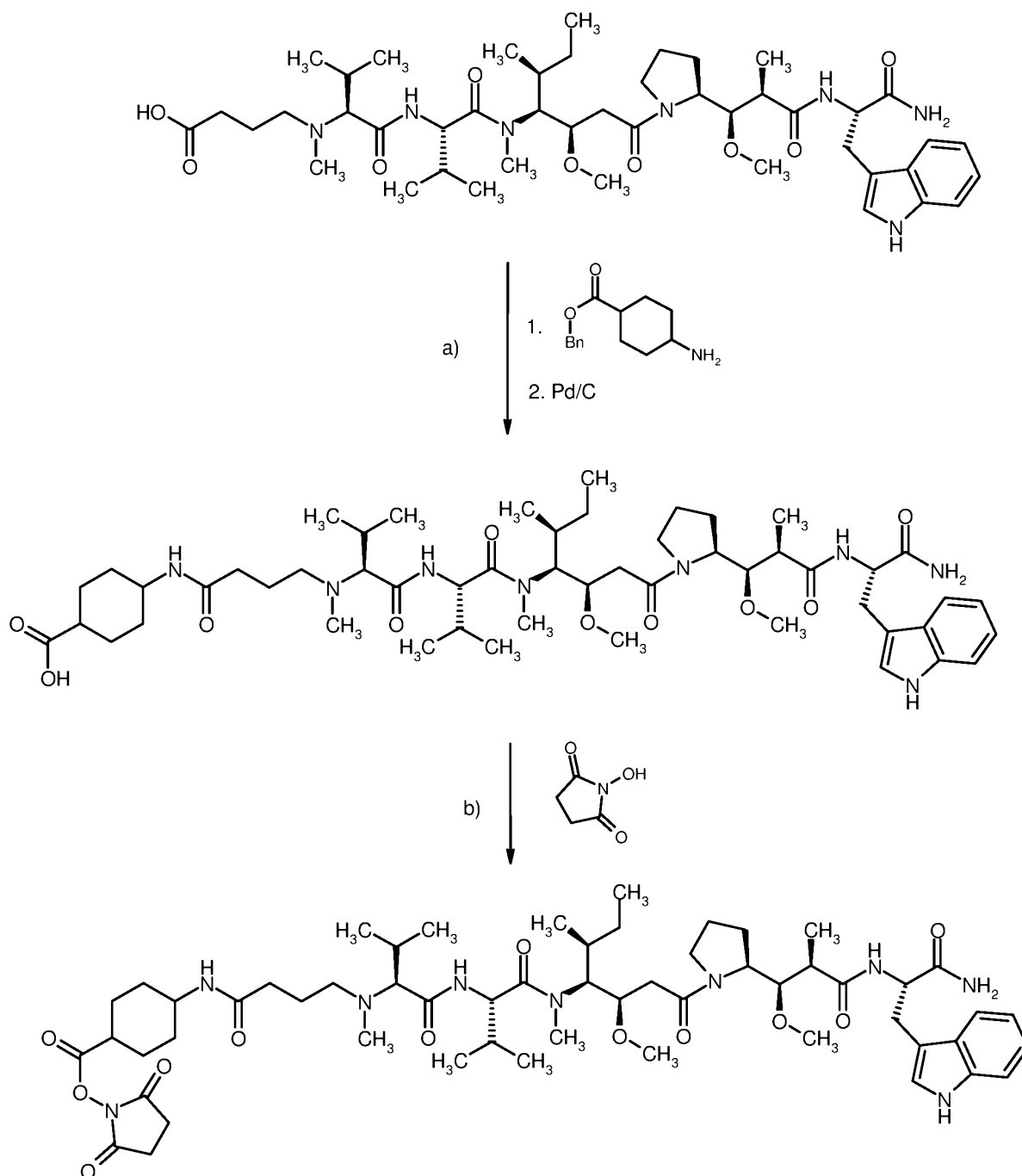
[a): 1. EDCI, DMAP, dichloromethane, RT; 2. H₂, methanol, RT ; b): HATU, diisopropylamine, DMF, RT].

Scheme 8



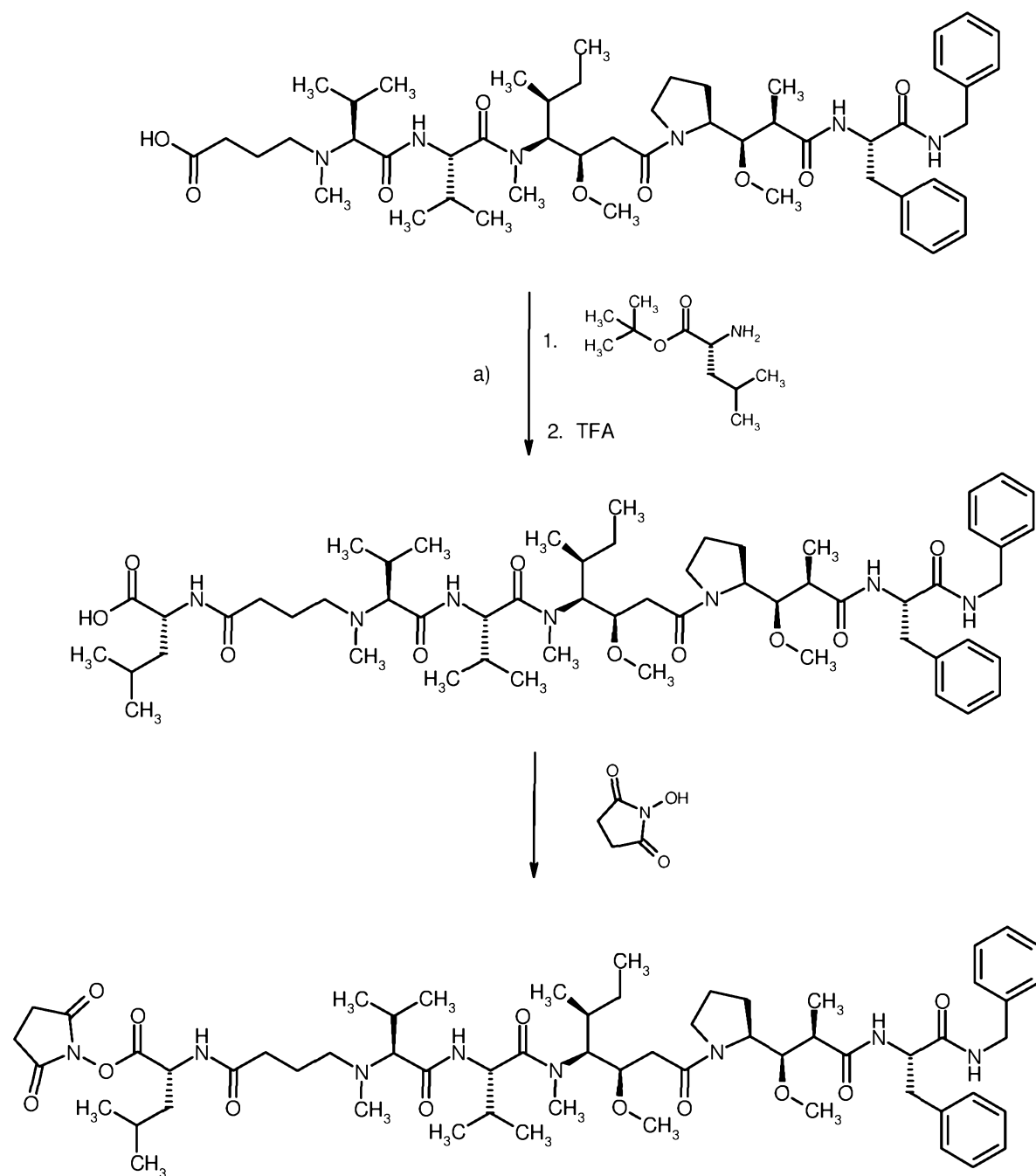
[a): EDCI, dichloromethane, RT].

Scheme 9



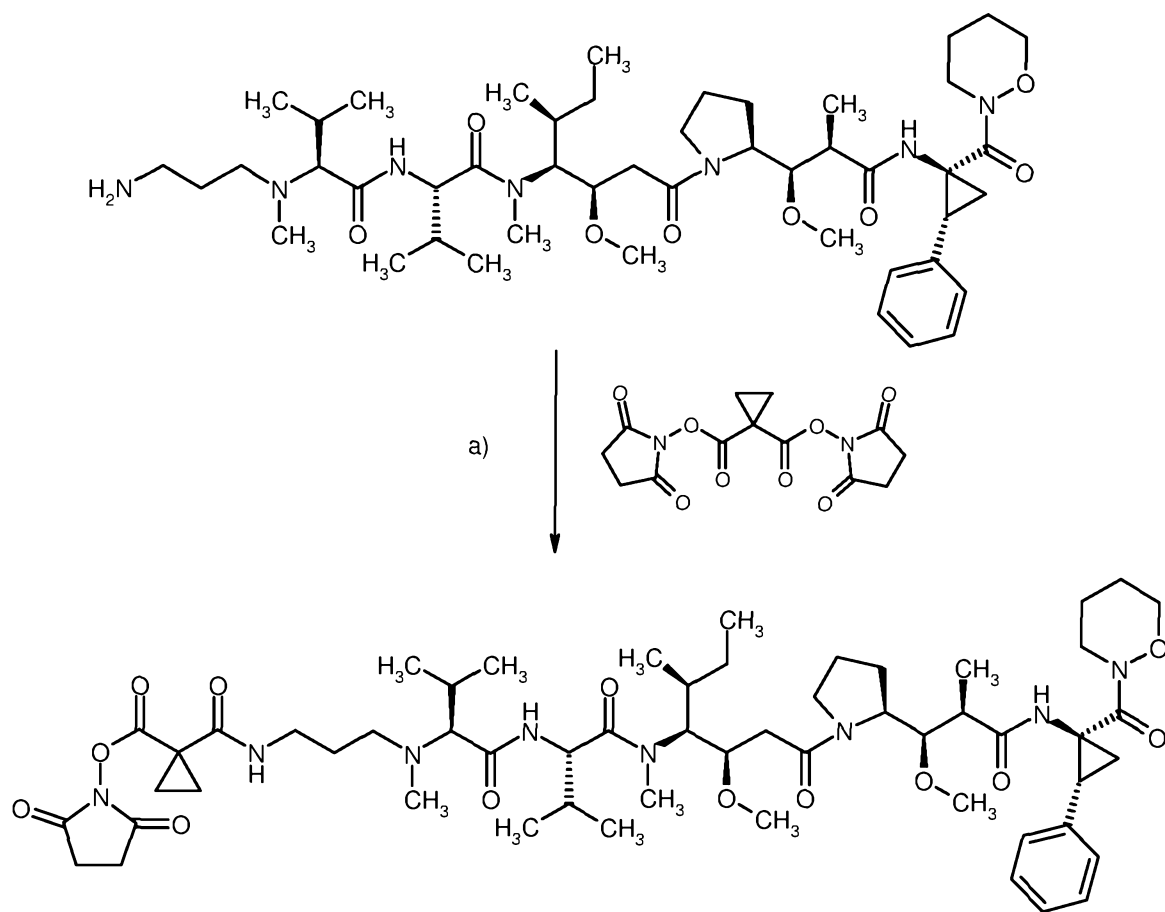
[a): HATU, diisopropylethylamine, DMF, RT; 2. H₂, methanol, RT; b): EDCI, DMAP,
5 dichloromethane, RT].

Scheme 10



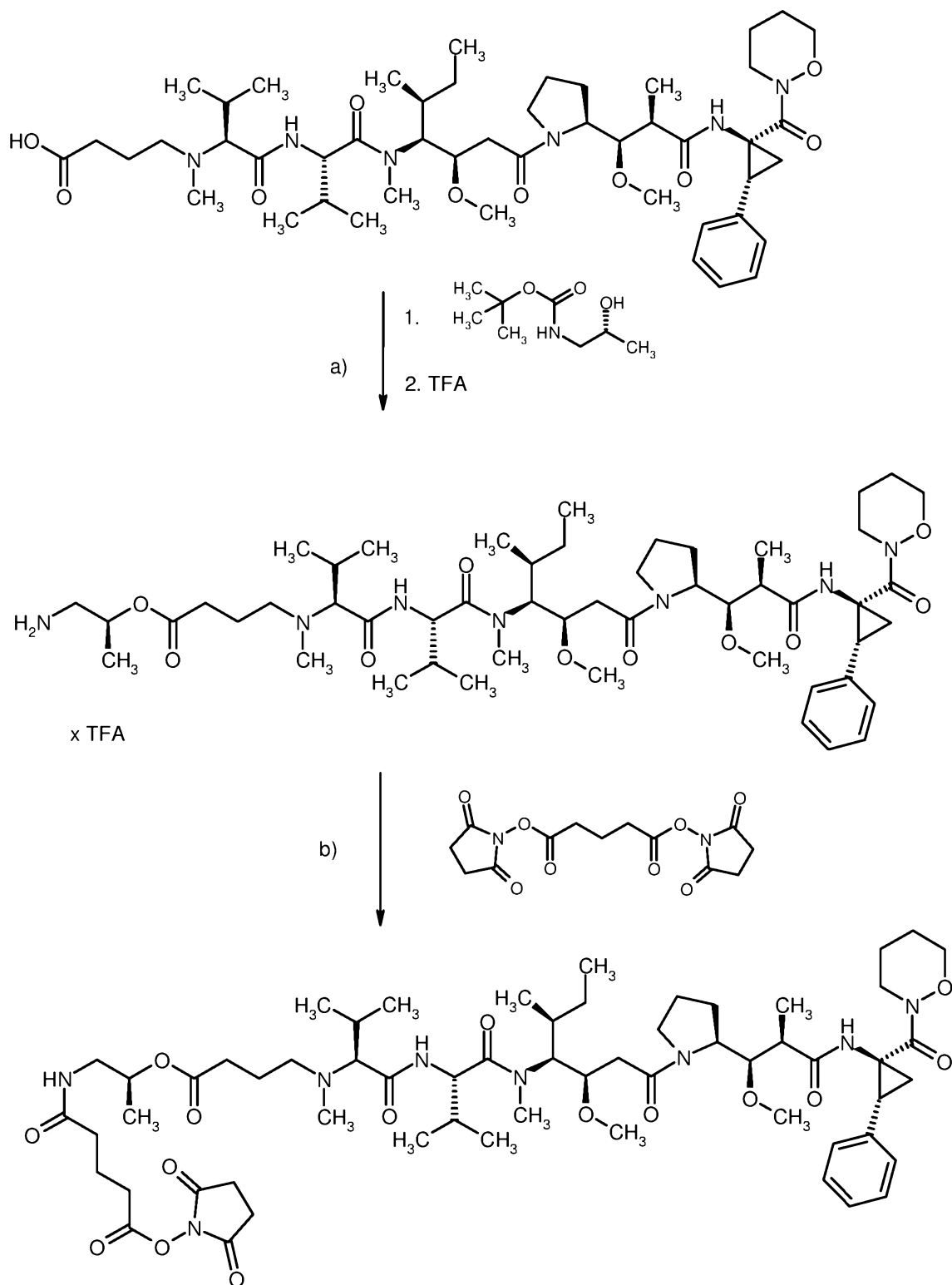
[a): 1. HATU, diisopropylethylamine, DMF, RT; 2. dichloromethane, RT; b): EDCI, DMAP,
 5 dichloromethane, RT].

Scheme 11

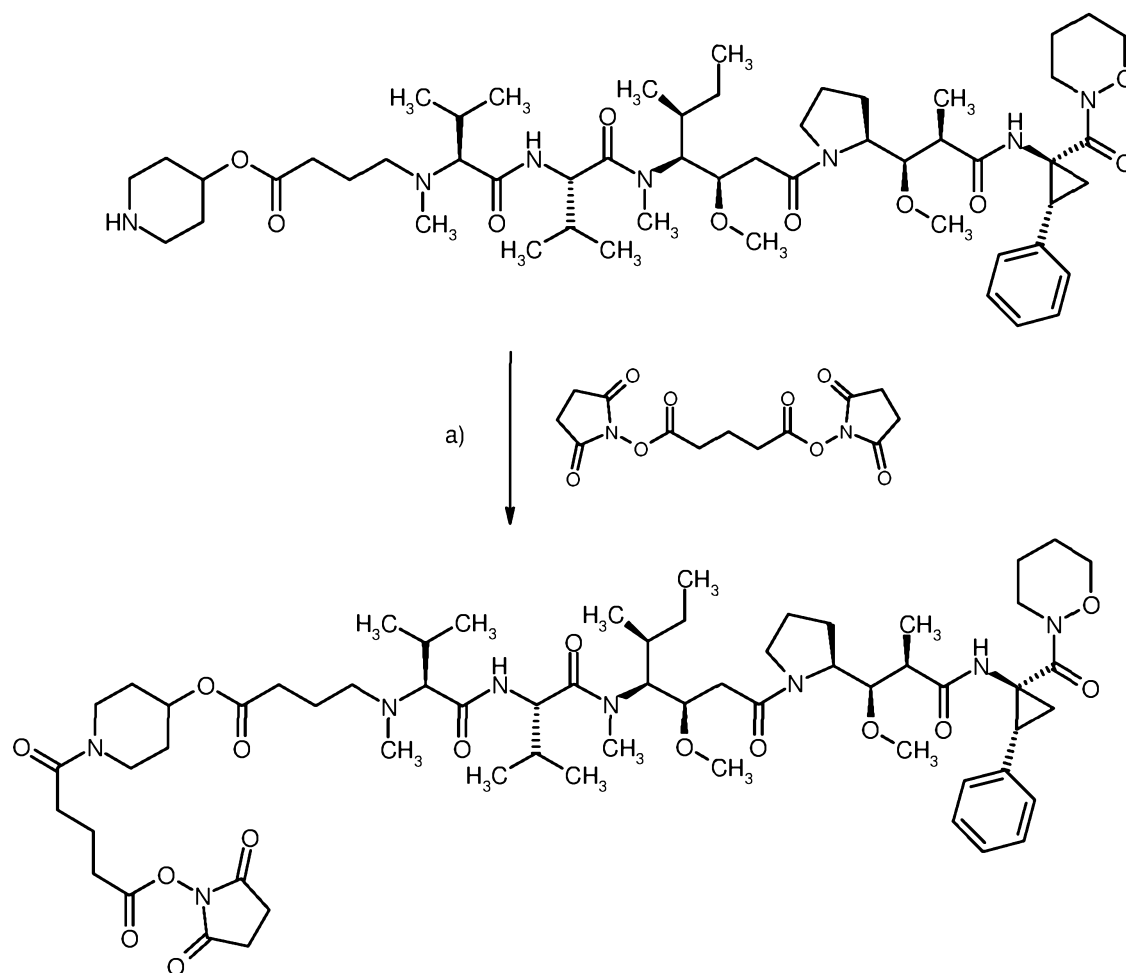


[a): Diisopropylethylamine, DMF, RT].

Scheme 12

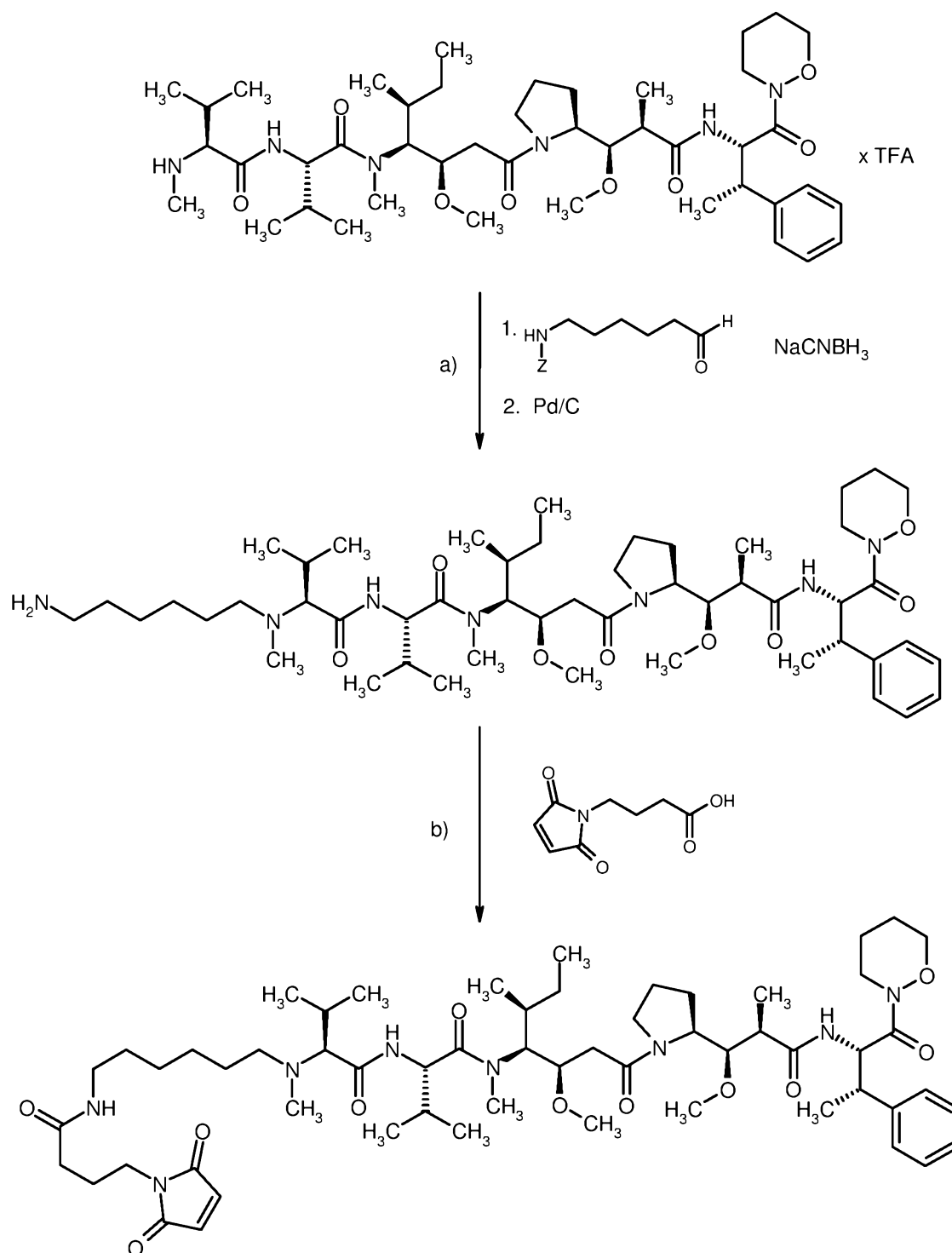


[a): 1. EDCI, DMAP, dichloromethane, RT; 2. dichloromethane, RT; b): diisopropylamine, DMAP, dichloromethane, RT].



[a): DMAP, diisopropylamine, dichloromethane, RT].

Scheme 18

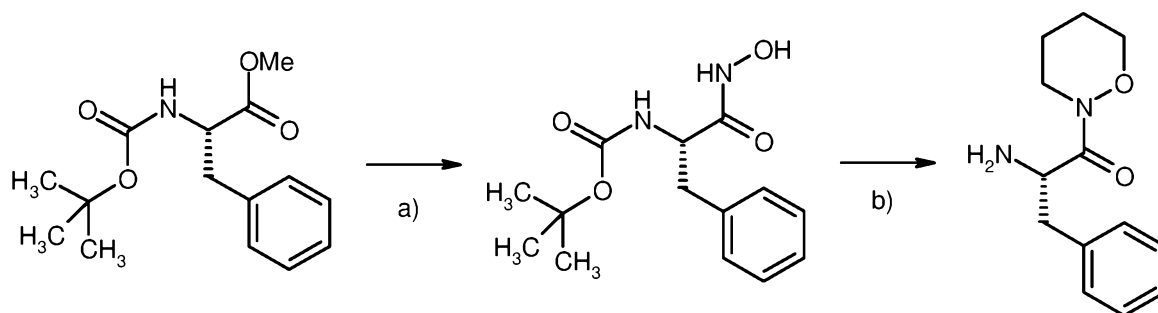


[a): 1. Water/dioxane, 1N HCl, 100°C; 2. H_2 , Pd/C, methanol, RT; b): HATU, diisopropylethylamine, RT].

- 5 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*

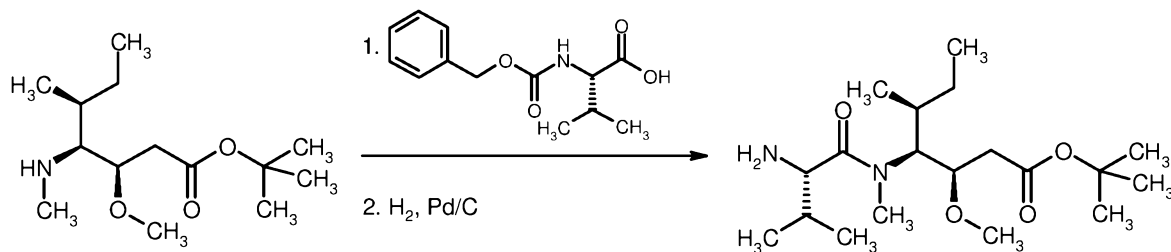
al., *Tetrahedron* 1994, 50, 5345. Pettit *et al.*, *J. Org. Chem.* 1994, 59, 1796) in analogy to processes known from the literature, in accordance with customary methods of peptide chemistry, and as described in the present experimental section. The synthesis schemes below (Scheme 14 to 16) illustrate the preparation by way of example.

5 Scheme 14



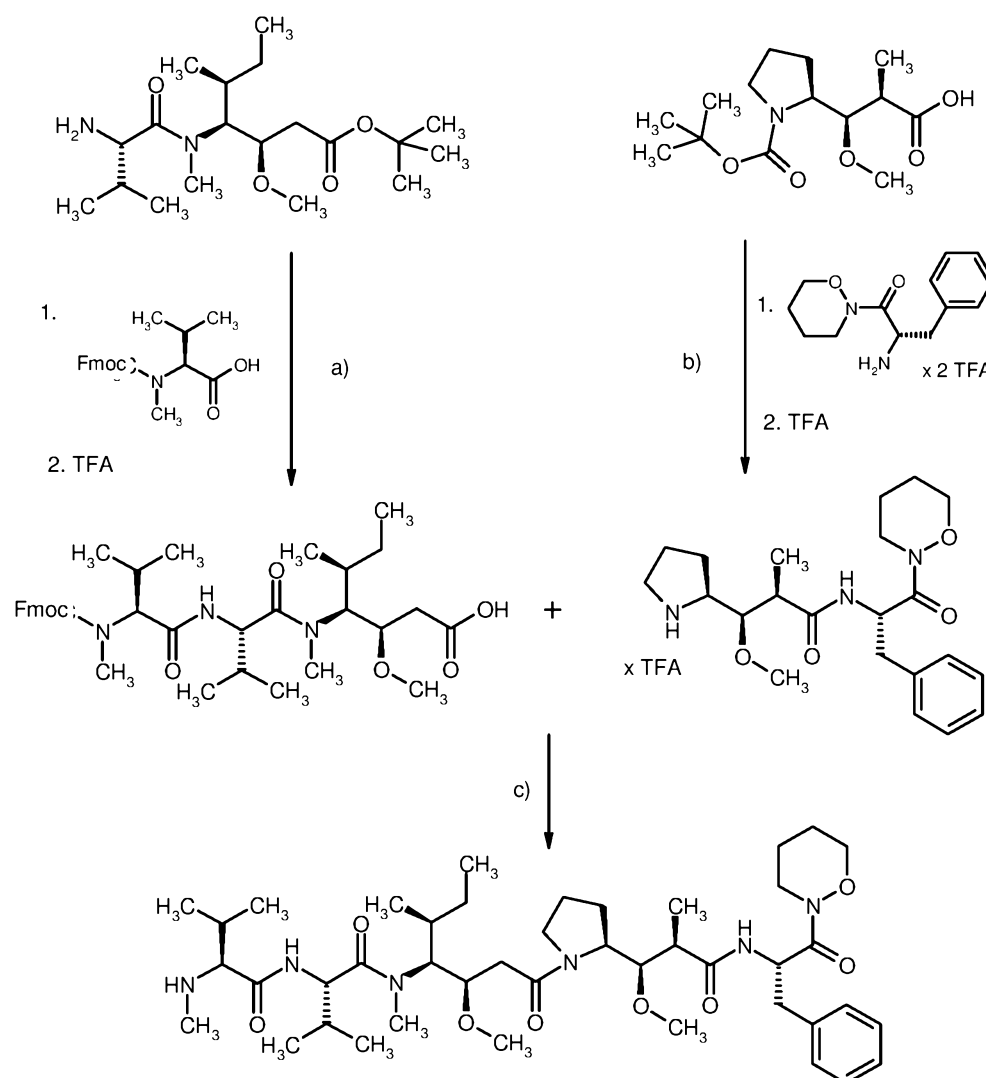
[a): Hydroxylamine hydrochloride, KOH, MeOH, 0°C → RT; b): BrCH₂(CH₂)₂CH₂Br, K₂CO₃, acetone, reflux].

Scheme 15



[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].

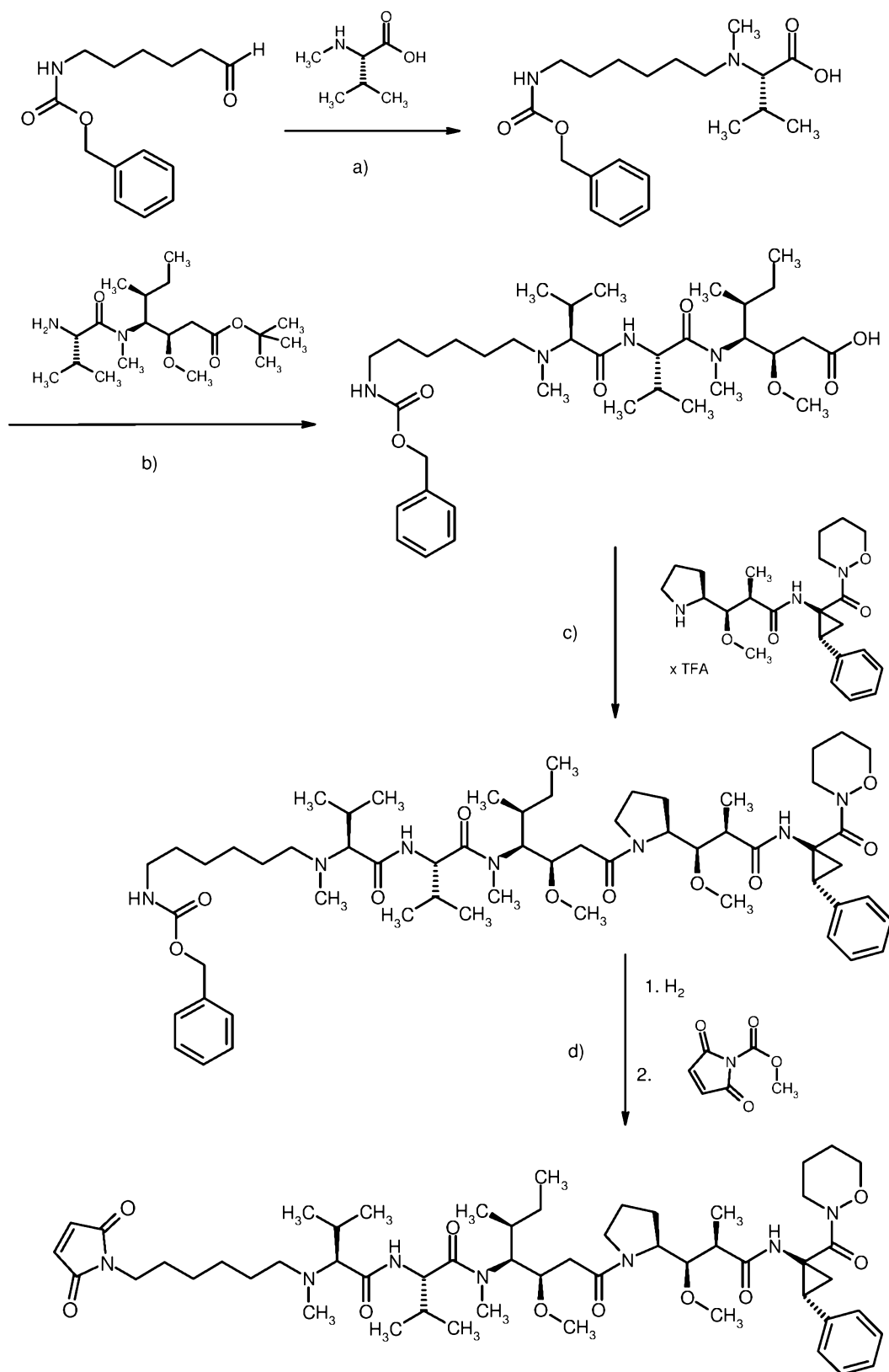
The compounds of the formulae (XI), (XIII), (XV), (XVII) and (XXI), including, where appropriate, chiral or diastereomeric forms thereof, are available commercially or are described as such in the literature, or they can be prepared by routes that are obvious to the skilled person, in analogy to methods 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.

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.

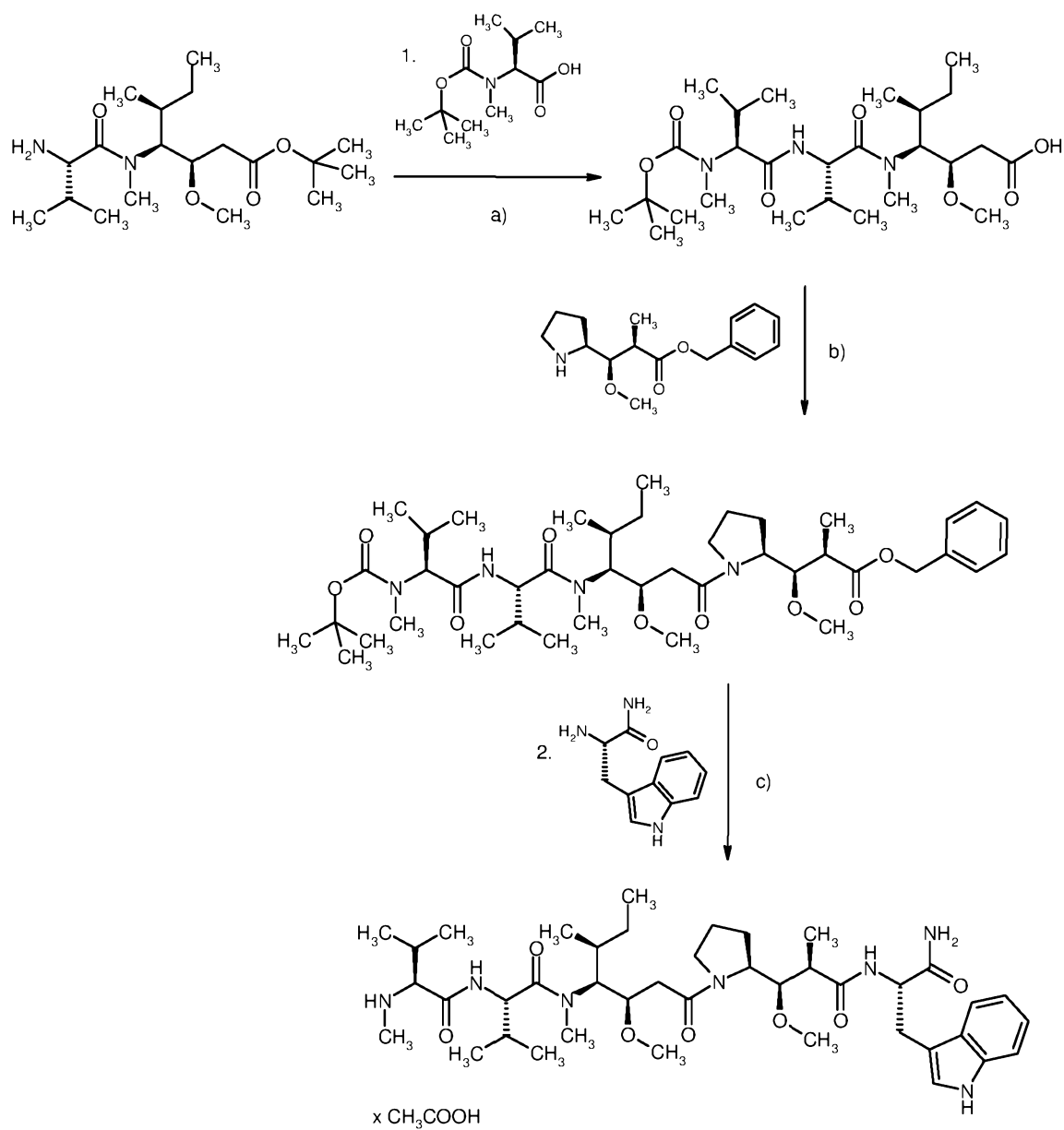
Alternatively, individual steps of the preparation sequence may be carried out in a different order. This approach is illustrated by way of example in the synthesis schemes below (Scheme 17, 19 and
5 20).

Scheme 17



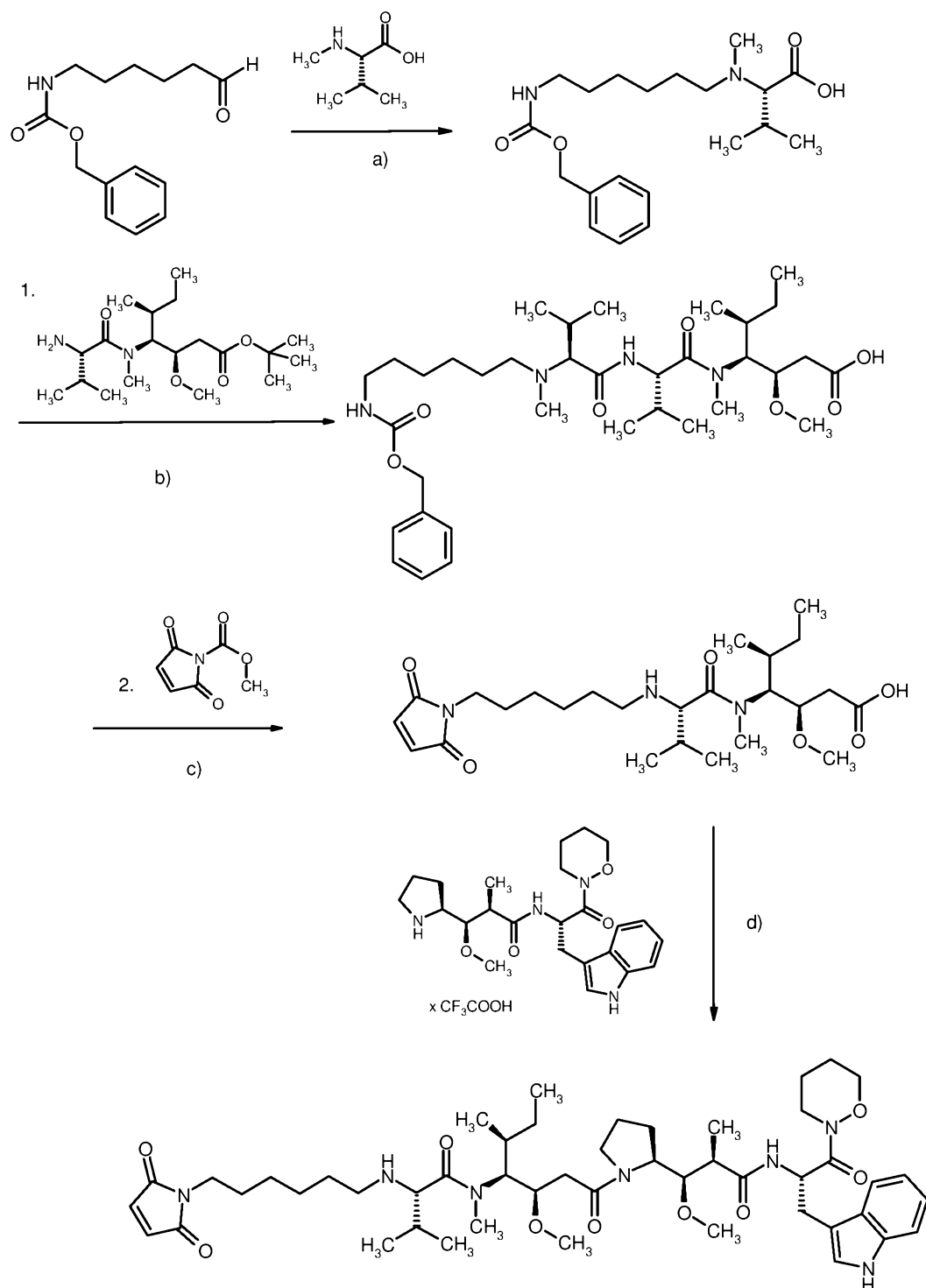
[a): Borane-pyridine complex, acetic acid, MeOH; b): 1. HOBt, EDCI, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; c): HATU, diisopropylethylamine, DMF, RT; d): 1. Pd/C, MeOH, RT; 2. NaHCO₃, dioxane, water].

Scheme 19



- [a): 1. HATU, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; 3. ((H₃C)₃C(C=O))₂O, DMF, diisopropylethylamine; b): diisopropylethylamine, BEP, DMF, RT; c):
- 5 1. H₂, Pd/C (10%), methanol, RT; 2. HATU, diisopropylethylamine, DMF, RT; 3. TFA, dichloromethane, RT].

Scheme 20



- [a): Borane-pyridine complex, acetic acid, MeOH; b): 1. HOBt, EDCI, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; c): 1. H₂, Pd/C, MeOH, RT; 2. NaHCO₃, dioxane, water; d): HATU, diisopropylethylamine, DMF, RT;].

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.

In another preferred embodiment the target molecule is a selective cancer target molecule.

In one particularly preferred embodiment the target molecule is a protein.

In one embodiment the target molecule is an extracellular target molecule. In one preferred embodiment the extracellular target molecule is a protein.

- 5 Cancer target molecules are known to the skilled person. Examples thereof are listed below.

Examples of cancer target molecules are as follows:

(1) EGF receptor (NCBI reference sequence NP_005219.2)

Sequence (1210 amino acids):

```

10 >gi|29725609|ref|NP_005219.2| epidermal growth factor receptor
    isoform a precursor [Homo sapiens]
    MRPSGTAGAALLALLAALCPASRALEEKKVCQGTSNKLTQLGTFEDHFLSLQRMFNNCEVVLGNLE
    ITYVQRNYDLSFLKTIQEVAGYVLIALNTVERIPLLENLQIIIRGNMYYENSYALAVLSNYDANKTGL
    KELPMRNLQEILHGAVRFSNNPALCNVESIQWRDIVSSDFLSNMSMDFQNLHGSCQKCDPSCPNGS
    CWGAGEENCQKLTKIICAQQCSGRCRGKSPSDCCHNQCAAGCTGPRESDCLVCRKFRDEATCKDTC
15 PPLMLYNPTTYQMDVNPEGKYSFGATCVKKCPRNYVVTDHGSCVRACGADSYEMEEDGVRKCKKCE
    GPCRKVCNGIGIGIEFKDLSINATNIKHFKNCTSSISGDLHILPVAFRGDSFTHTPPLDPQELDILK
    TVKEITGFLLIQAWPENRTDLHAFENLEIIRGRTKQHGGFSLAVVSLNITSLGLRSLKEISDGDVI
    ISGNKNLCYANTINWKKLFGTSGQKTKIISNRGENSKATGQVCHALCSPEGCWGPEPRDCVSCRN
    VSRGRECVDKCNLLEGEPRFVENSECIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKT
20 CPAGVMGENNTLVWKYADAGHVCHLCHPNCTYGCTGPGLEGCPTNGPKIPS IATGMVGALLLLLVV
    ALGIGLFMRRRHIVRKRTLRRLLQERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFGTV
    YKGLWIPERGEKVKIPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLITQL
    MPFGCLLDYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRLVHRDLAARNVLVKTPQHVKITDFGL
    AKLLGAEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTVWELMTFGSKPYDGIPASEIS
25 SILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMARDPQRYLVIQGDERMHLP
    SPTDSNFYRALMDEEDMDVDVDADEYLIPQQGFFSSPSTSRTPLLSSLSATSNNSTVACIDRNLQ
    SCPIKEDSFLQRYSSDPTGALTEDSIDDTFLPVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRD
    PHYQDPHSTAVGNPEYLNTPVQPTCVNSTFDSPAHWAKGSHQISLDNPDYQQDFFPKEAKPNGIFK
    GSTAENAEYLRVAPQSSEFIGA

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- 30 The extracellular domain is marked by underlining.

(2) Mesothelin (SwissProt reference Q13421-3)

Sequence (622 amino acids):

```

35 >sp|Q13421-3|MSLN_HUMAN Isoform 2 of Mesothelin OS=Homo sapiens
    GN=MSLN
    MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLGETGQEAAPLDGVLANPPNISS
    LSPRQLLGFPCEAVSGLSTERVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPL
    DLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQRLPAALACWGVRSLLSEA
    DVRALGGLACDLPGRFVAESA EVLLPRLVSCPGPLDQDQQAARAALQGGGPPYPGPSTW
    SVSTMDALRGLLPVLGQPIIRSIPQGIWAARQRSSRDPSWRQPERTILRPRFRREVEKT
40 ACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELY
    PQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETALKALLEVNKGHEMSPQVATLIDRFVK
    GRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA
    RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQ

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KLLGPHVEGLKAEERHRPVRDWILRQRQDDLDLTLGLGLQGGIPNGYLVLDLSMQEALSGT
PCLLGPGPVLTVLALLLASTLA

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
5 extracellularly.

(3) Carboanhydrase IX (SwissProt reference Q16790)

Sequence (459 amino acids):

>sp|Q16790|CAH9_HUMAN Carbonic anhydrase 9 OS=Homo sapiens GN=CA9
PE=1 SV=2
10 MAPLCPSFWLPLLIPAPAPGLTVQLLLSLLLVPVHPQRLPRMQEDSPLGGGSSGEDDPL
GEEDLPSEEDSPREEDPPGEEDLPGEEDLPGEEDLPEVKPKSEEEGSLKLEDLPTVEAPG
DPQEPQNNAHRDKEGDDQSHWRYGGDPPWPRVSPACAGRFQSPVDIRPQLAAFCPALRPL
ELLGFQLPPLPELRLRNNGHVSQLTLPGLMALGPGREYRALQLHLHWGAAGRPGSEHT
VEGHRFP AEIHVVHLSTAFARVDEALGRPGGLAVLAAFL EEGPEENSAYEQLLSRLEEIA
15 EEGSETQVPGLDISALLPSDFSRYFQYEGSLTTPPCAQGVITVFNQTVMLSAKQLHTLS
DTLWGPGDSRLQLNFRATQPLNGRVIEASFPAGVDSSPRAAEPVQLNSCLAAGDILALVF
GLLFAVTSVAFVLVQMRRQHRRGTKGGVSYRPAEVAETGA

The extracellular domain is marked by underlining.

(4) C4.4a (NCBI reference sequence NP_055215.2; Synonym LYPD3)

20 Sequence (346 amino acids):

>gi|93004088|ref|NP_055215.2| ly6/PLAUR domain-containing protein
3 precursor [Homo sapiens]
MDPARKAGAQAAMIWTAGWLLLLLLRGGAALECYSCVQKADDGCSPNKMKTVKCAPGVDVCTEAVG
25 AVETIHGQFSLAVRGCGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNAKLNLTSRALDPAGNESA
YPPNGVECYSCVGLSREACQGTSPPVVSCYNASDHVYKGCDFDGNVTLTAAANTVSLPVRGCVQDEF
CTRDGVTGPGFTLSGCCQGSRCNSDLRNKTYFSPRIPLVRLPPPEPTTVASTTSVTTSTTSAPVR
PTSTTKPMPAPTSQTPRQGV EHEASRDEEPRLTGGAAGHQDRSNSGQYPAKGGPQQPHNKGCVAPT
AGLAALLLAVAAGVLL

30 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]
MKRFLFLLLTISLLVMVQIQTLGSGQNDTSQTSSPSASSNISGGIFLFFVANAIHLFCFS

35 (6) Her2 (NCBI reference sequence NP_004439.2)

>gi|54792096|ref|NP_004439.2| receptor tyrosine-protein kinase
erbB-2 isoform a [Homo sapiens]
MELAALCRWGLLLALLPPGAASTQVCTGTDMLRLPASPETHLDMRLHLYQGCQVVQGNLELTYP
TNASLSFLQDIQEVQGYVLI AHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGA
40 SPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTIDTNRSRACHPCSPM
CKGSRCWGESSEDCQSLTRTV CAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLFHNHSGIC
ELHCPALVTYNTDTFESMPNPEGRTYFGASCVTACPYNYLSTDVGSCTLVCPHNLNQEVTAEEDGTQR

CEKCSKPCARVCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQ
 LQVFETLEEITGYLYISAWPDSLPLDSVFNQLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELG
 SGLALIHNNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQC
 VNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDP
 5 FCVARCPSGVKPDLSPYIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIIISAVVG
 ILLVVVLGVVFGILIKRRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVKVL
 GSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSFYVSRLLGICLTS
 TVQLVTQLMPYGCLLDHVRENRRGLGSQDLLNWCMIKAGMSYLEDVRLVHRDLAARNVLVKSPNH
 VKITDFGLARLLDIDETEHADGGKVPKWMMALESILRRRFTHQSDVWSYGVTVWELMTFGAKPYD
 10 GIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWMIDSECRPRFRELVSFSESRMARDPQRFVVIQ
 NEDLGPASPLDSTFYRSLLEDDDMGDLVDAEYLVLPQQGFFCPDPAPGAGGMVHHRHRSSTRSGG
 GDLTLGLEPSEEEAPRSPLAPSEGAGSDVFDGDLGMAAGLQSLPTHDPSPQLQRYSEDPTVPLPS
 ETDGYVAPLTCSPQPEYVNQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFG
 GAVENPEYLTQGGAAPQPHPPAFSPAFLNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVP
 15 V

(7) CD20 (NCBI reference sequence NP_068769.2)

>gi|23110987|ref|NP_068769.2| B-lymphocyte antigen CD20 [Homo
 sapiens]
 MTPRNSVNGTFPAEPMKGPIAMQSGPKPLFRMRSSLVGPTQSFFMRRESKTLGAVQIMNGLFHIAL
 20 GGLLMIPAGIYAPICVTVWYPLWGGIMYIISGSLAATEKNSRKCLVKGMIMNSLSLFAAISGMI
 LSIMDILNIKISHFLKMESLNFIRAHTPYINIYNCEPANPSEKNSPSTQYCYSIQSLFLGILSVML
 IFAFFQELVIAGIVENEWKRTCSRPKSNIVLLSAEEKKEQTIEIKEEVVGLTETSSQPKNEEDIEI
 IPIQEEEEETETNFPPEPPQDQESSPIENDSSP

(8) The lymphocyte-activating antigen CD30 (SwissProt ID P28908)

25 >gil68348711ref|NP_001234.2| tumor necrosis factor receptor superfamily member 8 isoform 1
 precursor [Homo sapiens]
 MRVLLAALGLLFLGALRAFPQDRPFEDTCHGNPSHYDDKAVRRCCYRCPMGLFPTQQCPQRPTDCR
 KQCEPDYYLDEADRCTACVTCSRDDLVEKTPCAWNSSRVCECRPGMFCSTSAVNSCARCFHSHVCP
 AGMIVKFPGTATQKNTVCEPASPGVSPACASPENCKEPSSGTIPQAKPTPVSPATSSASTMPVRGGT
 30 RLAQEAASKLTRAPDSPSSVGRPSSDPGLSPTQPCPEGSGDCRKQCEPDYYLDEAGRCTACVSCSR
 DDLVEKTPCAWNSSRTCECRPGMICATSATNSRARCVYPICAAETVTKPQDMAEKDITTFEAPPLG
 TQPDNCNTPENGEPASTSPTQSLLVDSQASKTLPIPTSAVALSSTGKPVLDAGPVLFVWILVLV
 VVVGSSAFLCHRRACRKIRQKLHLCPVQTSQPKLELVDSRPRRSSTQLRSGASVTEPVAEERG
 LMSQPLMETCHSVGAAYLESPLQDASPAGGPSSPRDLPEPRVSTEHTNNKIEKIYIMKADTVIVG
 35 TVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPPLGSCSDVMLSVEEEGKEDPLPTAASG
 K

(9) The lymphocyte adhesion molecule CD22 (SwissProt ID P20273)

>gil157168355ref|NP_001762.2| B-cell receptor CD22 isoform 1 precursor [Homo sapiens]
 MHLLGPWLLLLLVLEYLAFSDSSKWVFEHPETLYAWEGACVWIPCTYRALDGDLESFILFHNPEYNK
 40 NTSKFDGTRLYESTKDGKVPSEQKRVQFLGDKNKNCTLSIHPVHLNDSGQLGLRMESKTEKWMERI
 HLNVSERPFPHIQLPPEIQESQEVTLTCLLNFSCYGYPIQLQWLLEGVPMRQAAVTSTSLTIKSV
 FTRSELKFSPQWSSHGKIVTCQLQDADGKFLSNDTVQLNVKHTPKLEIKVTPSDAIVREGDSVTMT
 CEVSSSNPEYTTVSWLKDGTSLKKQNTFTLNLREVTKDQSGKYCCQVSNDVGPGRSEEVFLQVQYA
 PEPSTVQILHSPAVEGSQVEFLCMSLANPLPTNYTWYHNGKEMQGRTEEKVHHPKILPWAGTYSC
 45 VAENILGTGQRGPGAELDVQYPPKKVTTVIQNPMPIREGDVTLSNYSNNSNPSTRYEWWKPHGAW
 EEPGLGVKIQNVGWDNTTIIACAACNSWCSWASPVALNVQYAPRDVVRKIKPLSEIHSNNSVSLQ
 CDFSSSHPKVEVQFFWEKNGRLLGKESQLNFDISIPEDAGSYSCWVNSISIGQTASKAWTLEVLYAPR
 RLRVMSMPGDQVMGKKSATLTCESDANPPVSHYTWFDWNNQSLPYHSQKLRLPVKVQHSYGAYWCQ
 GTNSVGKGRSPLSTLTVYYSPTIGRRVAVGLGSCILAILAICGLKLQRRWKRTQSQQGLQENSS
 50 GQSFFVRNKKVRRAPLSEGPLSLGCYNPMMEDGISYTTLRFPENIPRTGDAESSEMQRPPDCDD
 TVTYSALHQRQVGDYENVIPDFPEDEGIHYSELIQFGVGERPQAQENVYVILKH

(10) The myloid cell surface antigen CD33 (SwissProt ID **P20138**)

>gil130979981|reflNP_001763.3| myeloid cell surface antigen CD33 isoform 1 precursor [Homo sapiens]

5 MPLLLLLLPLLWAGALAMDPNFWLQVQESVTVQEGLCVLVPCTFFHPIPIYYDKNSPVHGYWFREGAI
ISRDSPVATNKLDQEVQEETQGRFRL LGDPSRNNCSLSIVDARRRDNGSYFFRMERGSTKYSYKSP
QLSVHVTDLTHRPKILIPGTLEPGH SKNLTC SVSWACEQGTPIFSWLSAAPTSLGPRTTHSSVLI
ITPRPDHGTNLTCQVKFAGAGVTTERTIQ LNVITYVPQNPTTGIFPGDGSQKQETRAGVVHGAIGG
AGVTALLALCLCLIFFIVKTHRRKAARTAVGRNDTHPTTGSASPKHQKSKLHGPTETSSCSGAAP
TVEMDEELHYASLNFHGMNPSKDTSTEYSEVRTQ

10 (11) The transmembrane glycoprotein NMB (SwissProt ID **Q14956**)

>gil52694752|reflNP_001005340.1| transmembrane glycoprotein NMB isoform a precursor [Homo sapiens]

15 MECLYYFLGFLLLAARLPLDAAKRFHDVLGNERPSAYMREHNQLNGWSSDENDWNEKLYPVWKRGD
MRWKNSWKGGRRVQAVLTSDSPALVGSNITFAVNLI FPRCQKEDANGNIVYEKNCRNEAGLSADPYV
YNWTAWSESDSGENGTGQSHHNVFPDGKPFPHHPGWRRWNFIYVFHTLGQYFQKLGRCSVRVSVNT
ANVTLGPQLMEVTVYRRHGRAYVPIAQVKDVYVVDQIPVFVTMFQKNDNRNSSDETFLKDLPI MFD
VLIHDP SHFLNYSTINYKWSFGDNTGLFVSTNHTVNHTYVLNGTFSNLTVKAAAPGPCPPPPPPP
RPSKPTPSLATTLKSYDSNTPGPAGDNPLELSRIPDENCQINRYGHFQATITIVEGILEVNI IQMT
20 DVLMPVPWPESSLIDFVVT CQGSIPTEVCTIISDPTCEITQNTVCSPVDVDEMCLLTVRRTFNGSG
TYCVNLTLGDDTSLALTSTLISVPDRDPASPLRMANSALISVGCLAIFVTVISLLVYKKHKEYNPI
ENSPGNVVR SKGLSVFLNRAKAVFFPGNQEKDPLLKNQEFKGV S

(12) The adhesion molecule CD56 (SwissProt ID **P13591**)

>gil94420689|reflNP_000606.3| neural cell adhesion molecule 1 isoform 1 [Homo sapiens]

25 MLQTKDLIWTLFFLGTA VSLQVDIVPSQGEISVGESKFFLCQVAGDAKDKDISWFS PNGEKLTPNQ
QRISVVWNDDSSSTLT IYNANIDDAGIYKCVVTGEDGSESEATVN VKIFQKLMFKNAPT PQEFREG
EDAVIVCDVVS SLPPTI IWKHKGRD VILKKDVR FIVLSNNYLQIRGIKKTDEGTYRCEGRILARGE
INFKDIQVIVNVPPTI QARQNI VNATANLGQSVTLVCD AEGFPEPTMSWTKDGEQIEQEE DDEKYI
FSDDSSQLTIKKVDKNDEAEYICIAENKAGEQDATIHLKVFAKPKITYVENQTAMELEE QVTLTCE
ASGDPIPSITWRTSTRNISSEEKTL DGHMVVRSHARVSSLTLKSIQYTDAGEYICTASNTIGQDSQ
30 SMYLEVQYAPKLQGPVAVYTWE GN
QVNITCEVFAYPSATISWFRD GQLLPSSNYSNIKIYNTPSASYLEVTPDSE NDFGNYNCTAVNRIG
QESLEFILVQADTPSSPSIDQVEPYSS TAQVQFDEPEATGGVPILKYKA EWRAVGEEVWH SKWYDA
KEASMEGI VTI VGLKPETTYAVRLAALNGKGLGEISAASEFKTQPVQGEPSAPKLEGQMGEDGNSI
KVNLIKQDDGGSPIRHYLVRYRALSSEWKPEIRLP SGSDHVMLKSLDWN AEYEVYVVAENQQGKSK
35 AAHFVFRTSAQPTAIPANGSPTSGLSTGAIVGILIVIFVLLLVVDITCYFLNKCGLFMCIAVNLC
GKAGPGAKGKDMEEGKAAF SKDESKEPIVEVRTEEERTPNHDGGKHTEPNETTPLTEPEKGPVEAK
PECQETETKPAPAEVKTVPN DATQTKENESKA

(13) The surface molecule CD70 (SwissProt ID **P32970**)

>gil4507605|reflNP_001243.1| CD70 antigen [Homo sapiens]

40 MPEEGSGCSVRRRPYGCVLRAALVPLVAGLVICLVVCIQRFAQAQQQLPLESLGWDVAELQLNHTG
PQQDPRLYWQGGPALGRSFLHGP ELDKGQLRIHRDGIYMVHIQVTLAICSSTTASRHHTT LAVGI
CSPASRSISLLRLSFHQGCTIASQRLTPLARGDTLCTNLTGTLLPSRNTDETFFGVQWVRP

(14) The surface molecule CD74 (SwissProt ID **P04233**)

>gil10835071|reflNP_004346.1| HLA class II histocompatibility antigen gamma chain isoform b [Homo sapiens]

MHRRRSRSCREDQKPVMDQDRDLISNNEQLPMLGRRPGAPESKCSR GALYTGF S I LV T L L L A G Q A T
TAYFLYQQQGR LDKLT VTSQNLQLENLRMKLPKPPKPVSKMRMATPLLMQALPMGALPQGPMQNAT
5 KYGNMTE DHVMHLLQNADPLKVYPPLKGSFPENLRHLKNTMETIDWKVFESWMHHWLLFEMSRHSL
EQKPTDAPPKESLELEDPSSGLGVTKQDLGPVPM

(15) The B-lymphocyte antigen CD19 (SwissProt ID P15391)

>gil296010921|reflNP_001171569.1| B-lymphocyte antigen CD19 isoform 1 precursor [Homo sapiens]

10 MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESPLKPF LKL S L
GLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGELFRWNVSDLGGL
GCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGEPPCLPPRDSL NQSL SQDLTMAPGSTLWL
SCGVPPDSVSRGPLSWTHVHPKGP KSL SLEL KDDRPARDMWV METGLLLPRATAQDAGKYYCHRG
NLTMSFHLEITARPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRKRKRMTDPT
15 RRFFKVT PPPGSGPQNQYGNVLSLPTPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSRSP
PGVGPEEEEEEGEGYEEDPSEEDSEFYENDSNLGQDQLSQDGSYENPEDEPLGPEDEDSFSNAESYE
NEDEELTQP VARTMDFLSPHGS AWDP SREATSLAGS QSYEDMRGILYAAPQLRSIRGQPGPNHEED
ADSYENMDNPDGPDPAWGGGGRMG TWSTR

(16) The surface protein mucin-1 (SwissProt ID P15941)

20 >gil65301117|reflNP_002447.4| mucin-1 isoform 1 precursor [Homo sapiens]
MTPGTQSPFFLLLLLLTVLTVVTGSGHASSTPGGEKETSATQRSSVPSSTEKNALSTGVSFFFLSFH
ISNLQFNSSLED PSTDYQELQ RDI SEMFLQIYKQGGFLGLSNIKFRPGSVVVQLTLAFREGTINV
HDVETQFNQYKTEAASRYNLTISDVSVSDVPFPFSAQSGAGVPGWGIALLVLCVLVALAIVYLIA
LAVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTHGRYVPPSSTD RSPYEKVSAGNGGSSLSY TNP
25 AVAATSANL

(17) The surface protein CD138 (SwissProt ID P18827)

>gil29568086|reflNP_002988.3| syndecan-1 precursor [Homo sapiens]

30 MRRAALWLWL CALALSLQPALPQIVATNLPPEDQDGSGDDSDNFSGSGAGALQDITLSQQTPSTWK
DTQLLTA IPTSPEPTGLEATAASTSTLPAGEGPKEGEAVVLPEVEPGLTAREQEATPRPRETTQLP
TTHQASTTTATTAQE PATSHPHRDMQPGHETSTPAGPSQADLHTPHTEDGGPSATERAAEDGASS
QLPAAEGSGEQDFTFETSGENTAVVAVEPDRRNQSPVDQGATGASQGLLDRKEVLGGVIAGGLVGL
IFAVCLVGFMLYRMKKKDEGSYSLEEPKQANGGAYQKPTKQEEFYA

(18) The integrin alphaV (Genbank Accession No.: NP_002201.1)

>gil4504763|reflNP_002201.1| integrin alpha-V isoform 1 precursor [Homo sapiens]

35 MAFPPRRRLRLGPRGLPLLLSGLLLPLCRAFNLDVDSPA EYSGPEGSYFGFAVDFFVPSASSRMFL
LVGAPKANTTQPGIVEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWFGASVRSKQ
DKILACAPLYHWRTEMKQEREPVGTCLQDGTKTVEYAPCRSQDIDADGQGFCQGGFSIDFTKADR
VLLGGPGSFYWQQQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAI FDDSYLGYSVAVGDFNGD
GIDDFVSGVPRAARTLGMVYIYDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYADVFI GAPLF
40 MDRGSDGKLQEVGQVS VSLQRASGDFQTTKLN GFV FARFGSAIAPLGDL DQDGFNDIAIAAPYGG
EDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSMPPSFGYSMKGATDIDKNGYPDLIVGAFGV DRA
ILYRARPVITVNAGLEVYPSILNQDNKTC SLPGTALKVSCFNVRFC LKADGKGVLPRKLN FQVELL
LDK LKQKGAI RRALFLYSRSPSHSKNMTISRGGMLQCEELIAYLRDESEFRDKLTPITIFMEYRLD
YRTAADTTGLQPI LNQFTPANISRQAHILLDCGEDNVCKPKLEVSVDSDQKKIYIGDDNPLTLIVK
45 AQNQGE GAYEAELIVSIPLQADFIGVVRNNEALARLSCAFKTENQTRQVVC DLGNPMKAGTQ LLAG

LRFSVHQQSEMDTSVKFDLQIQSSNLFDKVSPVVS HKVDLAVLAAVEIRGVSSPDHIFLPIPNWEH
KENPETEEDVGPVVQHIYELRNNGPSSFSKAMLHLQWPKYNNNTLLYILHYDIDGPMNCTSDMEI
NPLRIKISSLQTTEKNDTVAGQGERDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQVGRDLDRGKS
AILYVKSLLTWTFMKNENQNHSSYLSKSSASFNVIEFPYKNLP IEDITNSTLVTNTVTWGIQPAPM
5 PVPVWVILAVLAGLLLLAVLVFVMYRMGFFKRVRPPQEEQEREQLQPHENGEGNSET

(19) The teratocarcinoma-derived growth factor 1 protein TDGF1 (Genbank Accession No.: NP_003203.1)

>gi4507425|reflNP_003203.1| teratocarcinoma-derived growth factor 1 isoform 1 precursor
[Homo sapiens]

10 MDCRKMARFSYSVIWIMAI SKVFELGLVAGLGHQEFARPSRGYLAFRDDSIWPQEEPAIRPRSSQR
VPPMGIQHSKELNRTCCLNGGTCMLGSFCACPPSFYGRNCEHDVRKENC GSVPHDTWLPKKCSLCK
CWHGQLRCFPQAFLPGCDGLVMDEHLVASRTELPSPARTTTFMLVGICLSIQSY

(20) The prostate-specific membrane antigen PSMA (Swiss Prot ID: Q04609)

>gi4758398|reflNP_004467.1| glutamate carboxypeptidase 2 isoform 1 [Homo sapiens]

15 MWNLLHETDSAVATARRPRWLCAGALVLAGGFFLLGFLFGWFIKSSNEATNITPKHNMKAFLDELK
AENIKKFLYNFTQIPHLAGTEQNFQLAKQIQSQWKEFGLDSVELAHYDVLLSYPNKTHPNYISIIIN
EDGNEIFNTSLFEP PPPGYENVSDIVPPFSAFSPQGMPEGDLVYVNYARTEDFFKLERDMKINCSG
KIVARIYGVFRGNKVKNALAGAKGVILYSDPADYFAPGVKSYPDGWNLPGGGVQRGNIILNLNGA
GDPLTPGYPANAYARRGIAEAVGLPSIPVHPIGYDYDAQKLEKMGGSAPPDSSWRGSLKVYPYVNG
20 PGFTGNFSTQVKMHIHSTNEVTRIYNVIGTLRGAVEPDYVILGGHRDSWVFGGIDPQSGAAVH
EIVRSFGTLKKEGWRPRRTILFASWDAEEFLLGSTEWAEENSRLQERGVAYINADSSIEGNYTL
RVDCTPLMYSLVHNLTKELKSPDEGFEGKSLYESWTKKSPSPEFSGMPRIKLGSGNDFEVFFQRL
GIASGRARYTKNWETNKFSGYPLYHSVYETVELVEKFYDPMFKYHLTVAQVRGGMVFELANSIVLP
FDCRDYAVVLRKYADKIYSISMKHPQEMKTVSVSFDLSFSAVKNFTEIASKFSERLQDFDKSNPIV
25 LRMMNDQLMFLERAFIDPLGLPDRPFYRHVIYAPSSHNKYAGESFPGIYDALFDIESKVDPSKAWG
EVKRQIYVAAFTVQAAAETLSEVA

(21) The tyrosine protein kinase EPHA2 (Swiss Prot ID: P29317)

>gi3296731|reflNP_004422.2| ephrin type-A receptor 2 precursor [Homo sapiens]

MELQAARACFALLWGCALAAAAAQQKEVVLLDFAAAGGELGWLTHPYGKGWDLMQNIMNDMPIYM
30 YSVCNVMSGDQDNWLR TNWVYRGEAERIFIELKFTVRDCNSFPGGASSCKETFNLYYAESDLDYGT
NFQKRLFTKIDTIAPDEITVSSDFEARHVKNLVEERSVGPLTRKGFYLAQDQIGACVALLSVRVYY
KKCEPELLQGLAHFPETIAGSDAPSLATVAGTCVDHAVVPPGGEEPRMHCAVDGEWLVPIGQCLCQA
GYEKVEDACQACSPGFFKFEASESPCLECEHTLPSPGATSCECEEGFFRAPQDPASMPCTRPPS
APHYLTAVGMGAKVELRWTPPQDSGGREDIVYSVTCEQCWPESGECGPCEASVRYSEPPHGLTRTS
35 VTVSDLEPHMNYTFTVEARNGVSGLVTSRSFRTASVSINQTEPPKVRLEGRSTTSLSVSWSIPPPQ
QSRVWKYEVYRKKGDSNSYNVRTEGFSVTLDDLPDTTYLVQVQALTQEGQGAGSKVHEFQTL
PEGSGNLAVIGGVAVGVVLLLVLAGVGFFIHRRRKNQRARQSPEDVYFSKSEQLKPLKTYVDPHTY
EDPNQAVLKFTTEIHPSCVTRQKVI GAGEFGEVYKGMKLTSSGKKEVPVAIKTLKAGYTEKQRVDF
LGEAGIMGQFSHHNIIRLEGVISKYKPMIITEYMENGALDKFLREKDGFE SVLQLVGMLRGIAAG
40 MKYLANMNYVHRDLAARNILVNSNLVCKVSDFGLSRVLEDDPEATYTTSGGKIPIRWTAPAEISYR
KFTSASDVWSFGIWMVEVMTYGERPYWELSNHEVMKAINDGFR LPTPMDCPSAIYQLMMQCWQQR
ARRPKFADIVSILDKLIRAPDSLKT LADFDPVRSIRLPSTSGSEGVPFRTVSEWLESIKMQQYTEH
FMAAGYTAIEKVVQMTNDDIKRIGVRLPGHQKRIAYSLLGLKDQVNTVGIP I

(22) The surface protein SLC44A4 (Genbank Accession No: NP_001171515)

45 >gi295849282|reflNP_001171515.1| choline transporter-like protein 4 isoform 2 [Homo sapiens]

MGGKQRDEDDEAYGKPVKYDPSFRGPIKNRSCTDVICCVLFLLFILGYIVVGIVAWLYGDPRQVLY
PRNSTGAYCGMGENKDKPYLLYFNIFSCILSSNIISVAENGLQCPTPQTVITSLQQELCPSFLLPS
APALGRCFPWTNVTTPALPGITNDTTIQQGISGLIDSLNARDISVKIFEDFAQSWYWILVALGVAL
VLSLLFILLRLVAGPLVLVLILGVLGVLAYGIYYCWEEYRVLRDKGASISQLGFTTNLSAYQSVQ
5 ETWLAALIVLAVLEAILLLMLIFLRQRIRIAIALKEASKAVGQMMSTMFYPLVTFVLLLCIAYW
AMTALYLATSGQPQYVLWASNISPGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRS
VFNLQIYGVLGFLFWTLNWVLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAF
GALILTLVQIARVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNF
CVSAKNAFMLLMRNIVRVVLDKVTDLLLFFGKLLVGGVGVLSEFFFSGRIPGLGKDFKSPHLNY
10 YWLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYYSKSLKILGKNEAP
PDNKKRKK

- (23) The surface protein BMPR1B (SwissProt: O00238)
- (24) The transport protein SLC7A5 (SwissProt: Q01650)
- (25) The epithelial prostate antigen STEAP1 (SwissProt: Q9UHE8)
- 15 (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)
- 20 (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)
- 25 (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)
- 30 (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)
- 5 (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)
- 10 (51) The T-cell protein VTCN1 (SwissProt: Q7Z7D3).

In one preferred subject of the invention the cancer target molecule is selected from the group consisting of the cancer target molecules (1) – (51).

- 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) –
- 15 (51).

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).

- In one particularly preferred subject of the invention the cancer target molecule is selected from
- 20 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), more particularly C4.4a (NP_055215.2).

- 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),
- 25 mesothelin (Q13421-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; Q16790), more particularly C4.4a (NP_055215.2).

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 (Q13421-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; Q16790)), more particularly C4.4a (NP_055215.2).

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.

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.

Preferred antibody mimetics are affibodies, adnectins, anticalins, DARPs, avimers, or nanobodies. Preferred multispecific antibodies are bispecific and trispecific antibodies.

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.

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.

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.

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 Kimrnel (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 Biology, (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 (1988), 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

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:

25 Cetuximab light chain (kappa):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKAYASESISGIPSRFSGSG
SGTDFTLINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEEKHKVYACEVTH
QGLSPVTKSFNRGEC

30 Cetuximab heavy chain:

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTPTFTSR
LSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLTQVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
35 VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

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 10-11M.

10 Sequence:

Panitumumab light chain (kappa):

DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSG
SGTDFFTFISSLQPEDIAITYFCQHFHDLPLAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLSKADYEKHKVYACEVTH
15 QGLSSPVTKSFNRGEC

Panitumumab heavy chain:

QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLK
SRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGMVTVSSASTKGPSVFPLAP
CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQ
20 TYTCNVDPKPSNTKVDKTVKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDV
SHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPI
EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPML
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG

Nimotuzumab (INN number 8545) (EP 00586002, EP 00712863) is a humanized monoclonal IgG1
25 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.

30 Further embodiments of EGFR antibodies are as follows:

- Zalutumumab / 2F8 / HuMax-EGFr, from Genmab A/S (WO 02/100348, WO 2004/056847, INN number 8605)
- Necitumumab / 11F8, ImClone / IMC-11F8, from ImClone Systems Inc. [Eli Lilly & Co] (WO 2005/090407 (EP 01735348-A1, US 2007/0264253-A1, US 7,598,350, WO 2005/090407-A1), INN number 9083)

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- 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))
- RG-7160 / GA-201 / GA201 / R-7160 / R7160 / RG7160 / RO-4858696 / RO-5083945 / RO4858696 / RO5083945, from Glycart Biotechnology AG (Roche Holding AG) (WO 2010/112413-A1, WO 2010/115554)
- 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))
- ISU-101, from Isu Abxis Inc (ISU Chemical Co Ltd) / Scancell (WO 2008/004834-A1)
- 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)
- SYM-004 (consists of two chimeric IgG1 antibodies (992 and 1024)), from Symphogen A/S (WO 2010/022736-A2)
- MR1-1 /MR1-1KDEL, from IVAX Corp (Teva Pharmaceutical Industries Ltd) (Duke University), (Patent: WO2001/062931-A2)
- Antibody against the deletion mutant, EGFRvIII, from Amgen/Abgenix (WO 2005/010151, US 7,628,986)
- SC-100, from Scancell Ltd (WO 01/088138-A1)
- 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)
- Anti-EGFR-Mab, from Xencor (WO 2005/056606)
- DXL-1218 / anti-EGFR monoclonal antibody (cancer), InNexus, from InNexus Biotechnology Inc., Pharmaprojects PH048638

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.

In one particularly preferred embodiment the anti-EGFR antibodies are selected from the group consisting of cetuximab, panitumumab, nimotuzumab, zalutumumab, necitumumab and matuzumab.

5 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.

In a further embodiment, the anti-EGFR antibodies or antigen-binding antibody fragments are selected from the group consisting of

10 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.

In another embodiment the anti-EGFR antibodies or antigen-binding antibody fragments are selected from the group consisting of

15 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

20 Examples of antibodies which bind the cancer target molecule carbonahydrase IX are described in WO 2007/070538-A2 (e.g. Claims 1 – 16).

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
25 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).

In one preferred embodiment the anti-carboanhydrase IX antibodies or antigen-binding antibody
30 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),

5 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),

10 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),

15 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),

20 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),

25 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).

30

The here-indicated sequences of the CDR regions are disclosed in Figures 2a – 2c, page 128-130 in WO 2007/070538-A2.

In one preferred embodiment the anti-carboanhydrase IX antibodies or antigen-binding antibody fragments are selected from the group consisting of:

5 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 Figure 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
10 Figure 4c on page 138 and in Figure 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 Figure 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
15 Figure 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 Figure 4a on page 136,

20 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 Figure 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
25 Figure 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 Figure 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
30 Figure 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 Figure 4b on page 137.

In one particularly preferred embodiment the anti-carboanhydrase IX antibody is antibody 3ee9
5 from WO 2007/070538-A2.

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: GISSLGSTTTYADSVKG; VH3-CDR3: TGSPGTFMHGDH, see Figure 2a, page 128 in
10 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 Figure 2b, page 129 in WO 2007/070538-A2).

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
15 antibody 3ee9

(VH3:ELVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSGISSLGSTTTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARTGSPGTFMHGDHWGQGTL VTVSS, see Figure 4b, page 137 in WO 2007070538-A2) and the amino acid sequences of the variable light chain of the antibody 3ee9
20 (VLk1:DIQMTQSPSSLSASVGDRVTITCRASQDINNYLSWYQQKPGKAPKLLIYGASNLQSG VPSRFSGSGSGTDFTLTISLQPEDFAVYYCQQYYGRPTTFGQGTKVEIKRT, see Figure 4b, page 137 in WO 2007070538-A2).

In one preferred embodiment the anti-carboanhydrase IX antibody 3ee9 is an IgG antibody.

In one particularly preferred embodiment the anti-carboanhydrase IX antibody 3ee9 is an IgG1
25 antibody (3ee9-IgG1),

where the amino acid sequence of the heavy chain comprises the following sequence:

QVELVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSGISSLGSTTTYADSVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCARTGSPGTFMHGDHWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
30 TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

and the amino acid sequences of the light chain comprises the following sequence:

DIQMTQSPSSLSASVGDRVTITCRASQDINNYLSWYQQKPGKAPKLLIYGASNLQSGVPSRFSGSG
SGTDFTLTITSSLPEDFAVYYCQQYYGRPTTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACEVTH
5 QGLSSPVTKSFNRGEC

anti-carboanhydrase IX antibody 3ee9-IgG1:

A further aspect of the present invention is the provision of the anti-carboanhydrase IX antibody 3ee9-IgG1.

C4.4a antibodies:

- 10 Binders particularly preferred in accordance with the invention are anti-C4.4a antibodies, more particularly human or humanized anti-C4.4a antibodies. The antibodies preferably have an affinity of at least 10^{-7} M (as K_d value; in other words preferably those with smaller K_d 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 K_d values may be determined, for example, by means of surface plasmon resonance spectroscopy.
- 15 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).

- 20 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).
- 25 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
30 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.

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
5 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,
10 more particularly by a factor of not more than ten, from the affinity for the human target protein.

Anti-C4.4a antibodies are described for example in WO 01/23553 or WO 2011070088. These antibodies can be used in accordance with the invention.

Examples of C4.4a antibodies and antigen-binding fragments are described below. The sequences
15 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.

20 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.

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).

In one embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments thereof, after
25 binding to a cell which expresses C4.4a, are internalized by the cell.

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
30 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.

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.

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.

- 5 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.

- 10 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.

In another embodiment the CDR sequences of the anti-C4.4a antibodies or antigen-binding antibody fragments comprise

- 15 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

- 20 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).

- 25 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.

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.

- 30 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.

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.

In one preferred embodiment the C4.4a antibodies and the antigen-binding antibody fragments are selected from the group consisting of

- 5 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
- 10 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 and 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
- 15 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),
- 20 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
- 25 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
- 30 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),

5 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),

10 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).

15 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),

20 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),

25 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),

30 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),

35 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).

In another embodiment the anti-C4.4a antibodies comprise the light chain and the heavy chain of an antibody given in Table 2.

In one preferred embodiment the anti-C4.4a antibodies comprise the light chain and the heavy chain of an antibody given in Table 2.

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	SEQ ID NO: VH Protein	SEQ ID NO: VL Protein	SEQ ID NO: VH Nucleotide	SEQ ID NO: VL Nucleotide
M31-B01	5	9	13	17	21	25	33	29	41	37
M20-D02 S-A	6	10	14	18	22	26	34	30	42	38
M60-G03	7	11	15	19	23	27	35	31	43	39
M36-H02	8	12	16	20	24	28	36	32	44	40
B01-3	45	46	47	48	49	50	51	52	53	54
B01-5	55	56	57	58	59	60	61	62	63	64
B01-7	65	66	67	68	69	70	71	72	73	74
B01-10	75	76	77	78	79	80	81	82	83	84
B01-12	85	86	87	88	89	90	91	92	93	94
D02-4	95	96	97	98	99	100	101	102	103	104
D02-6	105	106	107	108	109	110	111	112	113	114
D02-7	115	116	117	118	119	120	121	122	123	124
D02-11	125	126	127	128	129	130	131	132	133	134
D02-13	135	136	137	138	139	140	141	142	143	144
B01-nn1	145	146	147	148	149	150	151	152	308	309
B01-nn2	153	154	155	156	157	158	159	160	310	311
B01-nn3	161	162	163	164	165	166	167	168	312	313
B01-nn4	169	170	171	172	173	174	175	176	314	315

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	SEQ ID NO: VH Protein	SEQ ID NO: VL Protein	SEQ ID NO: VH Nucleotide	SEQ ID NO: VL Nucleotide
B01-nn5	177	178	179	180	181	182	183	184	316	317
B01-2	185	186	187	188	189	190	191	192	318	319
B01-4	193	194	195	196	197	198	199	200	320	321
B01-6	201	202	203	204	205	206	207	208	322	323
B01-8	209	210	211	212	213	214	215	216	324	325
B01-9	217	218	219	220	221	222	223	224	326	327
B01-11	225	226	227	228	229	230	231	232	328	329
B01-12	233	234	235	236	237	238	239	240	330	331
D02-ogl	241	242	243	244	245	246	247	248	332	333
D02-5	249	250	251	252	253	254	255	256	334	335
D02-8	257	258	259	260	261	262	263	264	336	337
D02-9	265	266	267	268	269	270	271	272	338	339
D02-10	273	274	275	276	277	278	279	280	340	341
D02-11	281	282	283	284	285	286	287	288	342	343
D02-12	289	290	291	292	293	294	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

Antibody	Light chain SEQ ID NO:	Heavy chain SEQ ID NO:
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
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:

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
5 in Table 2.

Mesothelin antibody

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
10 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).

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
15 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.

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
5 and the sequence of the light chain represented by the sequence SEQ ID NO:409.

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
10 SEQ ID NO: 411.

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.

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
15 binding.

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
20 described in WOv2009/068204-A1 (Table 7; page 61 – 63).

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
25 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
30 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

5 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).

In one particularly preferred embodiment the mesothelin antibodies or antigen-binding antibody fragments are selected from the group consisting of

10 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),

15 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),

20 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:

25 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
30 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.

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).

- 5 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).

- 10 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).

- 15 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.

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).

- 20 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).

- 25 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).

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).

- 30 An example of an antibody which binds the cancer target molecule CD19 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.

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
5 WO 2003/106495-A2, WO 2008/028686-A2. Examples of anti-mucin conjugates are disclosed in WO 2005/009369-A2.

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.

10 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 US 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
15 WO 2007/024536-A2.

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, US 7,318,924, WO 2003/083041-A2 and WO 2002/088170-A2. Examples of anti-TDGF1 conjugates are disclosed in WO 2002/088170-A2.

20 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.

Examples of antibodies which bind the cancer target molecule EPHA2, can be used for preparing a
25 conjugate and can be used for the treatment of cancer are disclosed in WO 2004/091375-A2.

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.

An example of an antibody which binds the cancer target molecule HLA-DOB is the antibody
30 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.

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.

5 The compounds of the invention possess valuable pharmacological properties and can be used for the prevention and treatment of diseases in humans and animals.

10 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-6.). 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, 15 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.

20 The compatibility of the ADCs with a stable 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.

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 C4.4a. The activity with 30 respect to tumour cells which do not express C4.4a is significantly weaker at the same time.

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.

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 myelogenous and hairy 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.

25 Preferred hyperproliferative diseases for anti-CA9 binder-drug conjugates

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.

5

Preferred hyperproliferative diseases for anti-EGFR binder-drug conjugates

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-parvicellular carcinomas, bronchial carcinoma), including preferably non-
10 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.

15

Preferred hyperproliferative diseases for anti-mesothelin binder-drug conjugates

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
20 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.

25

Preferred hyperproliferative diseases for anti-C4.4a binder-drug conjugates

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
30 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
35 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;
5 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.

10 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.

In the context of this invention the term "treatment" or "treat" is used in the conventional sense and means attending to, caring for and nursing a patient with the aim of combating, reducing, attenuating or alleviating an illness or health abnormality and improving the living conditions
15 impaired by this illness, such as, for example, with a cancer disease.

The present invention furthermore provides the use of the compounds of the invention for the treatment and/or prevention of diseases, in particular the abovementioned diseases.

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
20 abovementioned diseases.

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.

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
25 the compounds of the invention.

The anti-C4.4a 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 C4.4a expression. Treatment is administered more preferably to patients whose C4.4a expression in cancer cells is higher than in healthy cells.

30 One method of identifying patients who respond advantageously to an anti-C4.4a binder-drug conjugate for the treatment of cancer involves determining the C4.4a expression in cancer cells of the patient. In one embodiment the C4.4a expression is determined by C4.4a 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 C4.4a expression is determined by means of immunohistochemistry with an anti-C4.4a 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 C4.4a target protein.

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.

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, anzmec, 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 diftiox, 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, ethylol, 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-2 α , interferon-alpha-2 β , interferon-alpha-n1, interferon-alpha-n3, interferon-beta, interferon-gamma-1 α , 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,
 5 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, sizofiran, sobuzoxane, solu-medrol, streptozocin, strontium-89 chloride, synthroid,
 10 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,
 15 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-
 20 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,
 25 vapreotide, vatalanib, verteporfin, vinflunin, Z-100, zoledronic acid and combinations of these.

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:

aminogluthethimide, L-asparaginase, azathioprine, 5-azacytidine, bleomycin, busulfan, carboplatin,
 30 carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine,
 dactinomycin, daunorubicin, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, doxorubicin
 (adriamycin), epirubicin, epothilone and its derivatives, erythro-hydroxynonyladenine, ethinyl-
 estradiol, etoposide, fludarabin phosphate, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine mono-
 phosphate, 5-fluorouracil, fluoxymesterone, flutamide, hexamethylmelamine, hydroxyurea,
 35 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
5 and vinorelbine.

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
10 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.

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:

- 15 • 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;
- the possibility of employing the chemotherapeutics used in a lower dosage than in monotherapy;
- the possibility of a more tolerable therapy with few side effects compared with individual
20 administration;
- the possibility of treatment of a broader spectrum of tumour diseases;
- the achievement of a higher rate of response to the therapy;
- a longer survival time of the patient compared with present-day standard therapy.

The compounds according to the invention can moreover also be employed in combination with
25 radiotherapy and/or surgical intervention.

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.

The compounds of the invention can act systemically and/or locally. They can be administered in a
30 suitable manner for this purpose, such as for example orally, parenterally, pulmonally, nasally,

sublingually, lingually, buccally, rectally, dermally, transdermally, conjunctivally, otically or as an implant or stent.

The compounds of the invention can be administered in suitable administration forms for these administration routes.

- 5 Administration forms which function according to the prior art, release the compounds of the invention rapidly and/or in a modified manner and contain the compounds of the invention in crystalline and/or amorphized and/or dissolved form are suitable for oral administration, such as e.g. tablets (non-coated or coated tablets, for example with coatings which are resistant to gastric juice or dissolve in a delayed manner or are insoluble and control the release of the compound of the invention), films/oblates or tablets, which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatine capsules), film-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

- 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, lyophilizates or sterile powders.

- For the other administration routes e.g. inhalation medicament forms (including powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets, films/oblates or capsules for lingual, sublingual or buccal administration, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, sprinkling powders, implants or stents are suitable.

- 25 Oral and parenteral administration are preferred, in particular oral and intravenous administration.

- The compounds of the invention can be converted into the administration forms mentioned. This can be effected in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include inter alia carrier substances (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecyl sulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants, such as, for example, ascorbic acid),

colorants (e.g. inorganic pigments, such as, for example, iron oxides) and taste and/or odour correctants.

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
5 achieve effective results. In the case of oral administration the dosage is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg and very particularly preferably 0.1 to 10 mg/kg of body weight.

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
10 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.

The following working examples illustrate the invention. The invention is not limited to the
15 examples.

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:**

A431NS	human tumour cell line
A549	human tumour cell line
ABCB1	ATP-binding cassette sub-family B member 1 (synonym for P-gp and MDR1)
abs.	absolute
ADC	antibody-drug-conjugate
Ac	acetyl
aq.	aqueous, aqueous solution
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein, an efflux transporter
Boc	<i>tert</i> -butoxycarbonyl
br.	broad (in NMR)
Ex.	example
<i>ca.</i>	<i>circa</i> , approximately
CAIX	carboanhydrase IX
CI	chemical ionization (in MS)
d	doublet (in NMR)
d	day(s)
TLC	thin-layer chromatography
DCI	direct chemical ionization (in MS)
dd	doublet of a doublet (in NMR)
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMEM	Dulbecco's modified eagle medium (standardized nutrient medium for cell culture)
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulphoxide

DPBS, D-PBS, PBS	Dulbecco's phosphate-buffered saline solution PBS = DPBS = D-PBS, pH 7.4, from Sigma, No. D8537 Composition: 0.2 g KCl 0.2 g KH ₂ PO ₄ (anhydrous) 8.0 g NaCl 1.15 g Na ₂ HPO ₄ (anhydrous) make up to 1 l with H ₂ O
dt	doublet of a triplet (in NMR)
DTT	DL-dithiothreitol
EDC	<i>N</i> '-(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide hydrochloride
EGFR	epidermal growth factor receptor
EI	electron impact ionization (in MS)
ELISA	enzyme-linked immunosorbent assay
eq.	equivalent(s)
ESI	electrospray ionization (in MS)
ESI-MicroTofq	<u>ESI</u> - MicroTofq (name of the mass spectrometer, with ToF = time of flight and q = quadrupole)
FCS	foetal calf serum
Fmoc	(9 <i>H</i> -fluoren-9-ylmethoxy)carbonyl
sat.	saturated
GTP	guanosine 5'-triphosphate
h	hour(s)
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HCT-116	human tumour cell line
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulphonic acid
HOAc	acetic acid
HOBt	1-hydroxy-1 <i>H</i> -benzotriazole hydrate
HOSu	<i>N</i> -hydroxysuccinimide
HPLC	high-pressure, high-performance liquid chromatography
HT29	human tumour cell line
IC ₅₀	half-maximum inhibitory concentration
i.m.	intramuscular, administration into the muscle
i.v.	intravenous, administration into the vein
conc.	concentrated

LC-MS	liquid chromatography-coupled mass spectrometry
LLC-PK1 cells	Lewis lung carcinoma pork kidney cell line
L-MDR	human MDR1 transfected LLC-PK1 cells
m	multiplet (in NMR)
MDR1	multidrug resistance protein 1
min	minute(s)
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NCI-H292	human tumour cell line
NCI-H520	human tumour cell line
NMM	N-methylmorpholine
NMP	N-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectrometry
NMRI	mouse strain, originating from Naval Medical Research Institute (NMRI)
Nude mice	experimental animals
NSCLC	non-small cell lung cancer (non-parvicellular bronchial carcinoma)
PBS	phosphate-buffered saline solution
Pd/C	palladium on activated carbon
P-gp	P-glycoprotein, a transporter protein
PNGaseF	enzyme for sugar elimination
quant.	quantitative (for yield)
quart	quartet (in NMR)
quint	quintet (in NMR)
R _f	retention index (for TLC)
RT	room temperature
R _t	retention time (for HPLC)
s	singlet (in NMR)
s.c.	subcutaneous, administration beneath the skin
SCC-4	human tumour cell line
SCC-9	human tumour cell line
SCID mice	experimental mice with a severe combined immunodeficiency
t	triplet (in NMR)
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV	ultraviolet spectrometry

v/v	volume to volume ratio (of a solution)
Z	benzyloxycarbonyl

HPLC and LC-MS methods:**Method 1 (LC-MS):**

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8μ
5 50 mm x 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):

Instrument: Micromass QuattroPremier with Waters UPLC Acquity; column: Thermo Hypersil
10 GOLD 1.9μ 50 mm x 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):

Instrument: Micromass Quattro Micro MS with HPLC Agilent Series 1100; column: Thermo
15 Hypersil GOLD 3μ 20 mm x 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):

MS instrument: Micromass ZQ; HPLC instrument: HP 1100 Series; UV DAD; column:
20 Phenomenex Gemini 3μ 30 mm x 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):

Instrument: HP 1090 Series II; column: Merck Chromolith SpeedROD RP-18e, 50 mm x 4.6 mm;
preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm x 4.6 mm; injection
volume: 5 μl; eluent A: 70% HClO₄ 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):

Instrument: Waters 2695 with DAD 996; column: Merck Chromolith SpeedROD RP-18e, 50 mm x 4.6 mm; Ord. No.: 1.51450.0001, preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm x 4.6 mm; Ord. No.: 1.51470.0001, eluent A: 70% HClO₄ 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):

MS instrument: Waters ZQ; HPLC instrument: Agilent 1100 Series; UV DAD; column: Thermo Hypersil GOLD 3μ 20 mm x 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.

15 Method 8 (LC-MS):

MS instrument: Waters ZQ; HPLC instrument: Agilent 1100 Series; UV DAD; column: Thermo Hypersil GOLD 3μ 20 mm x 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):

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8μ 50 mm x 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):

Instrument: Agilent 1200 Series; column: Agilent Eclipse XDB-C18 5μ 4.6 mm x 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.

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 reagents 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):

Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 μ 30 x 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 $\rightarrow$ 1.2 min 5% A $\rightarrow$ 2.0 min 5% A oven: 50°C; flow rate: 0.60 ml/min; UV detection: 208 – 400 nm.

Method 12 (HPLC):

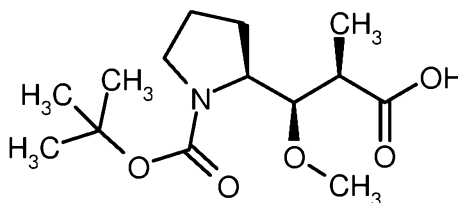
Instrument: Agilent 1200 Series with column oven and DAD; column: Merck Chromolith SpeedROD RP-18e, 50 mm x 4.6 mm; Ord. No.: 1.51450.0001; preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm x 4.6 mm; Ord. No.: 1.51470.0001; eluent A: 70% HClO₄ in water (4 ml/litre), eluent B: acetonitrile; gradient: 0.00 min 5% B $\rightarrow$ 0.50 min 5% B $\rightarrow$ 3.00 min 95% B $\rightarrow$ 4.00 min 95% B; flow rate: 5 ml/min; column temperature: 30°C.

Method 13 (LC-MS):

MS instrument: Waters (Micromass) Quattro Micro; Instrument HPLC: Agilent 1100 Series; column: YMC-Triart C18 3 μ 50 x 3 mm; eluent A: 1 l water + 0.01 mol ammonium carbonate, eluent B: 1 l acetonitrile; gradient: 0.0 min 100% A $\rightarrow$ 2.75 min 5% A $\rightarrow$ 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**

(2*R*,3*R*)-3-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Boc-dolaproine)



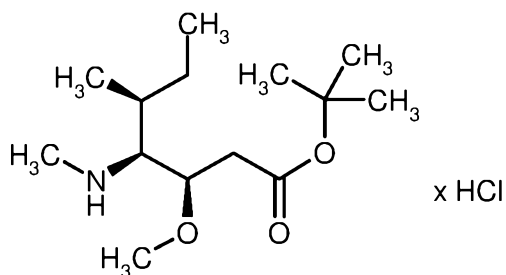
5

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.

10

Starting Compound 2a

tert-butyl (3*R*,4*S*,5*S*)-3-methoxy-5-methyl-4-(methylamino)heptanoate hydrochloride (dolaisoleucine-OtBu x HCl)



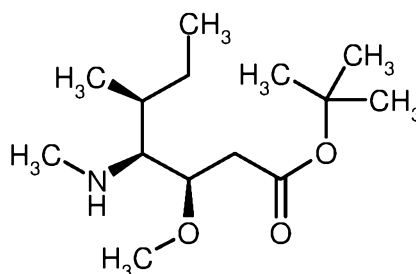
The title compound can be prepared in various ways according to literature methods; see, for example, Pettit *et al.*, *J. Org. Chem.* 1994, 59, 1796; Koga *et al.*, *Tetrahedron Lett.* 1991, 32, 2395; Shioiri *et al.*, *Tetrahedron Lett.* 1991, 32, 931; Shioiri *et al.*, *Tetrahedron* 1993, 49, 1913.

15

Starting Compound 2b

tert-butyl (3*R*,4*S*,5*S*)-3-methoxy-5-methyl-4-(methylamino)heptanoate (dolaisoleucine-O^tBu)

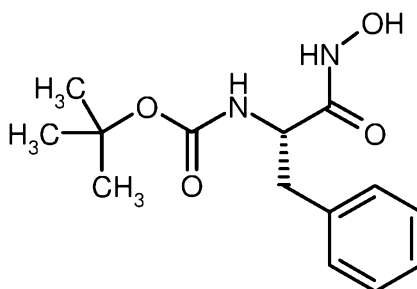
20



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

- 5 $N\alpha$ -(*tert*-butoxycarbonyl)-*N*-hydroxy-L-phenylalaninamide



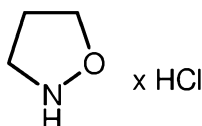
The title compound was prepared by the literature method (A. Ritter *et al.*, *J. Org. Chem.* 1994, 59, 4602).

Yield: 750 mg (75% of theory)

- 10 LC-MS (Method 3): $R_t = 1.67$ min; MS (ESIpos): $m/z = 281$ ($M+H$)⁺.

Starting Compound 4

1,2-oxazolidine hydrochloride

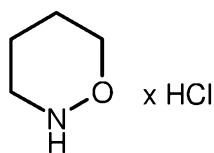


The title compound can be prepared by literature methods (see, for example, H. King, *J. Chem. Soc.* 1942, 432); it is also commercially available.

- 15

Starting Compound 5

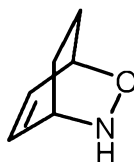
1,2-oxazinane hydrochloride



The title compound can be prepared by literature methods (see, for example, H. King, *J. Chem. Soc.* 1942, 432).

Starting Compound 6

- 5 2-oxa-3-azabicyclo[2.2.2]oct-5-ene

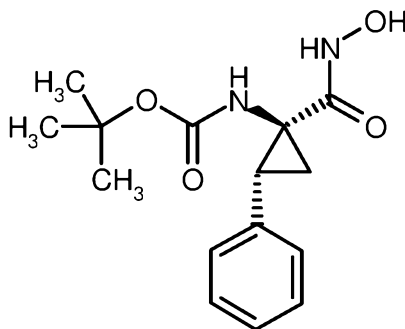


The title compound can be prepared in Boc-protected form by the literature method (see, for example, C. Johnson *et al.*, *Tetrahedron Lett.* 1998, 39, 2059); the deprotection was effected in a customary manner by treatment with trifluoroacetic acid and subsequent neutralization.

- 10 Yield: 149 mg (89% of theory)

Starting Compound 7

tert-butyl (1*S*,2*R*)-1-(hydroxycarbamoyl)-2-phenylcyclopropyl carbamate



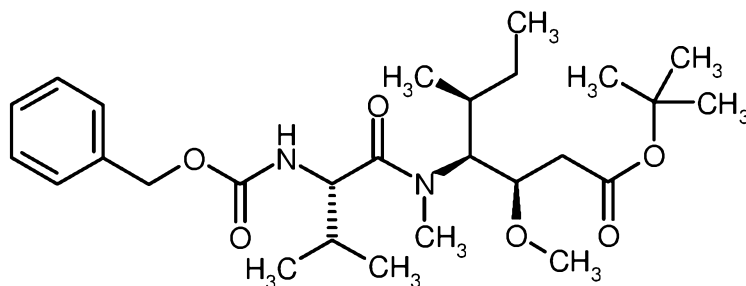
- 15 The title compound was prepared by a literature method (A. Ritter *et al.*, *J. Org. Chem.* 1994, 59, 4602) proceeding from commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid (C. Cativiela *et al.*, *Chirality* 1999, 11, 583).

Yield: 339 mg (59% of theory)

LC-MS (Method 1): $R_t = 0.82$ min; MS (ESIpos): $m/z = 293$ ($M+H$)⁺.

Intermediate 1

tert-butyl (3*R*,4*S*,5*S*)-4-[[*N*-[(benzyloxy)carbonyl]-*L*-valyl](methyl)amino]-3-methoxy-5-methylheptanoate



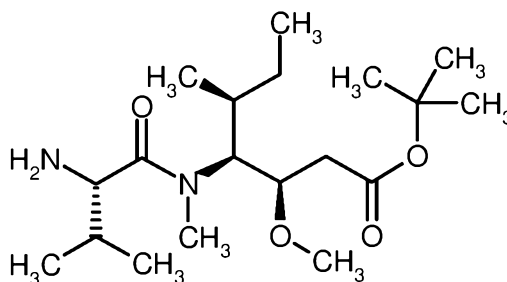
- 5 10.65 g (41.058 mmol) of *tert*-butyl (3*R*,4*S*,5*S*)-3-methoxy-5-methyl-4-(methylamino)heptanoate (starting compound 2b) were taken up in 250 ml of dichloromethane and the solution was cooled to -10°C. Then, while stirring, 10.317 g (41.058 mmol) of *N*-[(benzyloxy)carbonyl]-*L*-valine, 16.866 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.
- 10 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.

- 15 HPLC (Method 5): $R_t = 2.3$ min;

LC-MS (Method 2): $R_t = 1.59$ min; MS (ESIpos): $m/z = 493$ ($M+H$)⁺.

Intermediate 2

tert-butyl (3*R*,4*S*,5*S*)-3-methoxy-5-methyl-4-[methyl(*L*-valyl)amino]heptanoate



- 20 500 mg (1 mmol) of *tert*-butyl (3*R*,4*S*,5*S*)-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

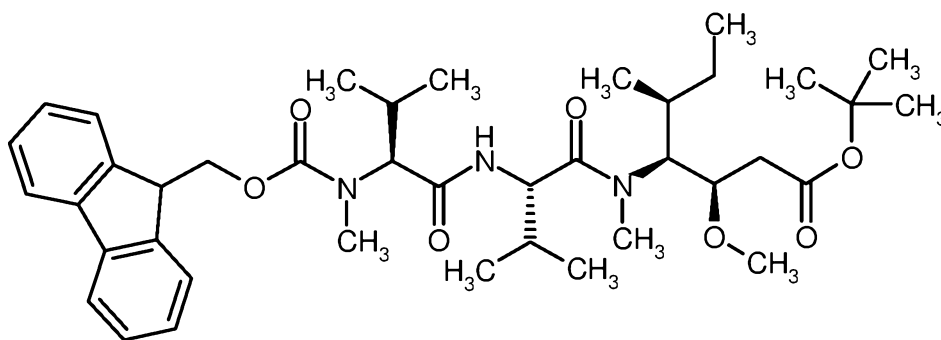
pressure at RT for 1 h. The catalyst was then filtered off and the solvent was removed under reduced pressure. This gave 370 mg (quant.) of the title compound as a virtually colourless oil.

HPLC (Method 5): $R_t = 1.59$ min;

LC-MS (Method 1): $R_t = 0.74$ min; MS (ESIpos): $m/z = 359$ (M+H)⁺.

5 **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



4.64 g (13.13 mmol) of *N*-[*(9H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valine were dissolved
10 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-1*H*-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
15 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.

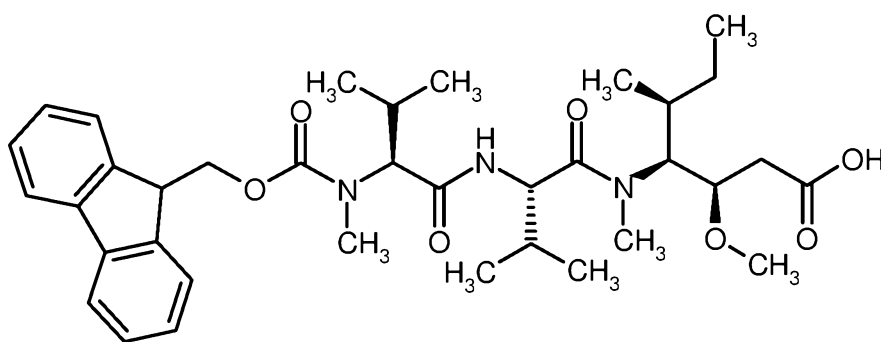
Yield: 9.1 g (quant., 60% purity)

20 HPLC (Method 5): $R_t = 2.7$ min;

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



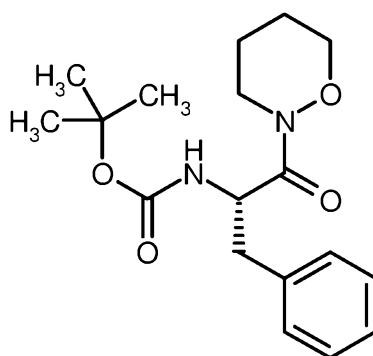
9.1 g of the crude product *N*-[*(9H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[*(3R,4S,5S)*-1-*tert*-butoxy-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 3) were taken up in 56.6 ml of dichloromethane, 56.6 ml of trifluoroacetic acid were added, and the mixture 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.

10 HPLC (Method 5): $R_t = 2.2$ min;

LC-MS (Method 1): $R_t = 1.3$ min; MS (ESIpos): $m/z = 638$ ($M+H$)⁺.

Intermediate 5

tert-butyl (2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl carbamate



15 500 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-oxazinan-2-yl hydrochloride (Starting Compound 5), 433 mg (2.3 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 382 mg (2.8 mmol) of 1-hydroxy-1*H*-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

20

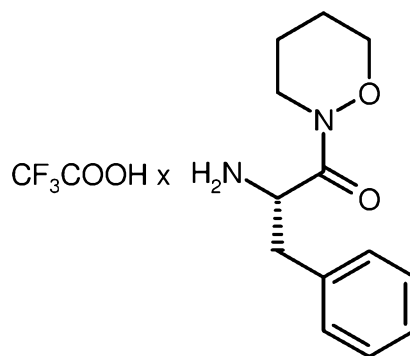
acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. 620 mg (98% of theory) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.8$ min;

- 5 LC-MS (Method 2): $R_t = 1.62$ min; MS (ESIpos): $m/z = 235$ ($M-C_4H_8-CO_2+H$)⁺.

Intermediate 6

(2*S*)-2-amino-1-(1,2-oxazinan-2-yl)-3-phenylpropan-1-one trifluoroacetate



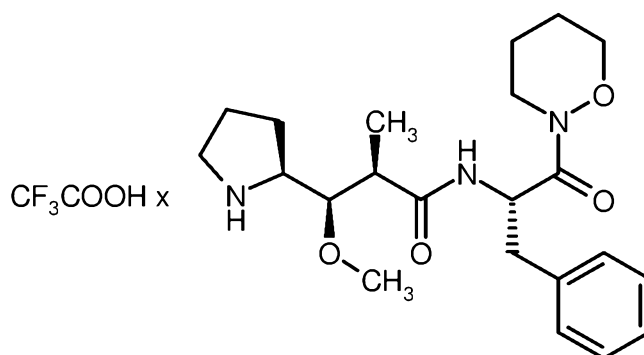
- 620 mg (1.85 mmol) of *tert*-butyl (2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl carbamate (Intermediate 5) were taken up in 5 ml of dichloromethane, 10 ml of trifluoroacetic acid were added and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under 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.

- 15 HPLC (Method 5): $R_t = 0.45$ min;

LC-MS (Method 3): $R_t = 1.09$ min; MS (ESIpos): $m/z = 235$ ($M+H$)⁺.

Intermediate 7

(2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2*S*)-pyrrolidin-2-yl]propanamide trifluoroacetate



360 mg (1.25 mmol) of (2*R*,3*R*)-3-[(2*S*)-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 (2*S*)-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 μ l 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 (2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino]-3-oxopropyl]pyrrolidine-1-carboxylate were obtained.

HPLC (Method 12): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 1.12$ min; MS (ESIpos): $m/z = 504$ ($M+H$)⁺.

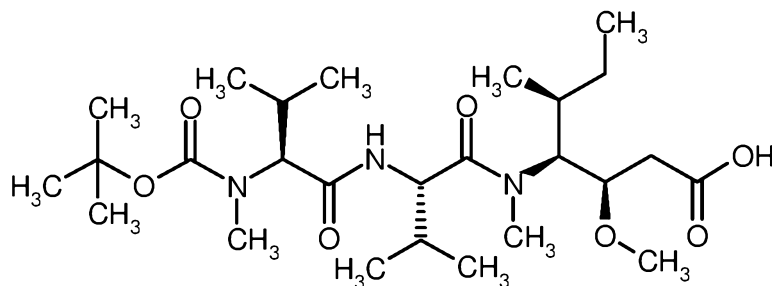
503 mg (1 mmol) of this intermediate were taken up in 20 ml of dichloromethane, 10 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and redistilled with dichloromethane. The remaining residue 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.

HPLC (Method 12): $R_t = 1.53$ min;

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*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide



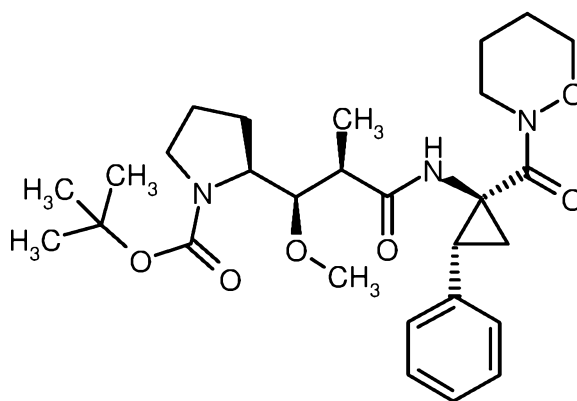
- 5 51 mg (0.08 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide (Intermediate 4) were dissolved in 10 ml of DMF, and 0.5 ml of piperidine was added. After stirring at RT for 10 min, the reaction 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
- 10 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
- 15 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.

- 20 HPLC (Method 6): $R_t = 2.2$ min;

LC-MS (Method 2): $R_t = 1.32$ min; MS (ESIpos): $m/z = 516$ ($M+H$)⁺.

Intermediate 9

tert-butyl (2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidine-1-carboxylate



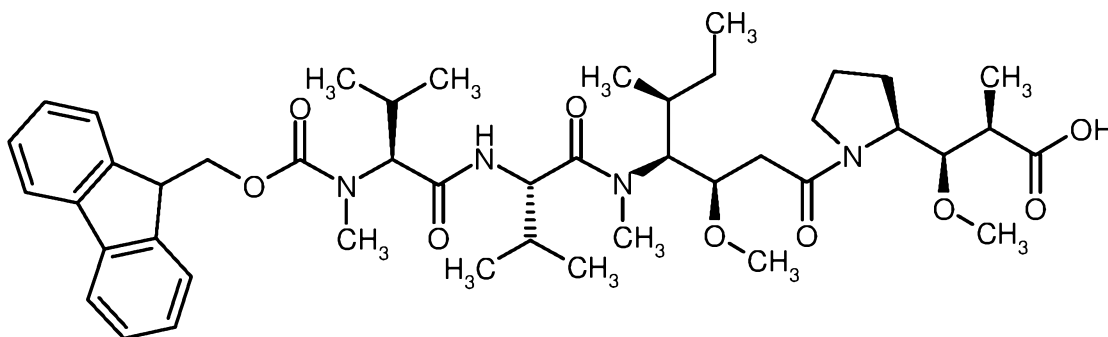
The title compound was prepared in analogy to the synthesis of Intermediates 5, 6 and 7 over three stages, by coupling of commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with 1,2-oxazinane hydrochloride (Starting Compound 5), subsequent deprotection with trifluoroacetic acid and coupling with Starting Compound 1. The end product was purified by preparative HPLC.

HPLC (Method 5): $R_t = 2.12$ min;

LC-MS (Method 2): $R_t = 1.25$ min; MS (ESIpos): $m/z = 516$ ($M+H$)⁺.

Intermediate 10

10 *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



315 mg (0.494 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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-1*H*-benzotriazole hydrate, and the mixture was stirred at RT for 90 min. Subsequently, 112 μ l of *N,N*-diisopropylethylamine and 149 mg (0.494 mmol) of (2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-

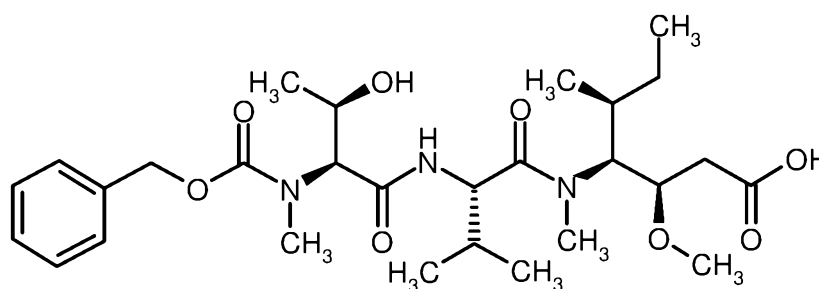
pyrrolidin-2-yl]propanoic acid trifluoroacetate, which had been prepared beforehand from Starting Compound 1 by elimination of the Boc protecting group by means of trifluoroacetic acid, were added. The mixture was stirred at RT for 2 h and then concentrated under high vacuum. The remaining residue was purified twice by preparative HPLC. 140 mg (35% of theory) of the title compound were obtained in the form of a colourless foam.

HPLC (Method 5): $R_t = 2.40$ min;

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*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide



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 (3*R*,4*S*,5*S*)-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-1*H*-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*-[(3*R*,4*S*,5*S*)-1-*tert*-butoxy-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were thus obtained.

HPLC (Method 5): $R_t = 2.17$ min.

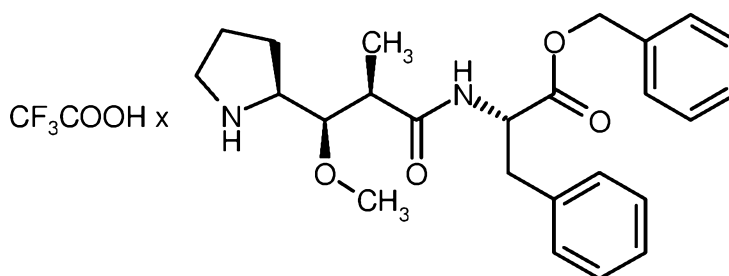
283 mg (0.466 mmol) of this intermediate were taken up in 5 ml of dichloromethane, 5 ml of anhydrous trifluoroacetic acid were added, and the mixture was stirred at RT for 2 h. Subsequently, the reaction mixture was concentrated under high vacuum and the remaining residue was purified by means of preparative HPLC. This gave 156 mg (61% of theory) of the title compound as a colourless foam.

HPLC (Method 5): $R_t = 1.50$ min;

LC-MS (Method 2): $R_t = 1.09$ min; MS (ESIpos): $m/z = 552$ (M+H)⁺.

Intermediate 12

benzyl *N*-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate



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.

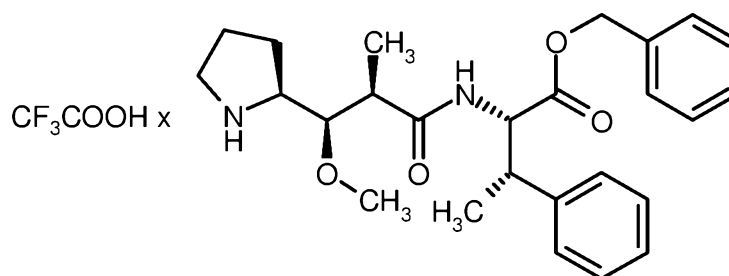
Yield: 650 mg (94% over 2 stages)

HPLC (Method 6): $R_t = 1.76$ min;

LC-MS (Method 2): $R_t = 1.68$ min; MS (ESIpos): $m/z = 425$ (M+H)⁺.

Intermediate 13

benzyl (β*S*)-*N*-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-β-methyl-L-phenylalaninate trifluoroacetate



First, (2*R*,3*R*)-3-[(2*S*)-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 (β *S*)- β -methyl-L-phenylalaninate trifluoroacetate [prepared from commercially available (β *S*)-*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 μ l 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 (β *S*)-*N*-{(2*R*,3*R*)-3-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoyl}- β -methyl-L-phenylalaninate.

HPLC (Method 6): R_t = 2.3 min;

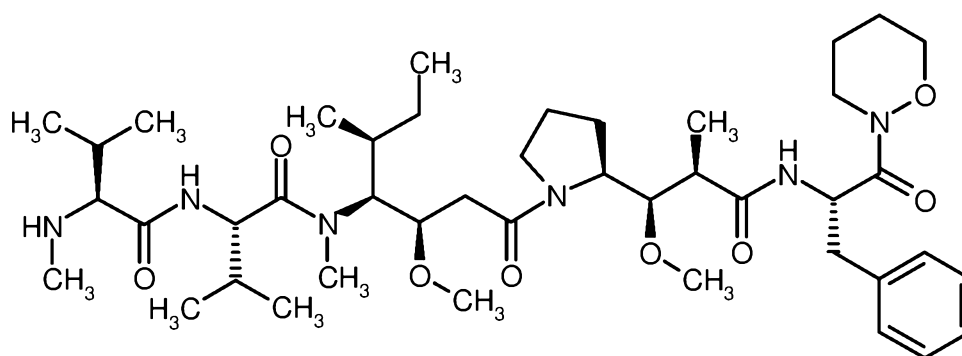
LC-MS (Method 1): R_t = 1.36 min; MS (ESIpos): m/z = 539 ($M+H$)⁺.

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.

HPLC (Method 6): R_t = 1.6 min.

Intermediate 14

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



x CF₃COOH

5

143 mg (0.223 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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 (2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2*S*)-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 μ l (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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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.

20 HPLC (Method 5): R_t = 2.73 min;

LC-MS (Method 4): R_t = 3.19 min; MS (ESIpos): m/z = 1023 ($M+H$)⁺.

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.

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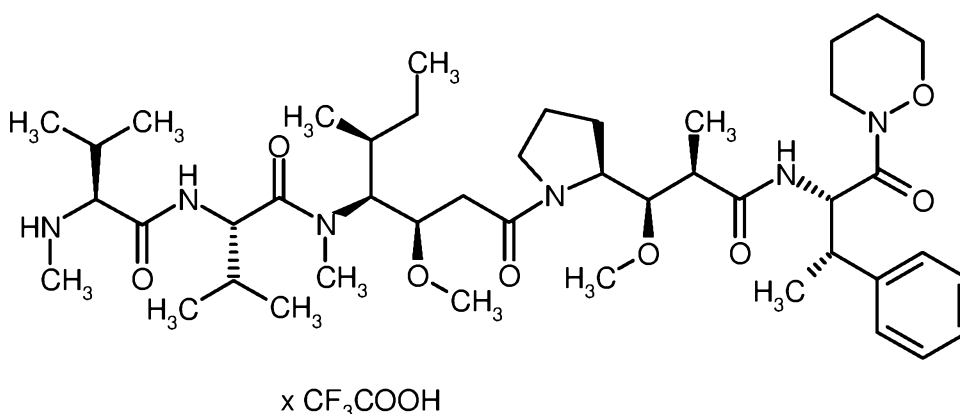
HPLC (Method 5): $R_t = 1.68$ min;

LC-MS (Method 2): $R_t = 1.03$ min; MS (ESIpos): $m/z = 801$ ($M+H$)⁺

¹H NMR (600 MHz, DMSO-*d*₆): $\delta = 8.8$ (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 H₂O peak].

Intermediate 15

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*,3*S*)-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



126 mg (0.198 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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 (2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(2*S*,3*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]-3-[(2*S*)-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-1*H*-benzotriazole hydrate and 79 μ l (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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*,3*S*)-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.

HPLC (Method 5): $R_t = 2.77$ min;

LC-MS (Method 1): $R_t = 1.5$ min; MS (ESIpos): $m/z = 1037$ ($M+H$)⁺.

5 220 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.

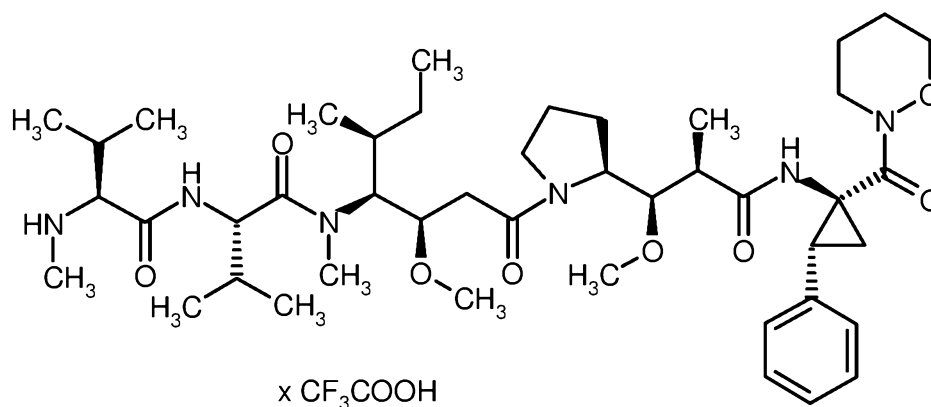
10 HPLC (Method 5): $R_t = 1.71$ min;

LC-MS (Method 1): $R_t = 0.9$ min; MS (ESIpos): $m/z = 815$ ($M+H$)⁺

¹H NMR (600 MHz, DMSO-d₆): $\delta = 8.87$ 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 H₂O peak].

Intermediate 16

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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



617 mg (1.2 mmol) of *tert*-butyl (2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 (2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]-3-[(2*S*)-pyrrolidin-2-yl]propanamide trifluoroacetate were
5 obtained as a crude product, which was used in the following stage without further purification.

470 mg (0.74 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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
10 (2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]-3-[(2*S*)-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 μ l (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.
15 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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide.
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HPLC (Method 5): R_t = 2.58 min;

LC-MS (Method 1): R_t = 3.10 min; MS (ESIpos): m/z = 1035 ($M+H$)⁺.

453 mg (0.438 mmol) of this intermediate were dissolved in 24 ml of DMF. After 2.4 ml of
25 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.

HPLC (Method 5): R_t = 1.64 min;

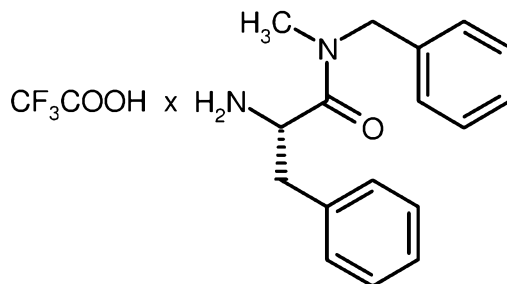
30 LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos): m/z = 813 ($M+H$)⁺

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 H₂O peak].

Intermediate 17

N-benzyl-*N*-methyl-L-phenylalaninamide trifluoroacetate



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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 μ l 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.

10
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HPLC (Method 6): R_t = 2.1 min;

LC-MS (Method 1): R_t = 1.14 min; MS (ESIpos): m/z = 369 (M+H)⁺.

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.

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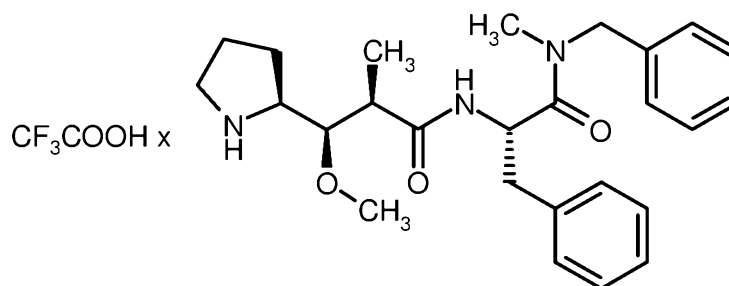
HPLC (Method 6): R_t = 1.6 min;

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LC-MS (Method 1): R_t = 0.6 min; MS (ESIpos): m/z = 269 (M+H)⁺.

Intermediate 18

N-benzyl-*N*^α-{[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-*N*-methyl-*L*-phenylalaninamide trifluoroacetate



- 5 First, (2*R*,3*R*)-3-[(2*S*)-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 μ l 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 (2*S*)-2-[(1*R*,2*R*)-3-((2*S*)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidine-1-carboxylate.
- 15
- 20

HPLC (Method 6): R_t = 2.2 min;

LC-MS (Method 2): R_t = 1.22 min; MS (ESIpos): m/z = 538 ($M+H$)⁺.

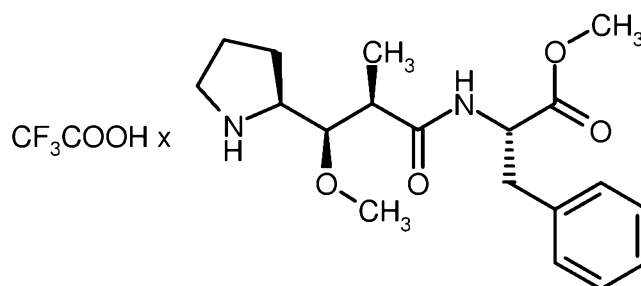
- 168 mg (0.312 mmol) of this intermediate were taken up in 15 ml of dichloromethane, 3 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was stirred first with dichloromethane, 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.
- 25

HPLC (Method 6): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.73$ min; MS (ESIpos): $m/z = 438$ ($M+H$)⁺.

Intermediate 19

5 methyl *N*-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate
trifluoroacetate



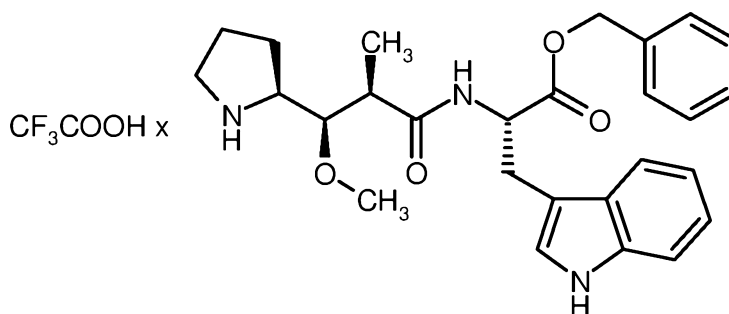
The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2*R*,3*R*)-3-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and methyl L-phenylalaninate hydrochloride.

HPLC (Method 5): $R_t = 0.6$ min;

LC-MS (Method 3): $R_t = 1.17$ min; MS (ESIpos): $m/z = 349$ ($M+H$)⁺.

Intermediate 20

15 benzyl *N*-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-L-tryptophanate
trifluoroacetate



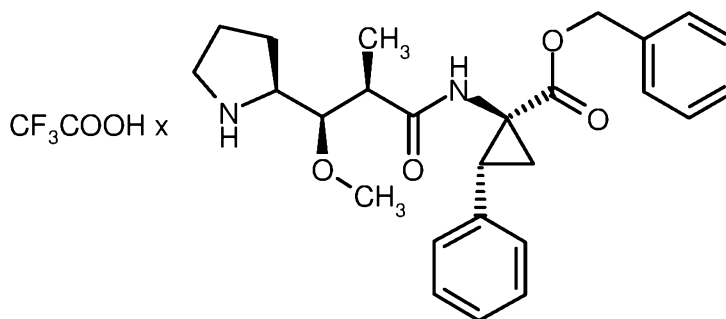
The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2*R*,3*R*)-3-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and benzyl L-tryptophanate.

HPLC (Method 6): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 0.8$ min; MS (ESIpos): $m/z = 464$ ($M+H$)⁺.

Intermediate 21

benzyl (1*S*,2*R*)-1-((2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl amino)-2-phenylcyclopropanecarboxylate trifluoroacetate



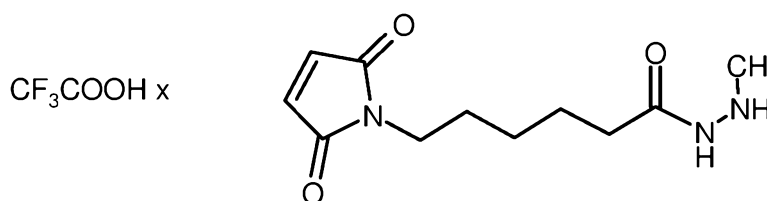
The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2*R*,3*R*)-3-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and benzyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate. Benzyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate had been prepared beforehand by standard methods, by esterifying commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with benzyl alcohol and subsequent Boc detachment with trifluoroacetic acid.

HPLC (Method 5): $R_t = 1.5$ min;

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-1*H*-pyrrol-1-yl)-*N*'-methylhexanehydrazide trifluoroacetate



100 mg (473 μ mol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoic acid were dissolved in 71 μ l of DMF and then admixed with 139 mg (947 μ mol) of *tert*-butyl 1-methylhydrazinecarboxylate, 182 mg (947 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 145 mg

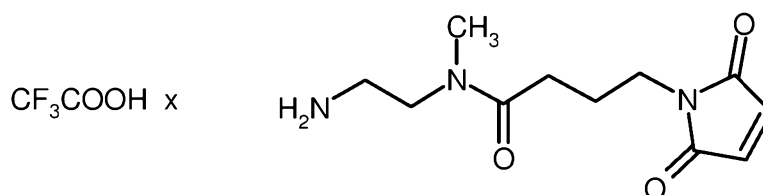
(947 μmol) of 1-hydroxy-1*H*-benzotriazole hydrate. The mixture was stirred at RT overnight and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane/water, 129 mg (80% of theory) of the protected intermediate were obtained as a colourless foam.

- 5 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.

LC-MS (Method 1): $R_t = 0.38$ min; MS (ESIpos): $m/z = 240$ ($M+H$)⁺

10 **Intermediate 23**

N-(2-aminoethyl)-4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-N-methylbutanamide trifluoroacetate



- First, 35 mg (164 μmol) of tert-butyl 2-(methyamino)ethyl carbamate hydrochloride trifluoroacetate, 30 mg (164 μmol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid, 75
15 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
20 intermediate were obtained.

HPLC (Method 12): $R_t = 1.6$ min;

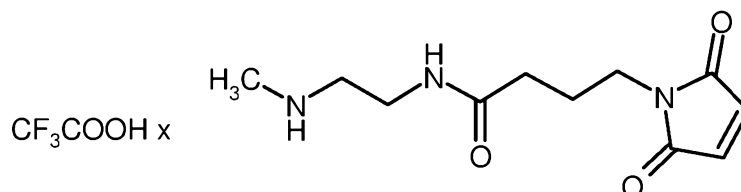
LC-MS (Method 1): $R_t = 0.71$ min; MS (ESIpos): $m/z = 340$ ($M+H$)⁺.

- 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
25 compound.

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-1*H*-pyrrol-1-yl)-*N*-[2-(methylamino)ethyl]butanamide trifluoroacetate



First, 35 mg (164 μ mol) of tert-butyl (2-aminoethyl)methyl carbamate hydrochloride
 5 trifluoroacetate, 30 mg (164 μ mol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid, 75
 mg (197 μ mol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
 and 57 μ l 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,
 10 by lyophilization from dioxane/water, 51 mg (91% of theory) of the protected intermediate were
 obtained.

HPLC (Method 12): R_t = 1.6 min;

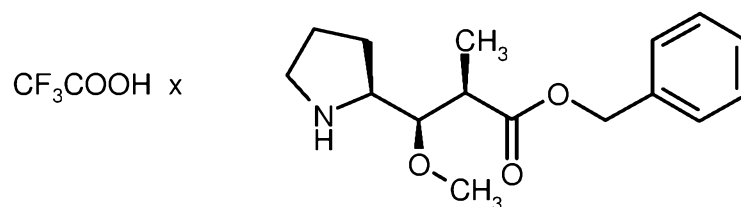
LC-MS (Method 1): R_t = 0.77 min; MS (ESIpos): m/z = 340 ($M+H$)⁺.

Subsequently, the entire amount was deprotected with 1 ml of trifluoroacetic acid in 5 ml of
 15 dichloromethane to obtain 45 mg (69% of theory) of the title compound.

LC-MS (Method 1): R_t = 0.19 min; MS (ESIpos): m/z = 240 ($M+H$)⁺.

Intermediate 25

benzyl (2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoate trifluoroacetate



20 First, (2*R*,3*R*)-3-[(2*S*)-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.

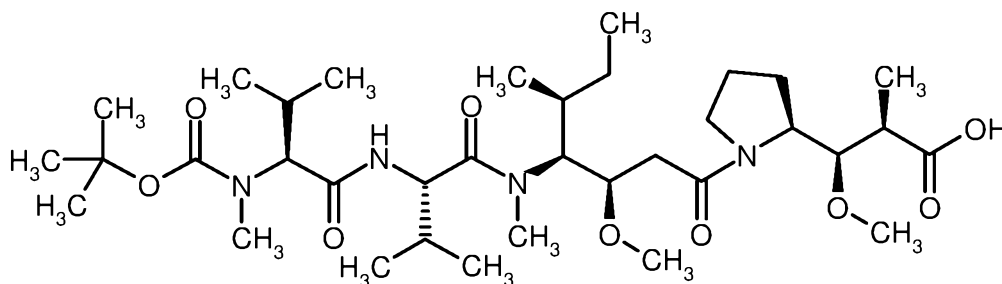
Subsequently, these 1170 mg were deprotected immediately with 5 ml of trifluoroacetic acid in 15 ml of dichloromethane. After stirring at RT for 15 min, the reaction mixture was concentrated under reduced pressure. The residue was lyophilized from dioxane. After drying under high vacuum, there remained 1333 mg (84% of theory) of the title compound as a yellow oil.

HPLC (Method 6): $R_t = 1.5$ min;

LC-MS (Method 1): $R_t = 0.59$ min; MS (ESIpos): $m/z = 278$ ($M+H$)⁺.

15 Intermediate 26

N-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



1200 mg (2.33 mmol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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 (2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-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 μ l 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-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.

- 5 LC-MS (Method 1): $R_t = 1.56$ min; MS (ESIpos): $m/z = 775$ ($M+H$)⁺.

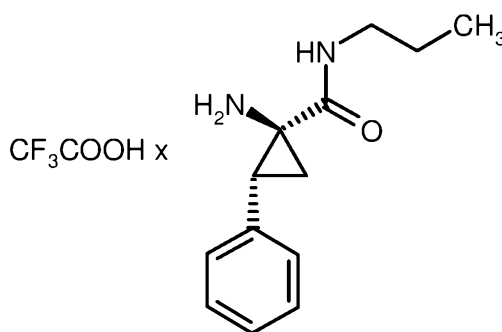
The entire amount of this intermediate obtained was taken up in 25 ml of a mixture of methanol and dichloromethane (20:1), and the benzyl ester group was removed by hydrogenation under standard hydrogen pressure with 10% palladium on activated carbon as a catalyst. After stirring at RT for 30 min, the catalyst was filtered off and the filtrate was concentrated under reduced
10 pressure. This gave 803 mg (91% of theory) of the title compound as a white solid.

HPLC (Method 6): $R_t = 2.1$ min;

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESIpos): $m/z = 685$ ($M+H$)⁺.

Intermediate 27

(1*S*,2*R*)-1-amino-2-phenyl-*N*-propylcyclopropanecarboxamide trifluoroacetate



15

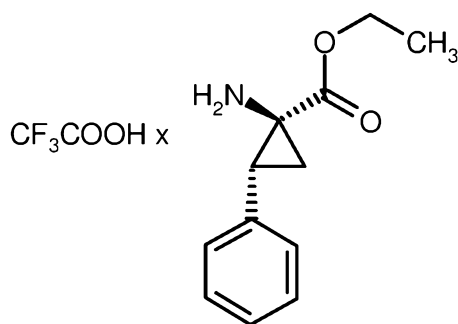
The title compound was prepared by coupling commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with *n*-propylamine in the presence of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and subsequent Boc detachment with trifluoroacetic acid (yield: 85% of theory over both stages).

- 20 HPLC (Method 6): $R_t = 1.2$ min;

LC-MS (Method 1): $R_t = 0.52$ min; MS (ESIpos): $m/z = 219$ ($M+H$)⁺.

Intermediate 28

ethyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate

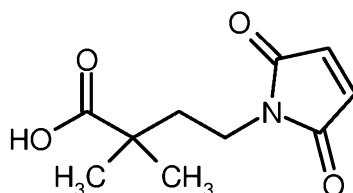


The title compound was prepared by standard methods, by esterifying commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with ethanol and subsequent Boc detachment with trifluoroacetic acid.

- 5 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-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoic acid

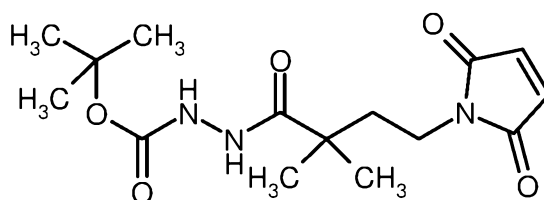


- To a solution of 1.39 g (8.95 mmol) of N-methoxycarbonylmaleimide in 44 ml of saturated sodium hydrogencarbonate solution were added, at 0°C, 1.5 g (8.95 mmol) of 4-amino-2,2-dimethylbutyric acid, and the mixture was stirred for 40 min. Subsequently, the cooling bath was removed and the reaction mixture 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.
- 10
15

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-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazinecarboxylate

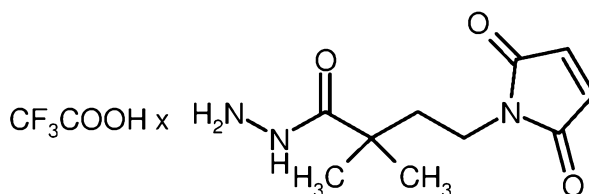


To a solution of 50 mg (237 μ mol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoic acid in 2 ml of THF were added, at 0°C, first 26 μ l (237 μ mol) of 4-methylmorpholine and then 31 μ l (237 μ mol) of isobutyl chloroformate. After removing the cooling bath and stirring at RT for a further 15 min, 31.3 mg (237 μ mol) 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.

LC-MS (Method 1): R_t = 0.71 min; m/z = 324 (M-H)⁻.

10 Intermediate 31

4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate

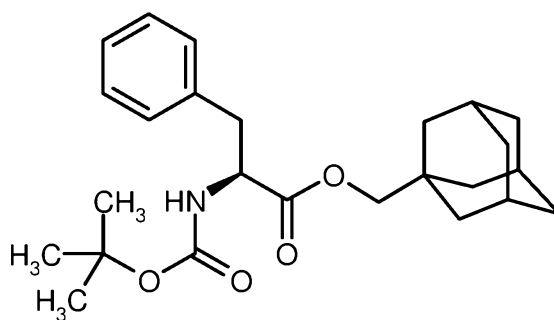


50 mg (154 μ mol) of *tert*-butyl 2-[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazinecarboxylate were dissolved in 2 ml of dichloromethane, and 0.4 ml of trifluoroacetic acid was added. The reaction mixture was stirred at RT for 30 min and then concentrated. 55.2 mg (93% purity, 99% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.36 min; m/z = 226 (M+H)⁺.

Intermediate 32

adamantan-1-ylmethyl *N*-(*tert*-butoxycarbonyl)-L-phenylalaninate

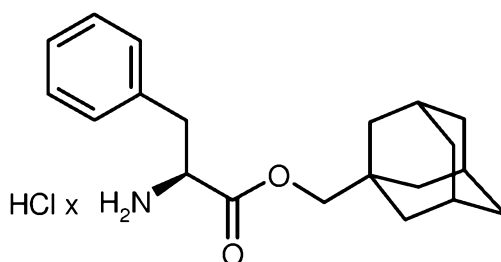


To a solution of 500 mg (1.89 mmol) of *N*-Boc-*L*-phenylalanine in 25 ml of dichloromethane were added, at RT, 1192 mg (6.2 mmol) of EDC, 578 μ l (4.1 mmol) of triethylamine, 345 mg (2.8 mmol) of DMAP and 345 mg (2.1 mmol) of 1-adamantylmethanol. The reaction mixture was stirred overnight, then diluted 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.

LC-MS (Method 2): R_t = 1.84 min; m/z = 414 ($M+H$)⁺.

10 **Intermediate 33**

adamantan-1-ylmethyl *L*-phenylalaninate hydrochloride

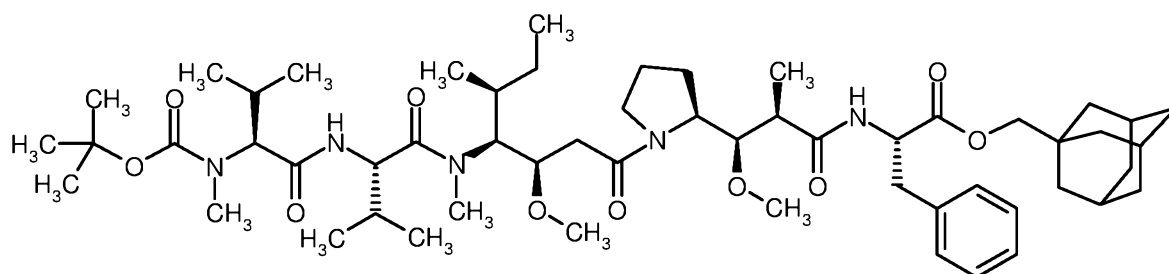


769 mg (1.86 mmol) of adamantan-1-ylmethyl *N*-(*tert*-butoxycarbonyl)-*L*-phenylalaninate (Intermediate 13) were dissolved in 25 ml of a 4 N solution of hydrogen chloride in dioxane and stirred at RT for 1 h. Subsequently, the reaction mixture was concentrated and the residue was dried under reduced pressure. 619 mg (95% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.82 min; m/z = 314 ($M+H$)⁺.

Intermediate 34

N-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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

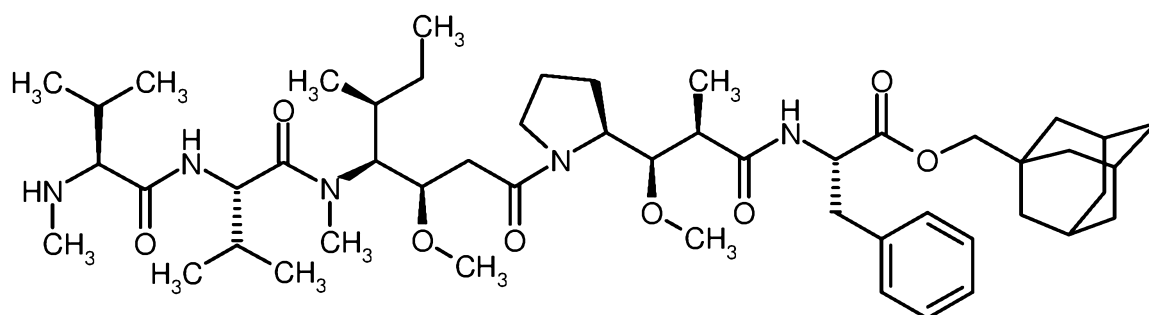


To a solution of 20 mg (29 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-
 5 4-yl]-*N*-methyl-L-valinamide in 1 ml of DMF were added, at RT, 15.3 μ l (88 μ mol) of *N,N*-
 diisopropylethylamine, 6.7 mg (44 μ mol) of HOBt and 6.7 mg (35 μ mol) of EDC, and the mixture
 was stirred for 30 min. Subsequently, 10.1 mg (32 μ mol) 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
 10 obtained.

LC-MS (Method 1): R_t = 1.70 min; m/z = 980 ($M+H$)⁺.

Intermediate 35

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(adamantan-1-ylmethoxy)-1-oxo-3-
 phenylpropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-
 15 methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide trifluoroacetate



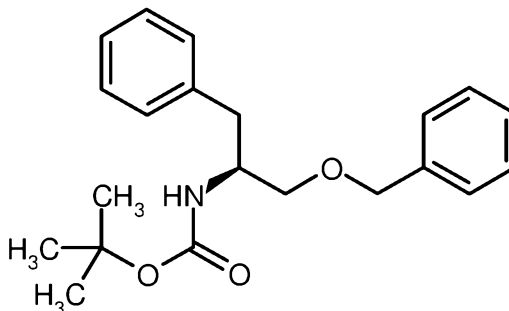
x CF₃COOH

27.5 mg (28 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-
 [(1*R*,2*R*)-3-[(2*S*)-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-
 20 valinamide were dissolved in 1.8 ml of dichloromethane, and 361 μ l 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.

LC-MS (Method 1): $R_t = 1.14$ min; $m/z = 880$ (M+H)⁺.

Intermediate 36

tert-butyl (2*S*)-1-(benzyloxy)-3-phenylpropan-2-yl carbamate

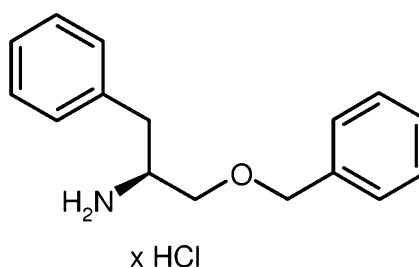


- 5 Under an argon atmosphere, 500 mg (1.99 mmol) of *N*-Boc-*L*-phenylalaninol were dissolved in 5 ml of DMF and cooled to 0°C. Subsequently, 159 mg (3.98 mmol) of a 60% suspension of sodium hydride in paraffin oil were added. The reaction mixture was stirred until the evolution of gas had ended and then 260 μ l (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
- 10 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.

LC-MS (Method 1): $R_t = 1.28$ min; $m/z = 342$ (M+H)⁺.

15 **Intermediate 37**

(2*S*)-1-(benzyloxy)-3-phenylpropan-2-amine hydrochloride

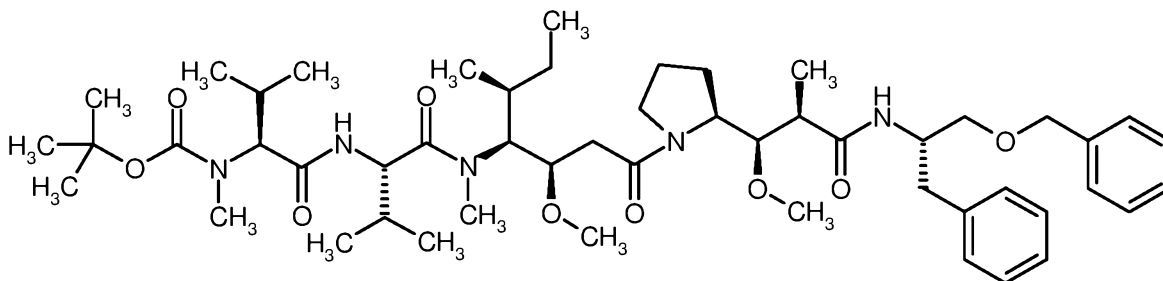


- 220 mg (644 μ mol) of *tert*-butyl (2*S*)-1-(benzyloxy)-3-phenylpropan-2-yl carbamate were dissolved in 11 ml of a 4 N solution of hydrogen chloride in dioxane and stirred at RT for 1 h.
- 20 Then the reaction mixture was concentrated and the residue was dried under reduced pressure. 138 mg (77% of theory) of the title compound were obtained.

LC-MS (Method 1): $R_t = 0.65$ min; $m/z = 242$ ($M+H$)⁺.

Intermediate 38

N-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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

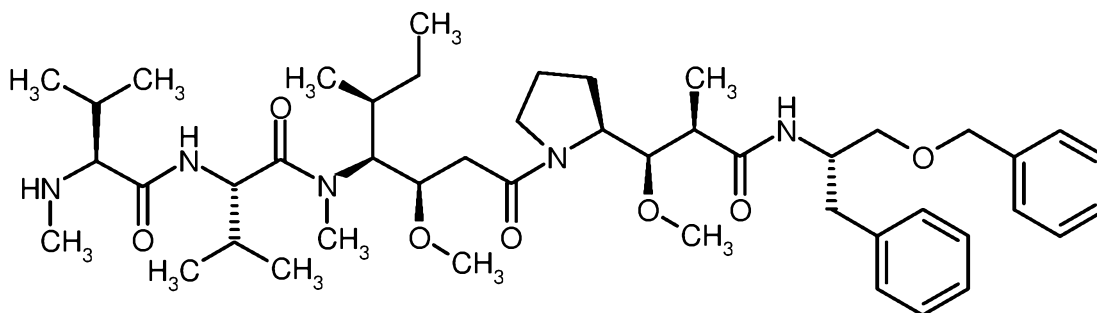


To a solution of 20 mg (29 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide in 1 ml of DMF were added, at RT, 15.3 μ l (88 μ mol) of *N,N*-diisopropylethylamine, 6.7 mg (44 μ mol) of HOBt and 6.7 mg (35 μ mol) of EDC, and the mixture was stirred for 30 min. Subsequently, 7.8 mg (32 μ mol) of (2*S*)-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.

LC-MS (Method 1): $R_t = 1.51$ min; $m/z = 909$ ($M+H$)⁺.

Intermediate 39

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



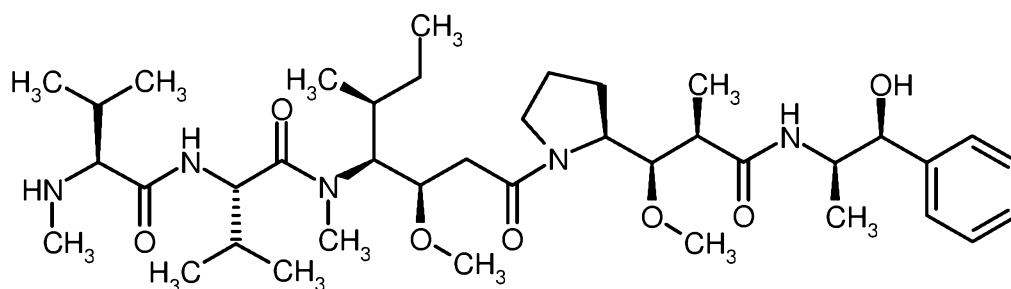
x CF₃COOH

26 mg (29 μmol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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.

LC-MS (Method 1): $R_t = 0.97$ min; $m/z = 809$ ($M+H$)⁺.

Intermediate 40

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



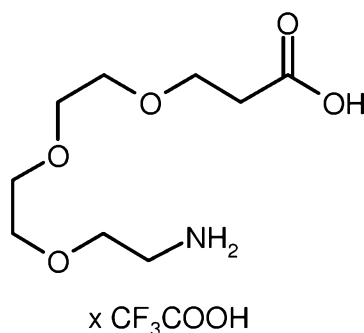
50 mg (70 μmol) of Intermediate 26 and 11 mg (70 μmol) of (1*S*, 2*R*)-2-amino-1-phenylpropan-1-ol in 10 ml of DMF were admixed with 42 mg (0.11 μmol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 25 μl of *N,N*-diisopropylethylamine, and the reaction mixture 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.

HPLC (Method 12): $R_t = 1.65$ min;

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



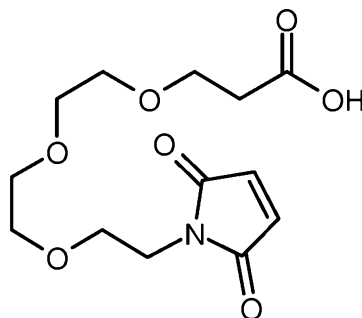
150 mg (541 μ mol) of *tert*-butyl 3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoate were dissolved in 3 ml of dichloromethane, 1.5 ml of trifluoroacetic acid were added, and the reaction mixture was stirred at RT for 1 h, then concentrated.

- 5 181 mg (100% of theory) of the title compound were obtained.

MS (EI): m/z 222 (M+H)⁺

Intermediate 42

3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanoic acid



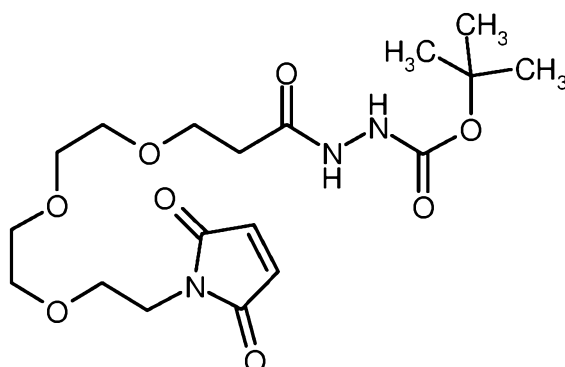
- 10 186 mg (555 μ mol) of 3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoic acid trifluoroacetate were dissolved in 2.6 ml of saturated sodium hydrogencarbonate solution and admixed at 0°C with 86 mg (555 μ mol) of N-methoxycarbonylmaleimide. The reaction mixture was stirred at 0°C for 40 min and at RT for 1 h, then cooled again to 0°C, adjusted to pH 3 with sulphuric acid and extracted 3x with 25 ml of ethyl acetate. The combined organic phases were dried over magnesium sulphate and concentrated.
- 15

126 mg (75% of theory) of the title compound were obtained.

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-1*H*-pyrrol-1-yl)-4-oxo-7,10,13-trioxa-2,3-diazapentadecan-1-oate



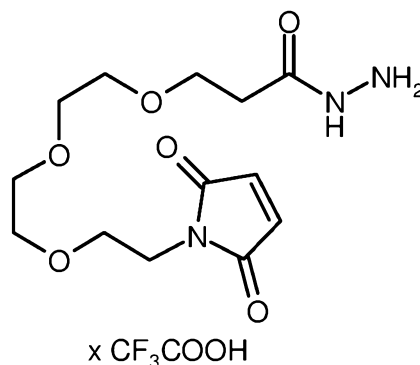
- 5 125 mg (417 μ mol) of 3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanoic acid were dissolved at 0°C in 2.1 ml of THF and admixed with 46 μ l (417 mmol) of 4-methylmorpholine and 54.5 μ l (417 μ mol) of isobutyl chloroformate. The ice bath was removed and the reaction mixture was stirred at RT for 30 min. Subsequently, at 0°C, 55 mg (417 μ mol) of *tert*-butoxycarbonyl hydrazide were added. The reaction mixture was warmed to RT overnight,
- 10 concentrated and purified by preparative HPLC.

60 mg (33% of theory) of the title compound were obtained.

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-1*H*-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanehydrazide
- 15 trifluoroacetate



60 mg (145 μ mol) of *tert*-butyl 15-(2,5-dioxo-2,5-dihydro-1*H*-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

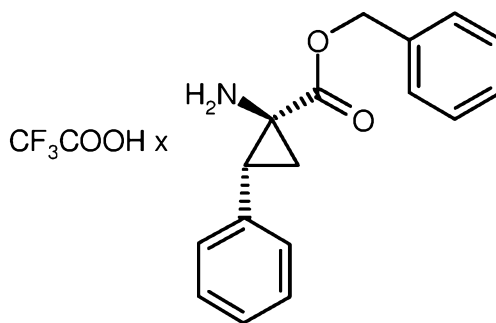
trifluoroacetic acid was added. The reaction mixture was stirred at RT for 30 min and then concentrated.

62 mg (100% of theory) of the title compound were obtained.

LC-MS (Method 1): $R_t = 0.35$ min; $m/z = 316$ ($M+H$)⁺.

5 **Intermediate 45**

benzyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate

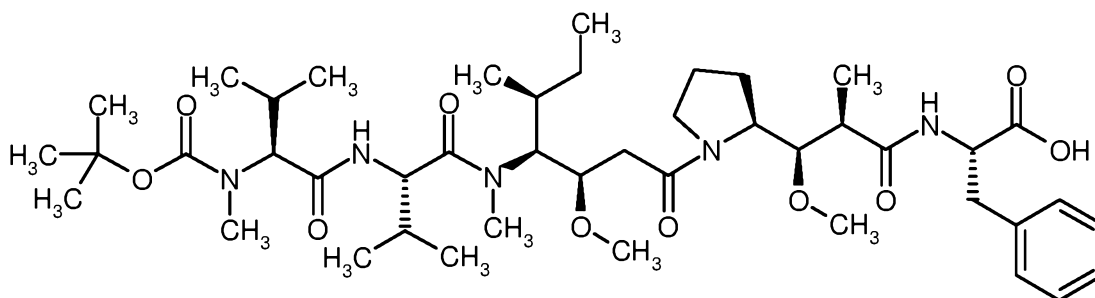


The title compound was prepared by standard methods, by esterifying commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with benzyl alcohol
10 and subsequent Boc detachment with trifluoroacetic acid.

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*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*)-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
15



383 mg (0.743 mmol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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*-[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-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 μ l 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.

LC-MS (Method 1): $R_t = 1.49$ min; MS (ESIpos): $m/z = 922$ ($M+H$)⁺.

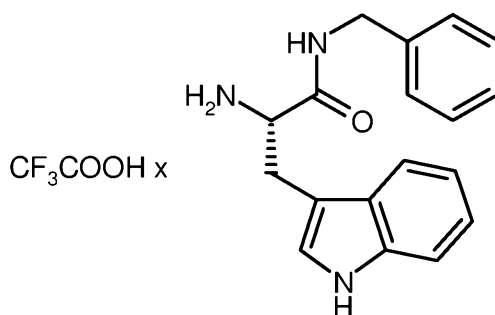
100 mg (0.11 mmol) of this intermediate were taken up in 15 ml of methanol and the benzyl ester group was removed by hydrogenation under standard hydrogen pressure with 10% palladium on activated carbon as a catalyst. After stirring at RT for 1 h, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. After lyophilization from dioxane, 85 mg (94% of theory) of the title compound were obtained as a solid.

HPLC (Method 12): $R_t = 2.4$ min;

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESIpos): $m/z = 832$ ($M+H$)⁺.

Intermediate 47

N-benzyl-L-tryptophanamide trifluoroacetate



20

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 μ l (630 μ mol) 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

25

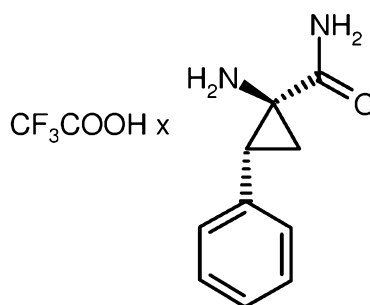
taken up in 10 ml of dichloromethane, and 3 ml of anhydrous trifluoroacetic acid were added. After stirring at RT for 45 minutes, the mixture was concentrated and the residue was purified by preparative HPLC. After drying under high vacuum, 117 mg (57% of theory over both stages) of the title compound were obtained.

5 HPLC (Method 12): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.66$ min; MS (ESIpos): $m/z = 294$ ($M+H$)⁺.

Intermediate 48

(1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxamide trifluoroacetate



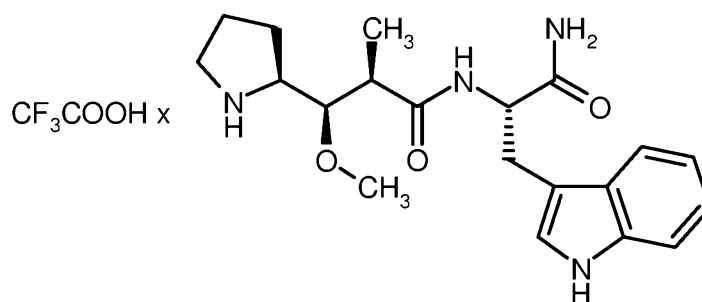
10 50 mg (180 μ mol) of commercially available (1*S*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid were dissolved in 5 ml of DMF, 94 μ l (541 μ mol) of *N,N*-diisopropylethylamine, 31 mg (270 μ mol) of *N*-hydroxysuccinimide and 41.5 mg (216 μ mol) of EDC were added, and then the mixture was stirred at RT overnight. The reaction mixture was then concentrated, the residue was taken up in dioxane, 71 mg (901 μ mol) of ammonium
15 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,
20 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.

HPLC (Method 6): $R_t = 0.38$ min;

LC-MS (Method 1): $R_t = 0.20$ min; MS (ESIpos): $m/z = 177$ ($M+H$)⁺.

Intermediate 49

25 *N*^α-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-*L*-tryptophanamide trifluoroacetate



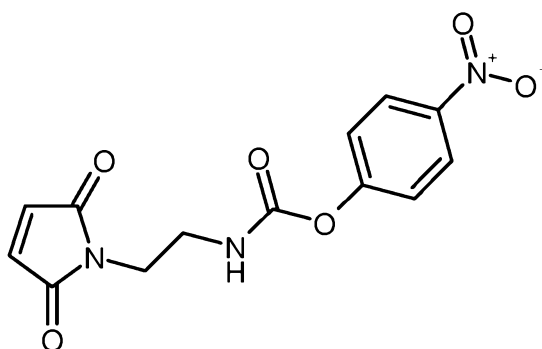
The title compound was prepared in analogy to the synthesis of Intermediate 13 from Starting Compound 1 and L-tryptophanamide hydrochloride.

HPLC (Method 5): $R_t = 1.4$ min;

- 5 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-1*H*-pyrrol-1-yl)ethyl carbamate



- 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.

After removing the Boc protecting group under standard conditions, 652 mg of 1-(2-aminoethyl)-1*H*-pyrrole-2,5-dione were obtained as the trifluoroacetate.

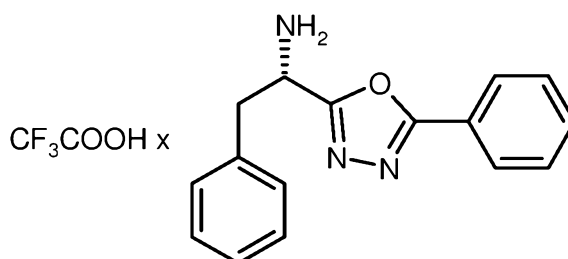
112.9 mg (543 μ mol) of nitrophenyl chloroformate were dissolved in 30 ml of THF and, after addition of 100 mg (271.6 μ mol) of 1-(2-aminoethyl)-1*H*-pyrrole-2,5-dione trifluoroacetate, the mixture was stirred at RT for 30 min. The mixture was filtered and the filtrate was concentrated to dryness and then slurried with diethyl ether. After filtration with suction and drying, 60 mg (95% of theory) of the title compound were obtained.

HPLC (Method 5): R_t = 0.65 min;

LC-MS (Method 1): R_t = 0.74 min; MS (ESIpos): m/z = 306 (M+H)+.

Intermediate 51

(1*S*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanamine trifluoroacetate



10

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 (1*S*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl carbamate were obtained.

20 LC-MS (Method 12): R_t = 1.15 min; MS (ESIpos): m/z = 366 (M+H)⁺

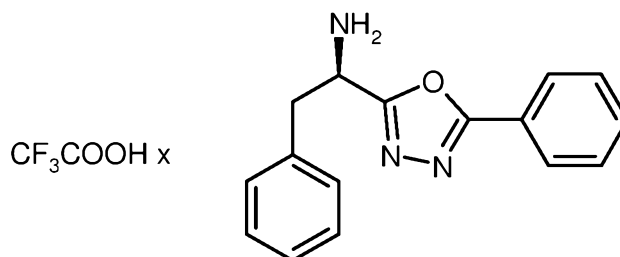
217 mg (0.59 mmol) of this intermediate were taken up in 3 ml of dichloromethane, 0.6 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was the reaction mixture dried further under reduced pressure and then lyophilized from dioxane. In this way, 214 mg (90% of theory) of the title compound were obtained.

25

LC-MS (Method 11): R_t = 0.62 min; MS (ESIpos): m/z = 266 (M+H)⁺

Intermediate 52

(1*R*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanamine trifluoroacetate



200 mg (0.75 mmol) of *N*-(*tert*-butoxycarbonyl)-D-phenylalanine were initially charged at 0°C in
5 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
10 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 (1*R*)-2-phenyl-1-(5-phenyl-1,3,4-
oxadiazol-2-yl)ethyl carbamate were obtained.

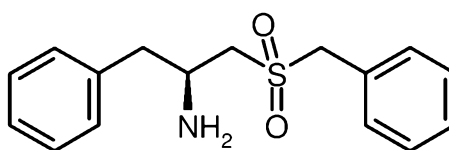
LC-MS (Method 2): $R_t = 1.36$ min; MS (ESIpos): $m/z = 366$ ($M+H$)⁺

219 mg (0.6 mmol) of this intermediate were taken up in 3 ml of dichloromethane, 0.6 ml of
15 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.

HPLC (Method 10): $R_t = 2.41$ min

20 **Intermediate 53**

(2*S*)-1-(benzylsulphonyl)-3-phenylpropan-2-amine



200 mg (1.13 mmol) of (4*S*)-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 (2*S*)-1-(benzylsulphonyl)-3-phenylpropan-2-amine intermediate was converted further directly, without workup.

HPLC (Method 10): $R_t = 2.63$ min

5 LC-MS (Method 1): $R_t = 0.67$ min; MS (ESIpos): $m/z = 258$ ($M+H$)⁺

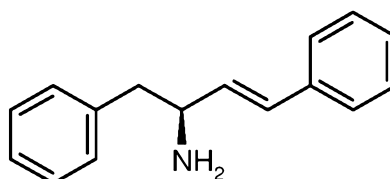
The crude intermediate obtained above was dissolved in a solution of 2 ml of 30% hydrogen peroxide and 5 ml of formic acid, and the mixture was stirred at RT for 12 h. Then the reaction mixture was added to saturated sodium sulphate solution and extracted three times with ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated under reduced
10 pressure. The crude product obtained was purified by means of preparative HPLC. 343 mg (61% of theory) of the title compound were thus obtained.

HPLC (Method 10): $R_t = 2.40$ min;

LC-MS (Method 12): $R_t = 0.65$ min; MS (ESIpos): $m/z = 290$ ($M+H$)⁺

Intermediate 54

15 (2*S*,3*E*)-1,4-diphenylbut-3-en-2-amine



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)
20 of (2*S*)-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
25 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.

HPLC (Method 10): $R_t = 2.46$ min;

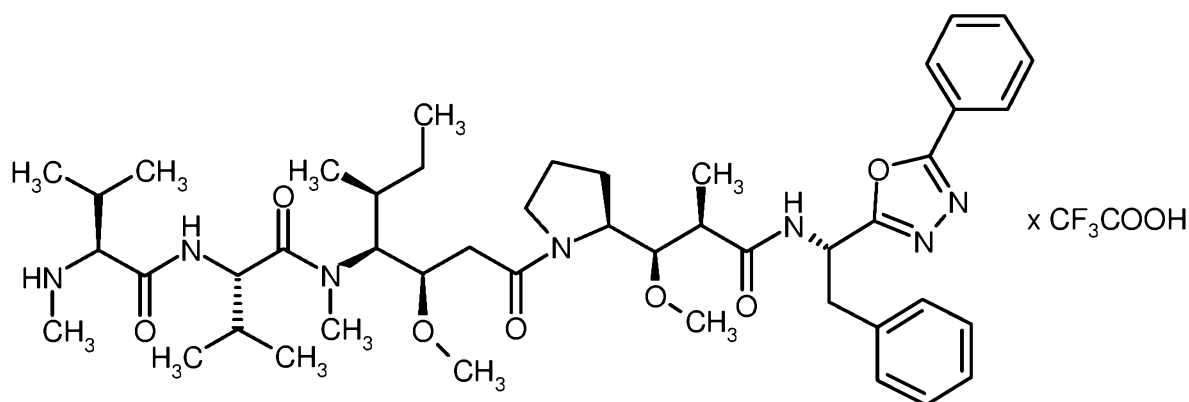
LC-MS (Method 12): $R_t = 0.75$ min; MS (ESIpos): $m/z = 224$ ($M+H$)⁺

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 μ m 250 mm x 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.

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] = 2.62 - 2.83 (m, 2 H) 3.52 - 3.71 (m, 1 H) 6.18 - 6.30 (m, 1 H) 6.34 - 6.46 (m, 1 H) 6.98 - 7.57 (m, 10 H) [further signals hidden under solvent peaks].

Intermediate 55

- 10 N-methyl-*L*-valyl-N-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*)-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



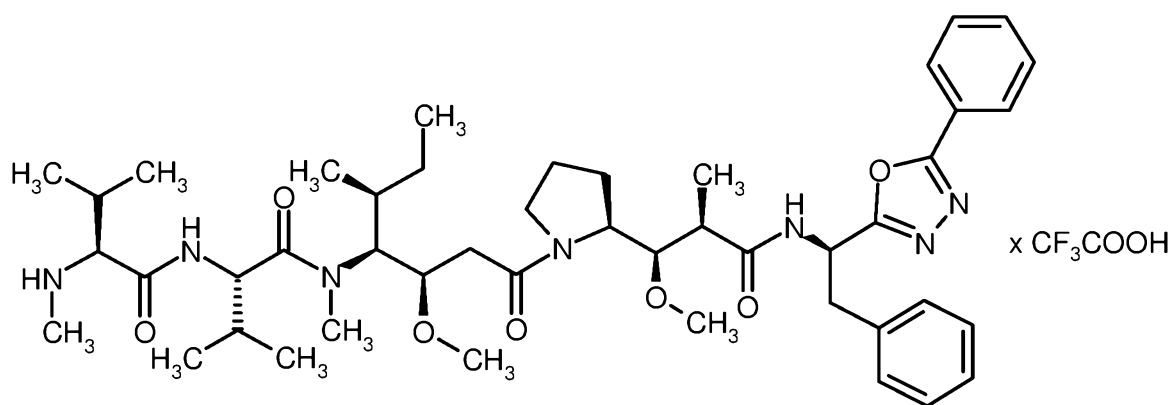
- 15 20 mg (29 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-valyl-*N*[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-*L*-valinamide were dissolved in 1 ml of DMF, 13.3 mg (35 μ mol) of HATU and 15.3 μ l (88 μ mol) of *N,N*-diisopropylethylamine were added, and the mixture was stirred at RT for 30 min. Subsequently, 12.2 mg (32 μ mol) of (1*S*)-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*[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*)-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.
- 25 LC-MS (Method 12): R_t = 1.45 min; MS (ESIpos): m/z = 933 ($M+H$) $^+$

By subsequently detaching the BOC protecting group with trifluoroacetic acid, 22.4 mg (98% of theory) of the title compound were then obtained.

LC-MS (Method 11): $R_t = 0.85$ min; MS (ESIpos): $m/z = 833$ ($M+H$)⁺

Intermediate 56

- 5 *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*R*)-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



- 10 *N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*R*)-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 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide
- 15 with 12.2 mg (32 μ mol) of (1*R*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanamine trifluoroacetate.

Yield: 17 mg (64% of theory)

HPLC (Method 10): $R_t = 3.74$ min;

LC-MS (Method 1): $R_t = 1.45$ min; MS (ESIpos): $m/z = 933$ ($M+H$)⁺

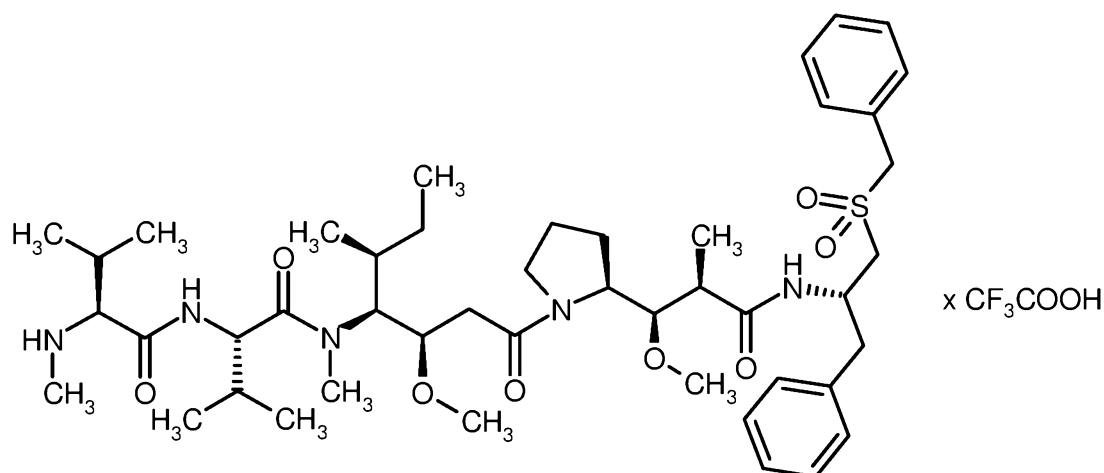
- 20 By subsequently detaching the BOC protecting group with trifluoroacetic acid, 17.1 mg (99% of theory) of the title compound were then obtained.

HPLC (Method 10): $R_t = 2.55$ min;

LC-MS (Method 11): $R_t = 0.85$ min; MS (ESIpos): $m/z = 833$ ($M+H$)⁺

Intermediate 57

N-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



5

N-(*tert*-Butoxycarbonyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-*L*-valinamide with 9.3 mg (20 μ mol) of (2*S*)-1-(benzylsulphonyl)-3-phenylpropan-2-amine.

10

Yield: 19.2 mg (68 % of theory)

HPLC (Method 10): R_t = 3.5 min;

15 LC-MS (Method 12): R_t = 1.41 min; MS (ESIpos): m/z = 957 ($M+H$)⁺

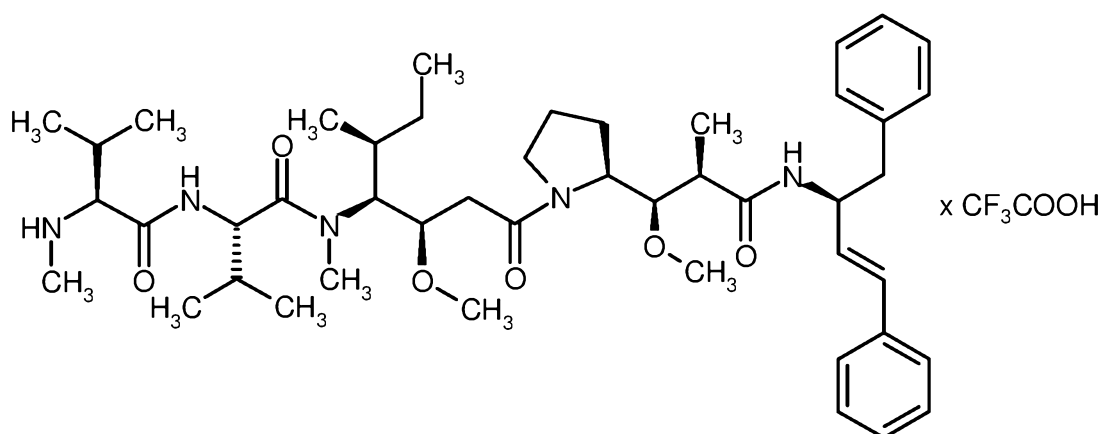
By subsequently detaching the BOC protecting group with trifluoroacetic acid, 19.3 mg (99% of theory) of the title compound were then obtained.

HPLC (Method 10): R_t = 2.52 min;

LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos): m/z = 857 ($M+H$)⁺

Intermediate 58

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*,3*E*)-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



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N-(*tert*-Butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*,3*E*)-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 μ mol) *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide with 7.1 mg (32 μ mol) of (2*S*,3*E*)-1,4-diphenylbut-3-en-2-amine.

10

Yield: 15.1 mg (58 % of theory)

HPLC (Method 10): R_t = 4.2 min;

15 LC-MS (Method 12): R_t = 1.51 min; MS (ESIpos): m/z = 891 ($M+H$)⁺

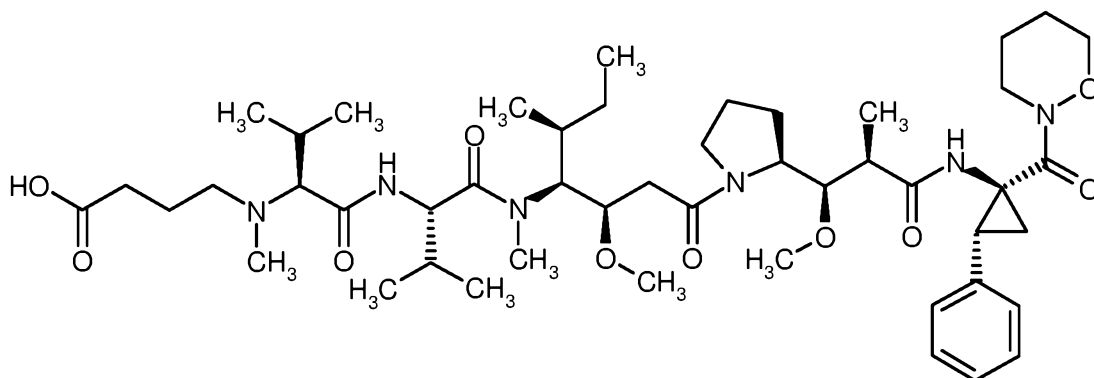
By subsequently detaching the BOC protecting group with trifluoroacetic acid, 15.7 mg (99% of theory) of the title compound were then obtained.

HPLC (Method 10): R_t = 2.62 min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



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50 mg (0.054 mmol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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.

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HPLC (Method 5): $R_t = 1.64$ min;

LC-MS (Method 9): $R_t = 4.76$ min; MS (ESIpos): $m/z = 899$ ($M+H$)⁺

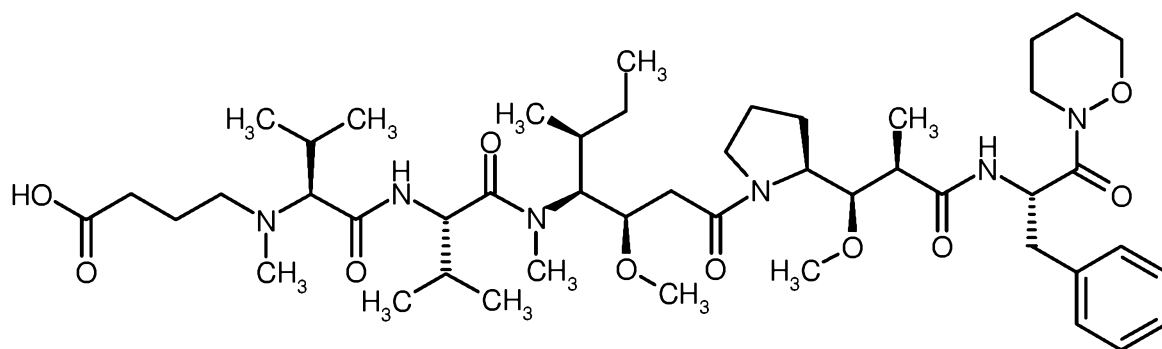
¹H NMR (500 MHz, DMSO-*d*₆): $\delta = 8.95$ and 8.8 (2m, 1H), 8.88 and 8.65 (2s, 1H), 7.4 - 7.1 (m, 5H), 5.0 , 4.78 , 4.65 and 4.55 (4m, 2H), 4.1 - 3.7 (m, 5H), 3.32 , 3.29 , 3.20 , 3.12 , 3.1 and 3.0 (6s,

25

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 H₂O and DMSO peaks].

Intermediate 62

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
5 methyl-3-[(2*S*)-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



The title compound was prepared in analogy to the synthesis of Intermediate 61, by reaction of
10 50 mg of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
{[(2*S*)-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.

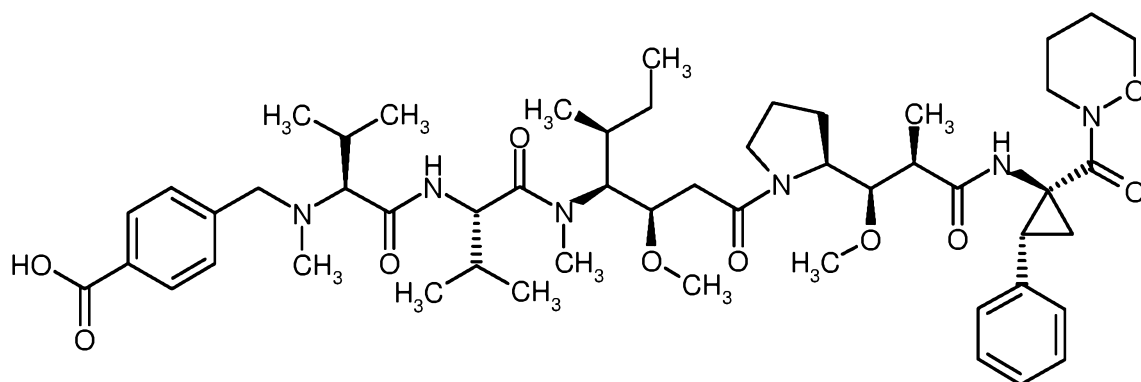
Yield: 34 mg (70% of theory)

15 HPLC (Method 5): $R_t = 1.64$ min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
20 oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



The title compound was prepared in analogy to the synthesis of Intermediate 61, by reaction of 15 mg of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
5 {[(1*S*,2*R*)-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.

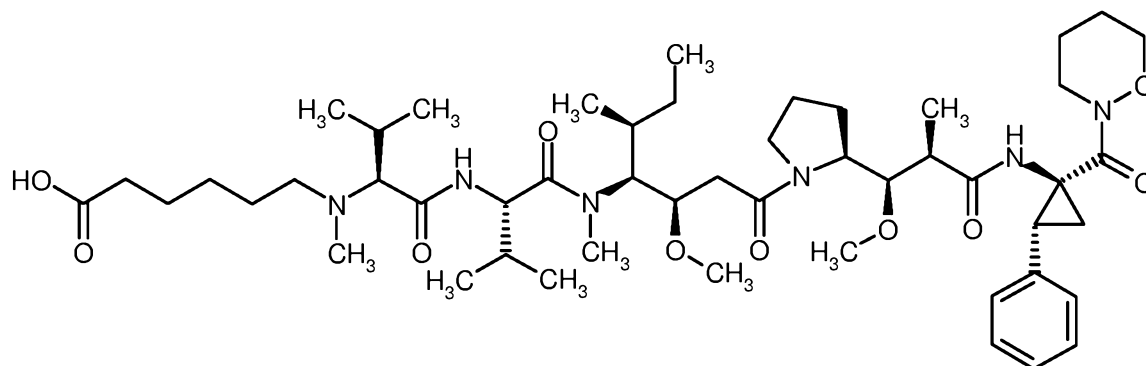
Yield: 7.5 mg (48% of theory)

HPLC (Method 5): $R_t = 1.75$ min;

LC-MS (Method 1): $R_t = 0.97$ min; MS (ESIpos): $m/z = 947$ ($M+H$)⁺.

10 **Intermediate 64**

N-(5-carboxypentyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



15 10 mg (0.011 mmol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
methoxy-2-methyl-3-[(1*S*,2*R*)-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-

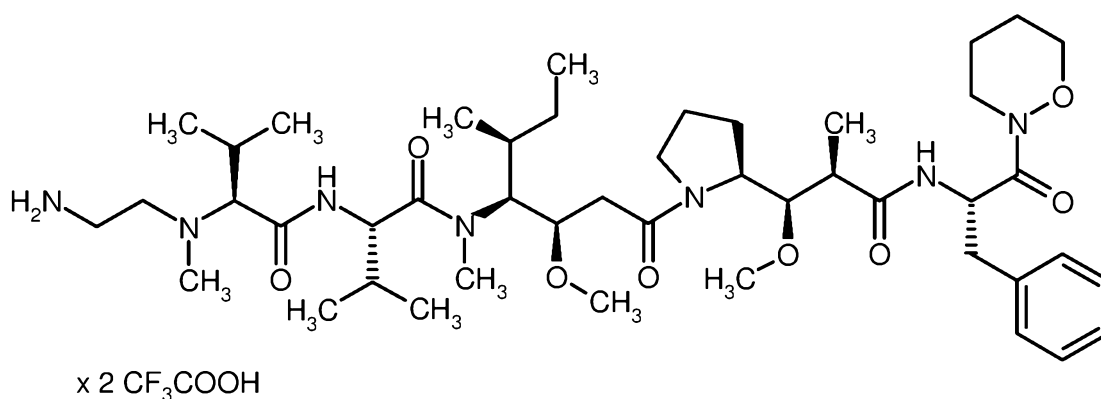
oxohexanoic acid were added. The reaction mixture was subsequently stirred at 100°C for 1 h. After cooling to RT, 0.75 mg (0.012 mmol) of sodium cyanoborohydride was added and the mixture was adjusted to a pH of 3 by adding 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100°C for a 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.

HPLC (Method 5): $R_t = 1.68$ min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



The title compound was prepared by reaction of 68 mg of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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.

Yield: 49 mg (62% of theory over two stages)

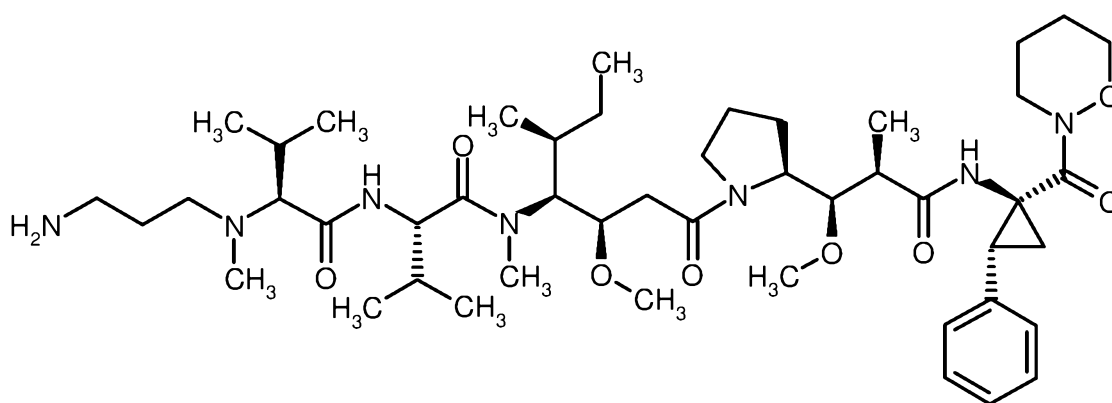
HPLC (Method 5): $R_t = 1.58$ min;

LC-MS (Method 2): $R_t = 1.05$ min; MS (ESIpos): $m/z = 844$ ($M+H$)⁺

¹H NMR (600 MHz, DMSO-d₆): $\delta = 8.25$ (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 H₂O peak].

Intermediate 66

N-(3-aminopropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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).

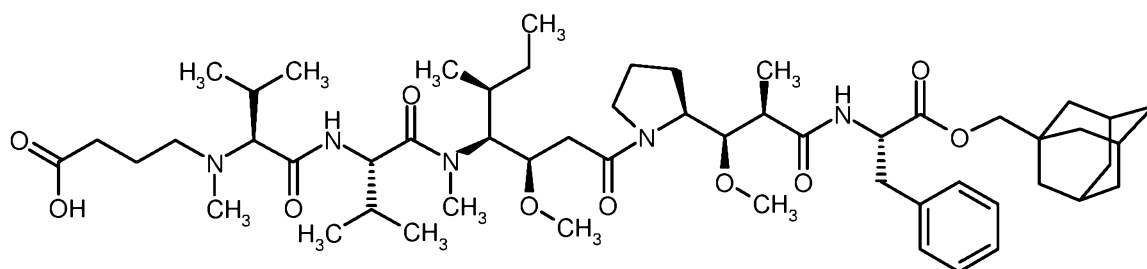
Yield: 11 mg (41% of theory over two stages)

HPLC (Method 5): $R_t = 1.53$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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

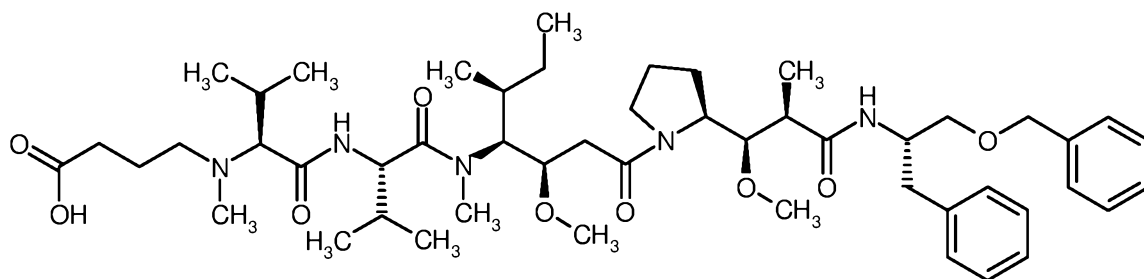


26 mg (26 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide trifluoroacetate and 33.9 μ l of a 15% aqueous succinaldehydic acid solution (53 μ mol) were dissolved in 957 μ l of a 1:1-dioxane/water mixture and heated to 100°C for 1 h. After brief cooling, 1.81 mg (29 μ mol) 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.

LC-MS (Method 1): R_t = 1.17 min; m/z = 967 ($M+H$)⁺.

Intermediate 68

15 *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



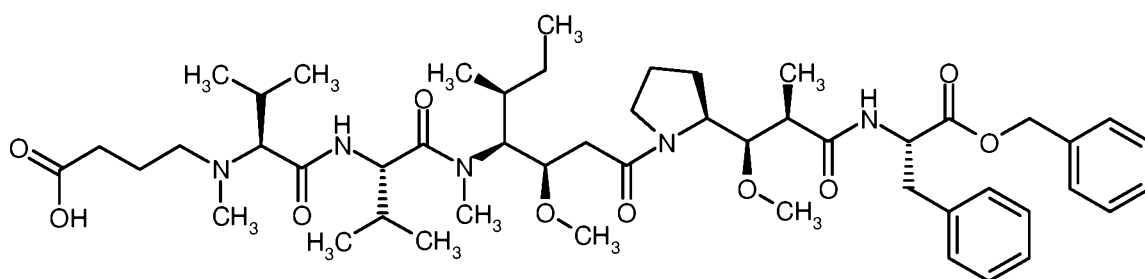
24 mg (26 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide trifluoroacetate and 33.7 μ l of a 15% aqueous succinaldehydic acid solution (52 μ mol) were dissolved in 953 μ l of a 1:1-dioxane/water mixture and heated to 100°C for 1 h. After brief cooling, 1.80 mg (29 μ mol) 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.

LC-MS (Method 1): $R_t = 1.01$ min; $m/z = 895$ ($M+H$)⁺

Intermediate 69

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



53 mg (84 μ mol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide (Intermediate 4) and 45 mg (84 μ mol) of benzyl *N*-[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-L-phenylalaninate trifluoroacetate (Intermediate 12) were taken up in 2 ml of DMF, 19 μ l of *N,N*-diisopropylethylamine, 14 mg (92 μ mol) of HOBt and 17.6 mg (92 μ mol) 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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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.

LC-MS (Method 1): $R_t = 1.55$ min; $m/z = 1044$ ($M+H$)⁺.

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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.

HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 1.01$ min; $m/z = 822$ (M+H)⁺.

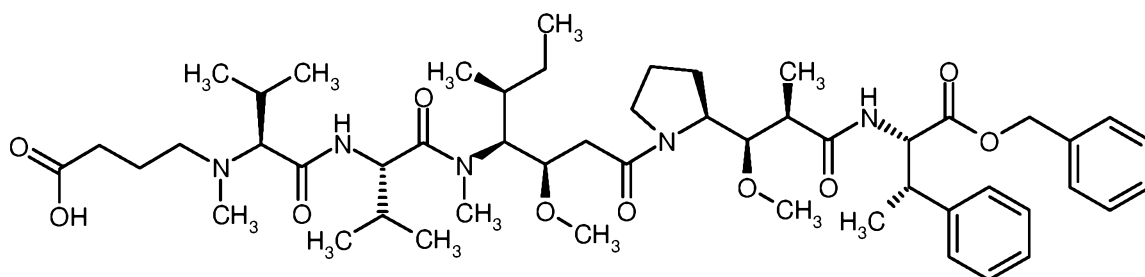
- 5 37 mg (0.045 mmol) of this intermediate were dissolved in 5 ml of dioxane/water and, analogously to the preparation of the compound in Intermediate 66, reacted with a 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. 16 mg (39% of theory) of the title compound were obtained in the form of a colourless foam.

HPLC (Method 6): $R_t = 2.1$ min;

- 10 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*S*)-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



15

First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 26, the amine compound *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*S*)-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.

- 20 30 mg (0.032 mmol) of this compound were dissolved in 6 ml of dioxane/water, and 41 μ l (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 μ l of 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100°C for a further 2 h. After
- 25 cooling, another 41 μ l (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

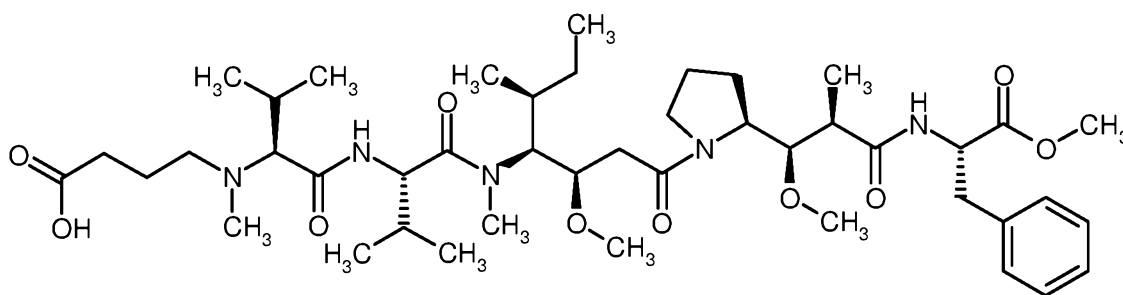
cyanoborohydride were added and about 300 µl of 0.1 N hydrochloric acid were subsequently used to adjust the pH back to 3. The reaction mixture was then stirred at 100°C for another 2 h. In the event of conversion still being incomplete, this procedure was repeated for a third time. The reaction mixture 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.

HPLC (Method 5): $R_t = 1.9$ min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-3-[(2*S*)-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



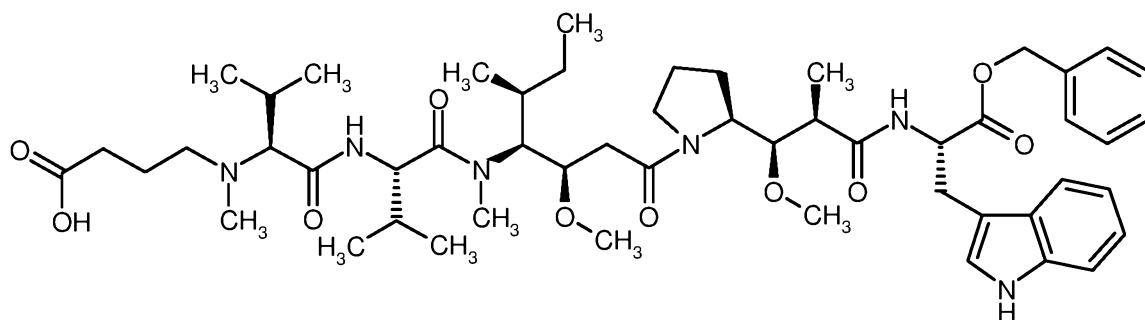
First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 39, the amine compound *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-3-[(2*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide 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.

HPLC (Method 6): $R_t = 1.9$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzyloxy)-3-(1*H*-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



212 mg (411 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide (Intermediate 8) and 237 mg (411 μ mol) of benzyl-*N*-{(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-L-tryptophanate trifluoroacetate (Intermediate 20) were taken up in 30 ml of DMF, and 188 mg (493 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 215 μ l *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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzyloxy)-3-(1*H*-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.

LC-MS (Method 1): R_t = 1.45 min; m/z = 961 ($M+H$)⁺.

50 mg (52 μ mol) 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzyloxy)-3-(1*H*-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.

LC-MS (Method 1): R_t = 0.99 min; m/z = 861 ($M+H$)⁺.

29 mg (0.03 mmol) of this intermediate were dissolved in 6 ml of dioxane/water, and 39 μ l (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 μ l of 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100°C for a further 2 h. After cooling, another 39 μ l (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

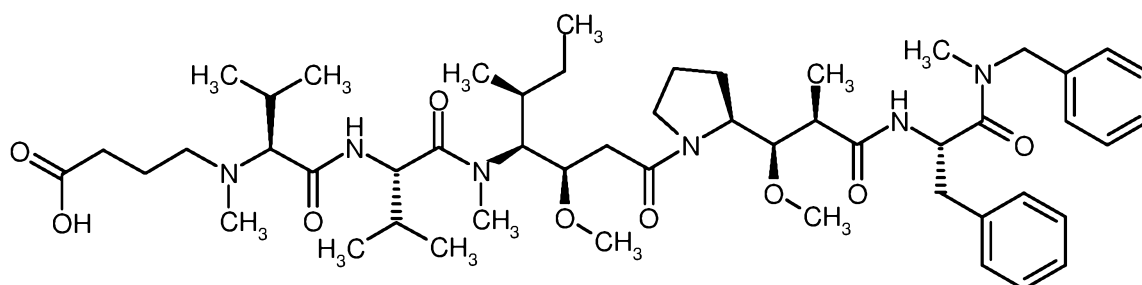
cyanoborohydride were added and about 300 μ l of 0.1 N hydrochloric acid were subsequently used to adjust the pH back to 3. The mixture was then stirred at 100°C for another 2 h. Thereafter, the reaction mixture was poured onto a 1:1 mixture of semisaturated aqueous ammonium chloride solution and ethyl 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.

HPLC (Method 5): R_t = 2.2 min;

LC-MS (Method 9): R_t = 5.04 min; MS (ESIpos): m/z = 947 (M+H)⁺.

10 **Intermediate 73**

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



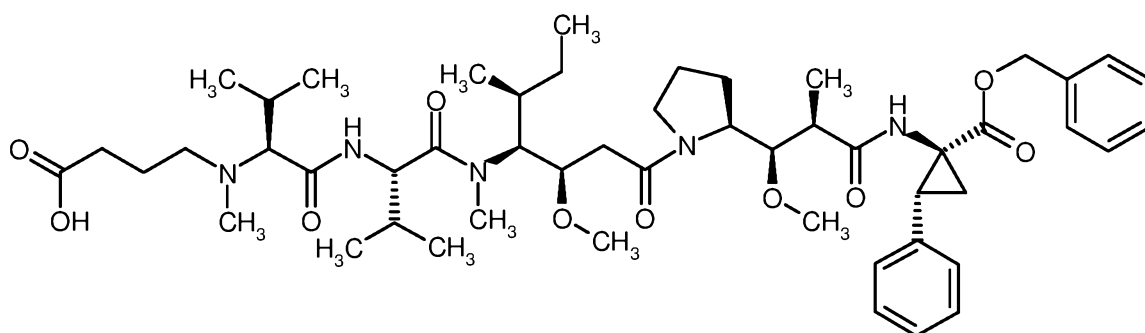
First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 38, the amine compound *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl]amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide 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.

HPLC (Method 12): R_t = 2.2 min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



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50 mg (73 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-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 μ mol) of benzyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate (Intermediate 45) were taken up in 5 ml of DMF, and 42 mg (110 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 38 μ l 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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.

LC-MS (Method 1): R_t = 1.52 min; m/z = 934 ($M+H$)⁺.

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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.

LC-MS (Method 1): R_t = 0.91 min; m/z = 834 ($M+H$)⁺.

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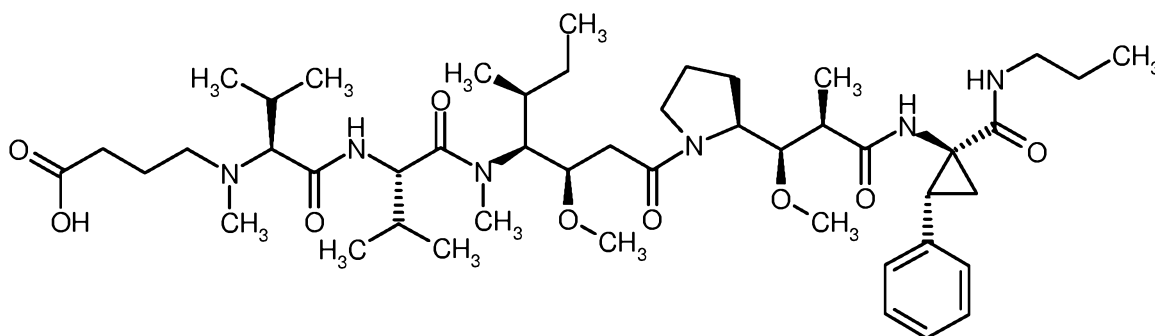
11 mg (0.011 mmol) of this intermediate were then used, in analogy to the preparation of Intermediate 66, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 2.5 mg (24% of theory) of the title compound in the form of a colourless foam.

HPLC (Method 12): $R_t = 2.2$ min;

5 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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*,2*R*)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



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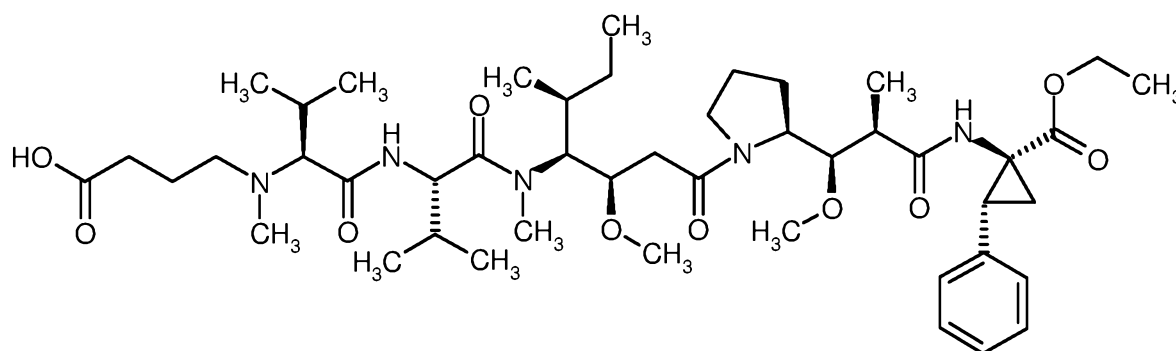
First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 26) and (1*S*,2*R*)-1-amino-2-phenyl-*N*-propylcyclopropanecarboxamide 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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*,2*R*)-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.

HPLC (Method 6): $R_t = 1.9$ min;

25 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



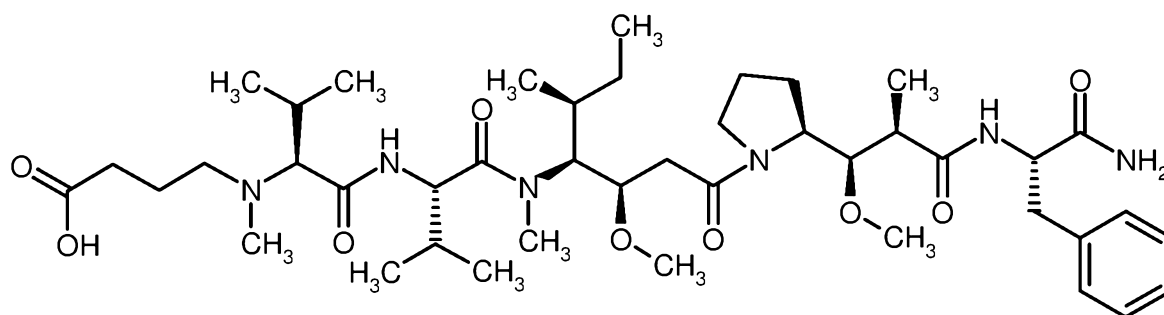
- 5 First, by coupling of Intermediate 46 (*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide) with Intermediate 48 (ethyl (1*S*,2*R*)-1-amino-2-phenylcyclopropanecarboxylate 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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.

HPLC (Method 6): $R_t = 1.9$ min;

LC-MS (Method 2): $R_t = 1.28$ min; MS (ESIpos): $m/z = 858$ ($M+H$)⁺

Intermediate 77

- 20 *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



First, in analogy to the synthesis described in Intermediate 75, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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-

10 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.

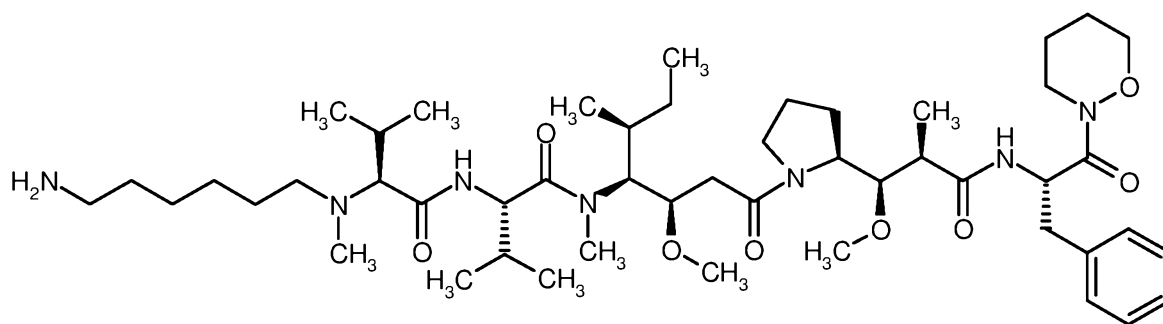
HPLC (Method 6): $R_t = 1.7$ min;

LC-MS (Method 9): $R_t = 4.44$ min; MS (ESIpos): $m/z = 817$ ($M+H$)⁺

15 ¹H NMR (500 MHz, DMSO-*d*₆): $\delta = 8.95$ 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

20 *N*-(6-aminohexyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



This compound was prepared in analogy to Intermediate 66 over 2 stages, proceeding from 20 mg (16 μ mol) of the compound from Intermediate 14 and benzyl 6-oxohexyl carbamate, and the hydrogenation was performed in methanol as the solvent.

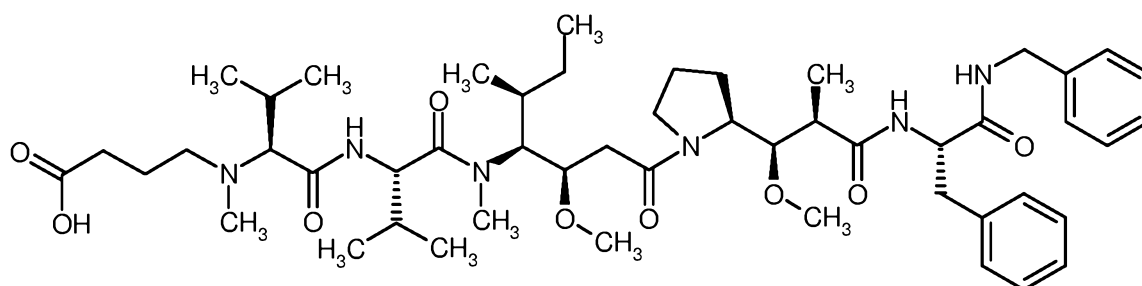
5 Yield: 7.6 mg (55% of theory over 2 stages)

HPLC (Method 6): R_t = 1.8 min;

LC-MS (Method 1): R_t = 0.7 min; MS (ESIpos): m/z = 901 ($M+H$)⁺.

Intermediate 79

10 *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



36 mg (43 μ mol) of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*)-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 μ mol) of benzylamine were taken up in 5 ml of DMF, 7.5 μ l (88 μ mol) of *N,N*-diisopropylethylamine, 10 mg (65 μ mol) of HOBt and 10 mg (52 μ mol) 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino]-1-methoxy-2-methyl-3-

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oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were obtained.

LC-MS (Method 1): $R_t = 1.43$ min; $m/z = 921$ ($M+H$)⁺.

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*-[(3*R*,4*S*,5*S*)-1-
5 {*(2S)*-2-[(1*R*,2*R*)-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.

10 LC-MS (Method 1): $R_t = 0.95$ min; $m/z = 821$ ($M+H$)⁺.

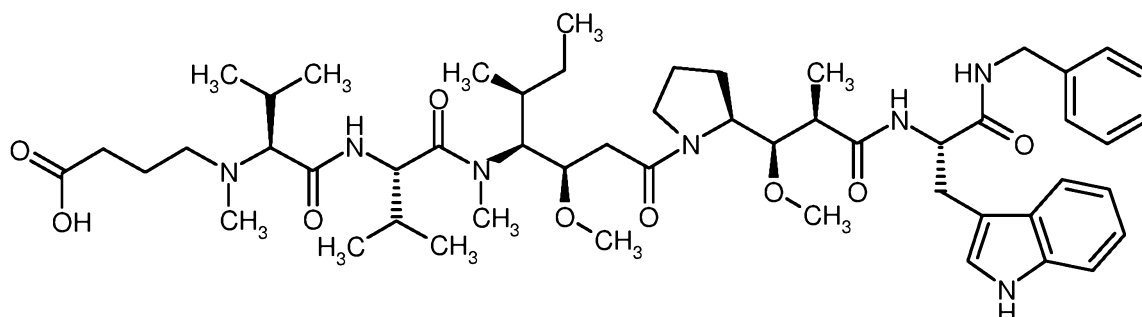
17 mg (0.018 mmol) of this intermediate were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 13 mg (80% of theory) of the title compound in the form of a colourless foam.

HPLC (Method 5): $R_t = 1.7$ min;

15 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*-[(3*R*,4*S*,5*S*)-1-[(*2S*)-2-[(1*R*,2*R*)-3-[[*(2S)*-1-(benzylamino)-3-(1*H*-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



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First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(*2S*)-2-[(1*R*,2*R*)-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
25 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzylamino)-3-(1*H*-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.

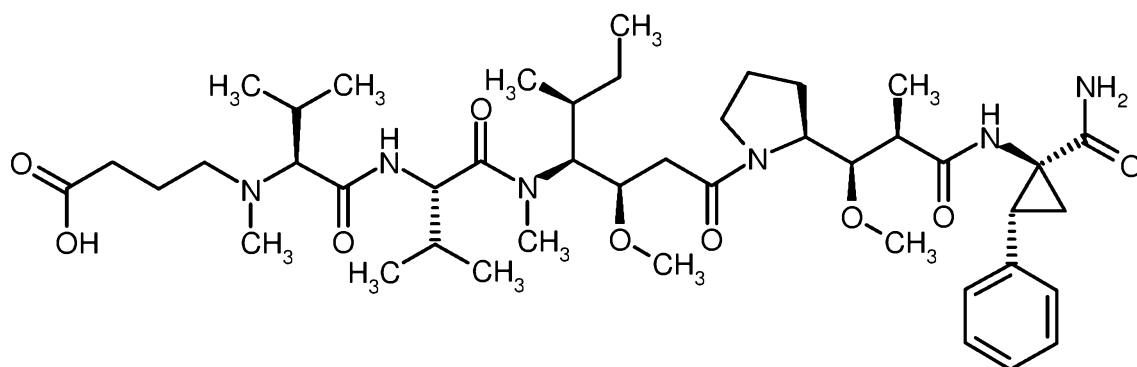
- 5 10 mg (0.01 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 2.5 mg (26% of theory) of the title compound.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 2): $R_t = 1.13$ min; MS (ESIpos): $m/z = 946$ ($M+H$)⁺.

10 **Intermediate 81**

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



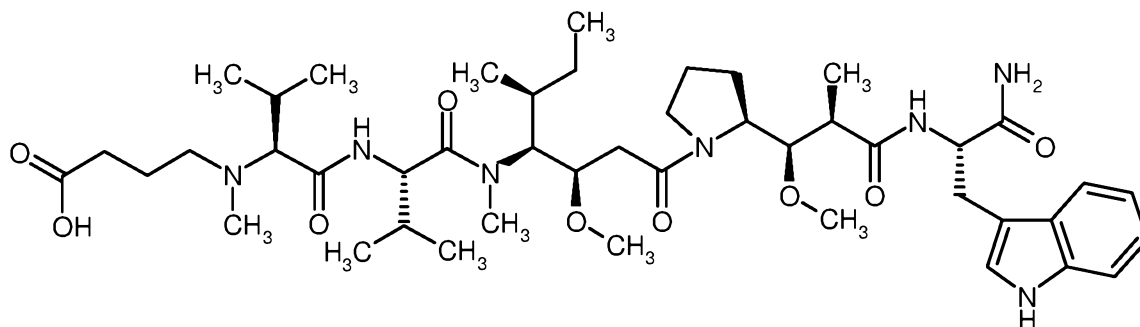
- 15 First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 26) and (1*S*,2*R*)-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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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
- 20 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.
- 25

HPLC (Method 5): $R_t = 1.6$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-
5 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



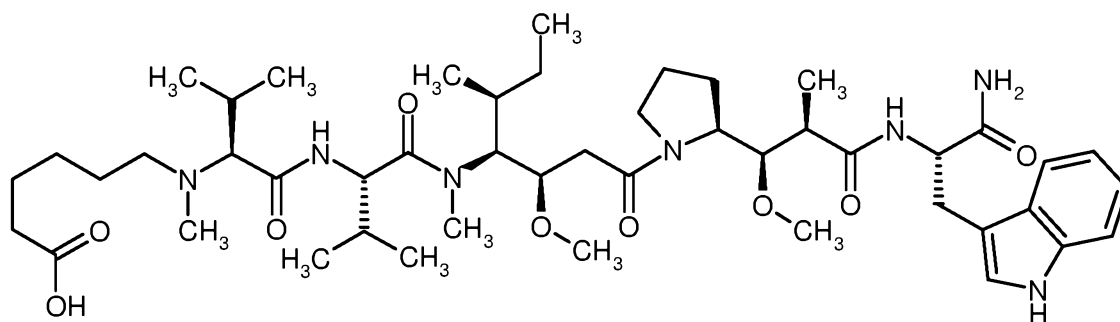
First, in analogy to the synthesis described in Intermediate 69, by coupling of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-
10 *N*-methyl-L-valinamide (Intermediate 4) and *N*^α-[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-L-tryptophanamide 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-
15 *N*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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.

20 HPLC (Method 5): $R_t = 1.8$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-
indol-3-yl)-1-oxopropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-
25 methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



This compound was prepared in analogy to the compound in Intermediate 82, proceeding from 20 mg (26 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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.

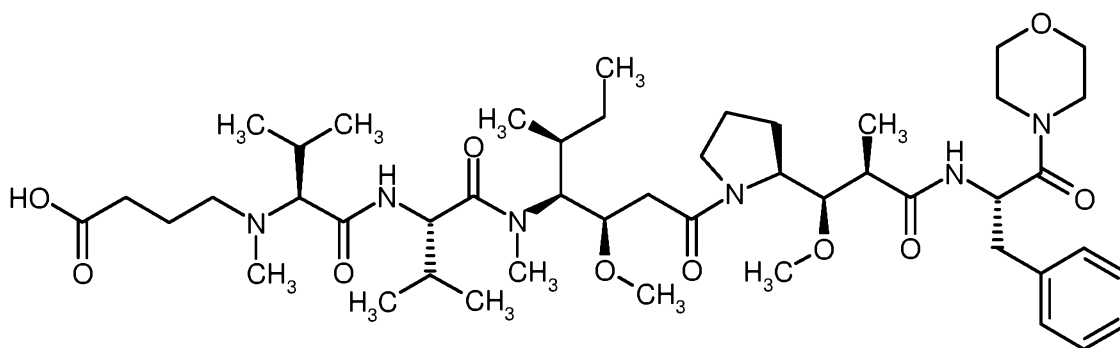
Yield: 5 mg (25% of theory)

HPLC (Method 5): R_t = 1.6 min;

LC-MS (Method 11): R_t = 0.72 min; MS (ESIpos): m/z = 884 ($M+H$)⁺.

10 **Intermediate 84**

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



15 First, in analogy to the synthesis described in Intermediate 79, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*)-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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-

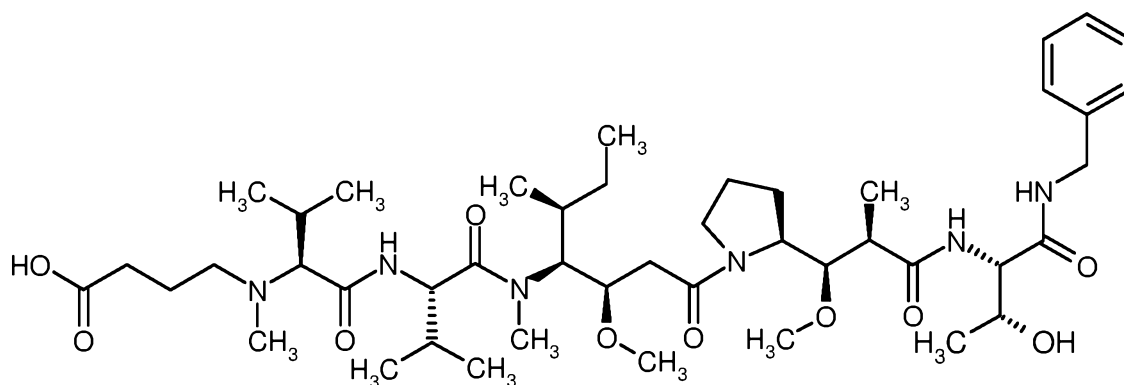
methoxy-2-methyl-3-[[*(2S)*-1-(morpholin-4-yl)-1-oxo-3-phenylpropan-2-yl]amino]-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide was prepared as the trifluoroacetate. 30 mg (0.033 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 22 mg (76% of theory) of the title compound.

HPLC (Method 5): $R_t = 1.6$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(*2S*)-2-[(1*R*,2*R*)-3-[[*(2S*,3*R*)-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



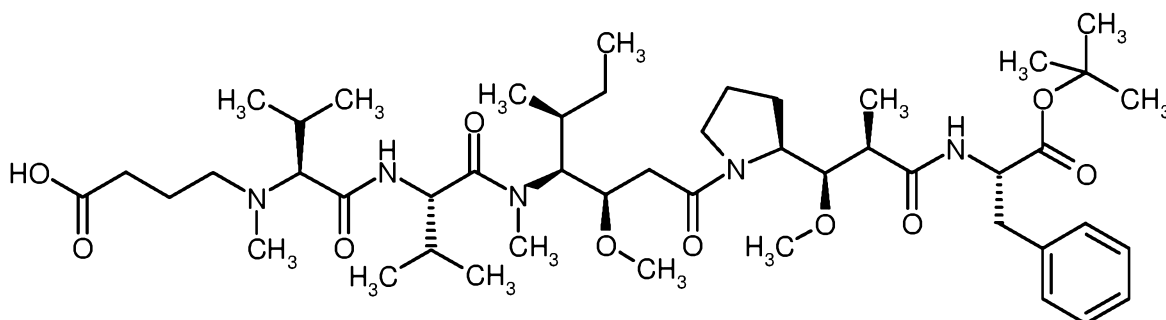
First, in analogy to the synthesis described in Intermediate 79, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(*2S*)-2-[(1*R*,2*R*)-3-[(1*S*)-1-carboxy-2-phenylethyl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (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*-[(3*R*,4*S*,5*S*)-1-[(*2S*)-2-[(1*R*,2*R*)-3-[[*(2S*,3*R*)-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.

HPLC (Method 5): $R_t = 1.54$ min;

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



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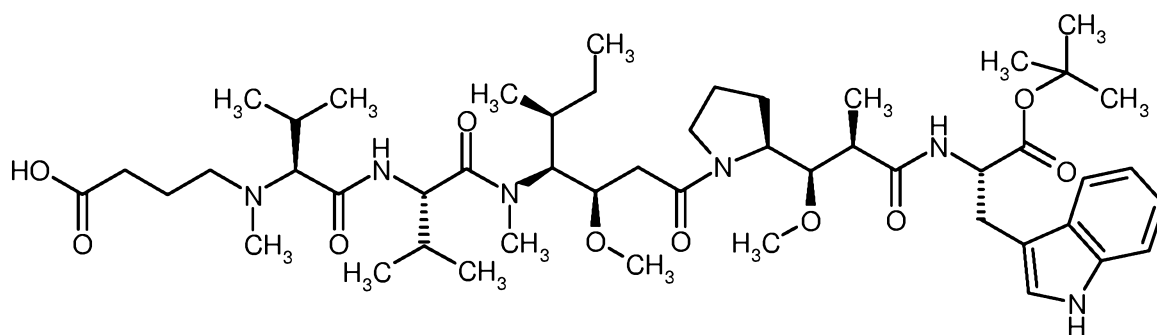
First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 26) and *tert*-butyl-L-phenylalaninate 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.

HPLC (Method 5): $R_t = 2.0$ min;

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



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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-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.

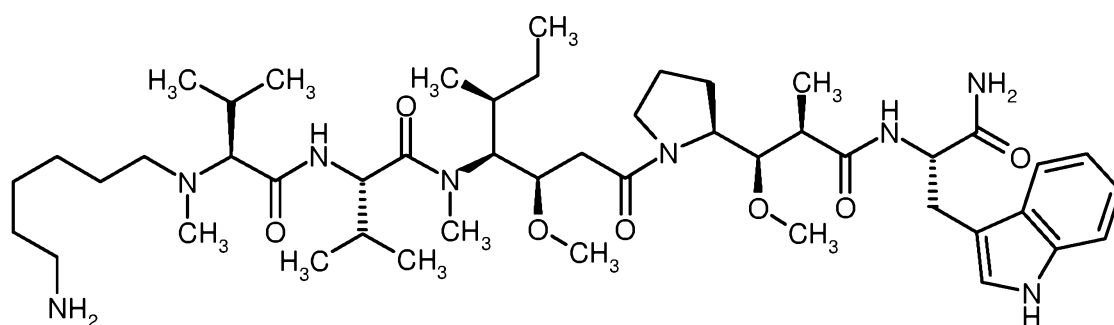
Yield: 95 mg (31% of theory over 3 stages)

HPLC (Method 5): $R_t = 2.0$ min;

LC-MS (Method 9): $R_t = 5.05$ min; MS (ESIpos): $m/z = 913$ ($M+H$)⁺.

10 **Intermediate 88**

N-(6-aminohexyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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



15 First, in analogy to the syntheses described in Intermediate 69, by coupling of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-L-valinamide (Intermediate 4) and *N* ^{α} -[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-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
20 detachment of the Fmoc protecting group by means of piperidine, the amine compound *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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
 5 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.

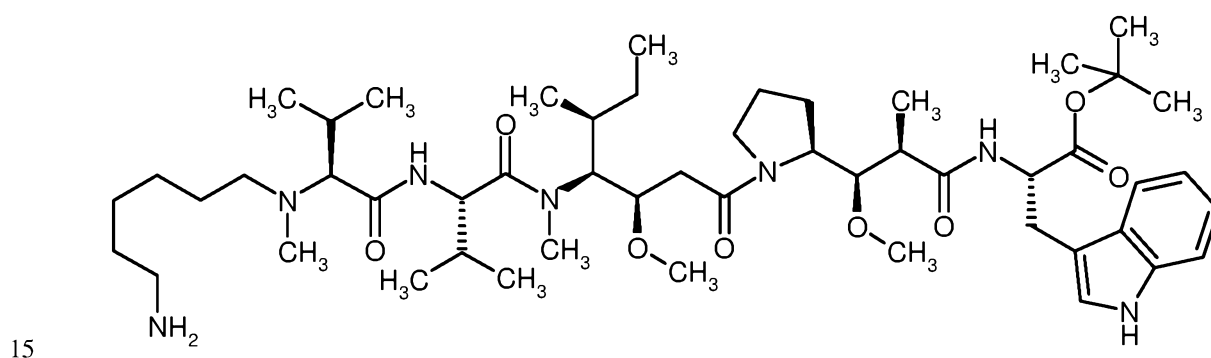
Yield: 14 mg (95% of theory)

HPLC (Method 5): $R_t = 1.5$ min;

10 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-*tert*-butoxy-3-(1*H*-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



First, in analogy to the synthesis described in Intermediate 86, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-*tert*-butoxy-3-(1*H*-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
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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.

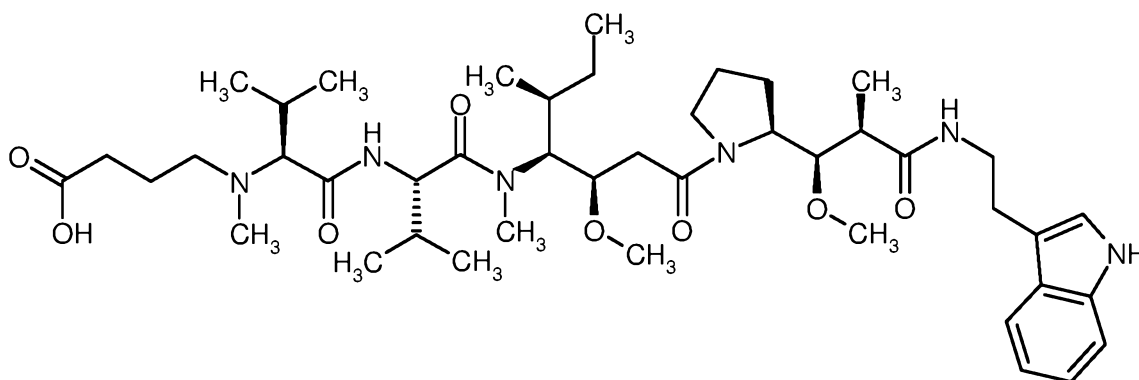
Yield: 30 mg (98% of theory)

5 HPLC (Method 5): Rt = 1.9 min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-{[2-(1*H*-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



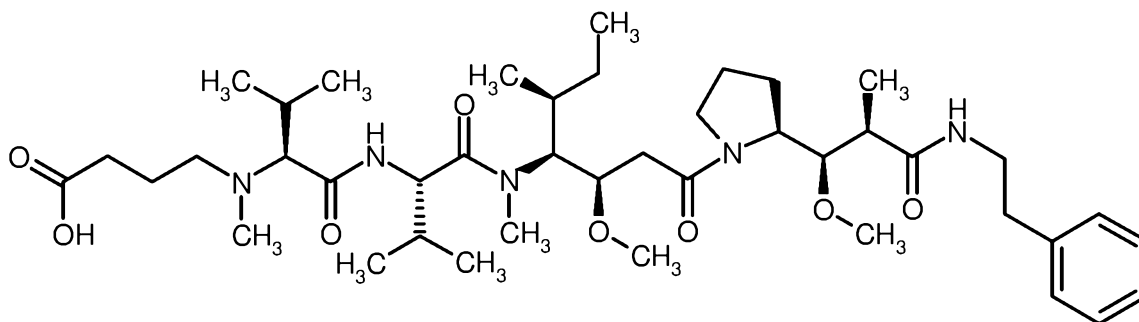
First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 26) and 2-(1*H*-indol-3-yl)ethanamine 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-{[2-(1*H*-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 15/2/0.2 to 15/4/0.5.

HPLC (Method 6): $R_t = 1.8$ min;

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*-{(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



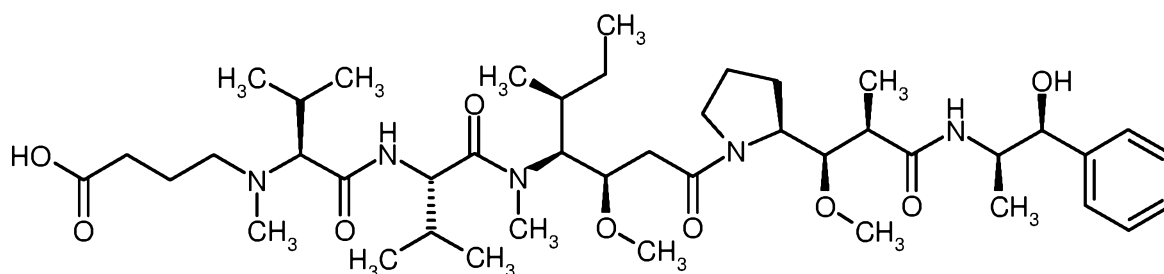
First, in analogy to the synthesis described in Intermediate 74, by coupling of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 26) and phenylethylamine 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*-{(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-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).

HPLC (Method 5): $R_t = 1.7$ min;

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*-{(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



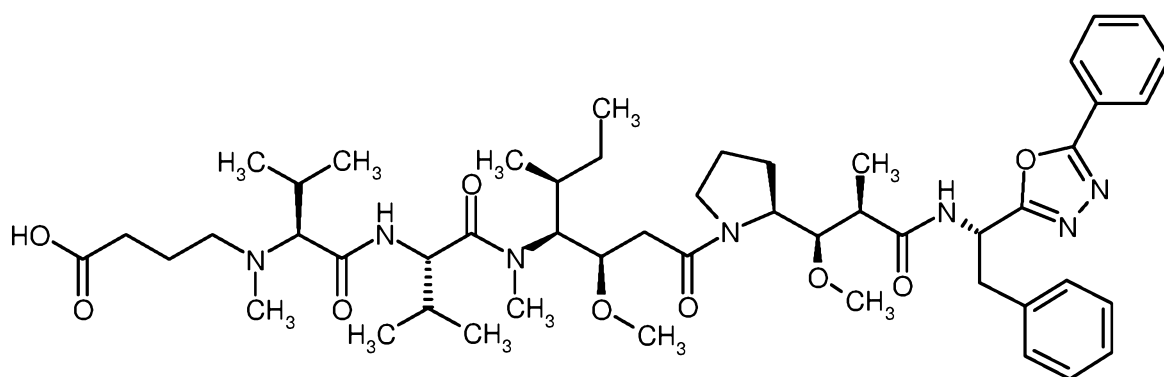
100 mg (0.139 mmol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 40) were used, in analogy to the preparation 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.

HPLC (Method 5): $R_t = 1.5$ min;

10 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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*)-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



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22.4 mg (24 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*)-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

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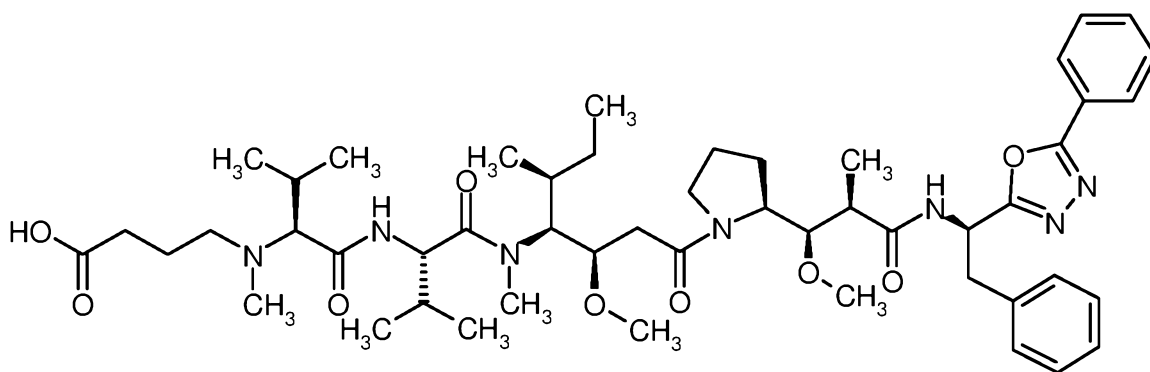
sodium cyanoborohydride. After lyophilization from dioxane, 8.2 mg (38% of theory) of the title compound were obtained in the form of a white solid.

HPLC (Method 10): $R_t = 2.54$ min

LC-MS (Method 12): $R_t = 0.94$ min; MS (ESIpos): $m/z = 919$ ($M+H$)⁺

5 **Intermediate 94**

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*R*)-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



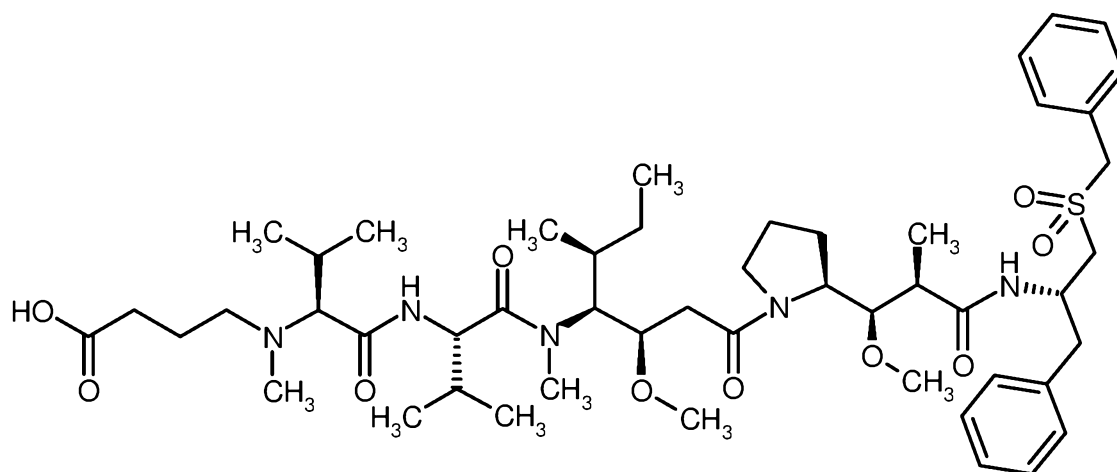
- 10 17.1 mg (18 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*R*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide trifluoroacetate were dissolved in 1.1 ml of dioxane/water and, analogously to the preparation of
- 15 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.

HPLC (Method 10): $R_t = 2.54$ min;

LC-MS (Method 12): $R_t = 0.92$ min; MS (ESIpos): $m/z = 919$ ($M+H$)⁺

Intermediate 95

- 20 *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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

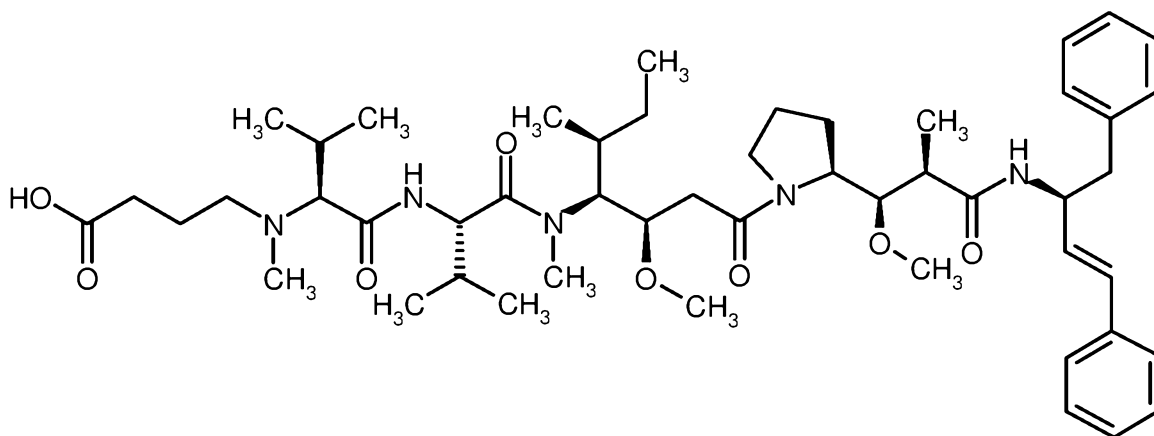


19.3 mg (20 μ mol) *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide trifluoroacetate were dissolved in 1.2 ml of dioxane/water 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.

LC-MS (Method 11): R_t = 0.85 min; MS (ESIpos): m/z = 943 ($M+H$)⁺

10 **Intermediate 96**

N-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*E*)-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



15.5 mg (10 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*E*)-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

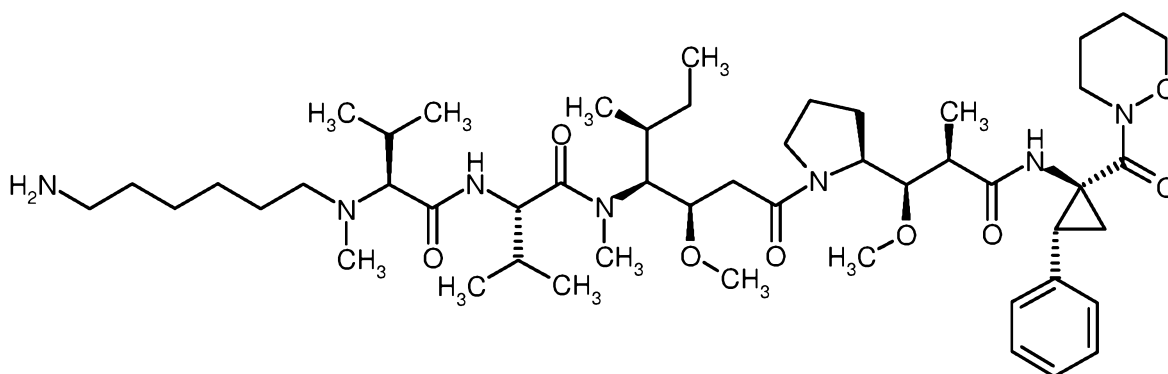
dioxane/water and, analogously to the preparation of Intermediate 61, reacted with 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. After lyophilization from dioxane, 10.3 mg (68% of theory) of the title compound were obtained in the form of a white solid.

5 HPLC (Method 10): $R_t = 2.59$ min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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).

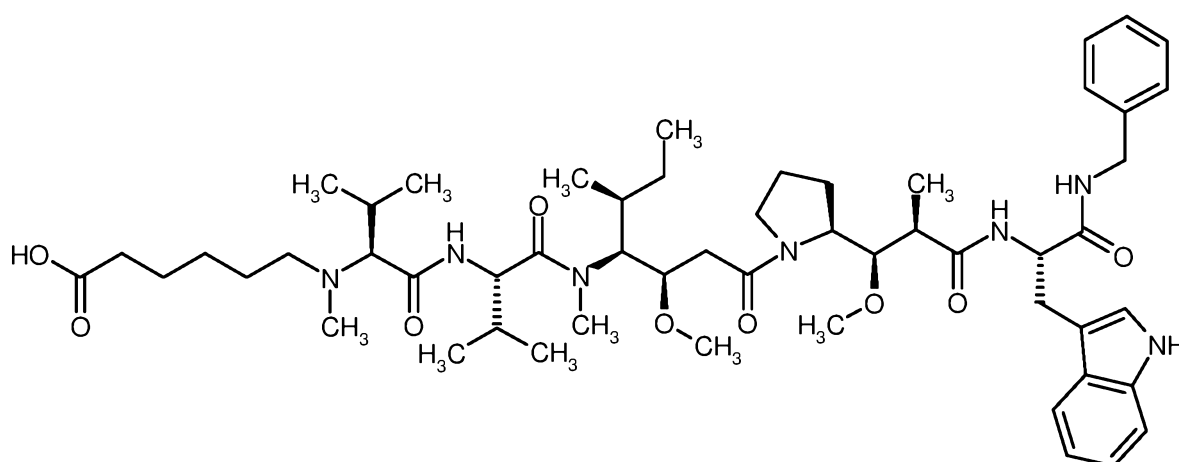
Yield: 69 mg (65% of theory over two stages)

HPLC (Method 5): $R_t = 1.7$ min;

20 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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzylamino)-3-(1*H*-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



This compound was prepared in analogy to the synthesis described in Intermediate 80. The purification was effected by preparative HPLC.

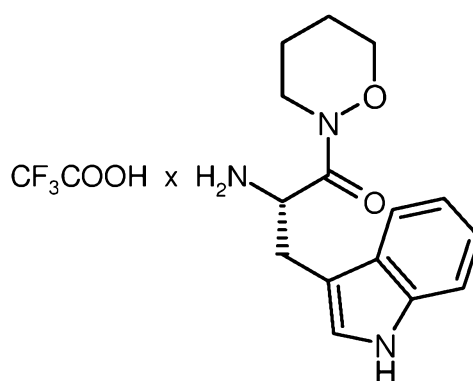
Yield: 40 mg (29% of theory over 3 stages)

5 HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.92$ min; MS (ESIpos): $m/z = 974$ ($M+H$)⁺.

Intermediate 99

(2*S*)-2-amino-3-(1*H*-indol-3-yl)-1-(1,2-oxazinan-2-yl)propan-1-one trifluoroacetate



- 10 324 mg (0.81 mmol) of 2,5-dioxopyrrolidin-1-yl *N*-(*tert*-butoxycarbonyl)-L-tryptophanate were dissolved in 20 ml of DMF, and 200 mg (1.62 mmol) of 1,2-oxazinan-2-yl hydrochloride (Starting Compound 5) and 850 μ l of *N,N*-diisopropylethylamine were added. The reaction mixture was stirred at 50°C overnight and then concentrated under reduced pressure. The residue was taken up in dichloromethane and extracted with water. The organic phase was dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography on silica gel with 4:1 dichloromethane/ethyl acetate as the eluent. The product fractions were concentrated and the residue was dried under high vacuum. This gave 147.5 mg (48% of theory) of the Boc-protected intermediate.
- 15

[(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.

HPLC (Method 12): $R_t = 1.85$ min;

- 5 LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 840$ ($M+H$)⁺.

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.

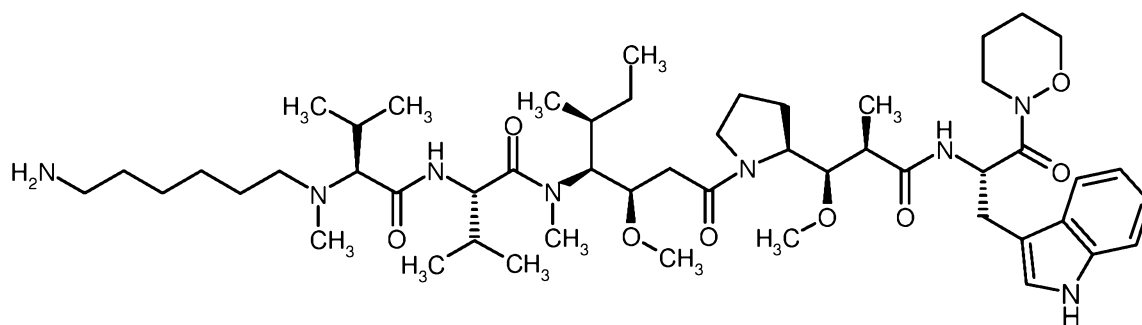
- 10 Yield: 21 mg (37% of theory)

HPLC (Method 12): $R_t = 2.1$ min;

LC-MS (Method 1): $R_t = 1.02$ min; MS (ESIpos): $m/z = 1073$ ($M+H$)⁺.

Intermediate 101

- 15 *N*-(6-aminoheptyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-3-(1*H*-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



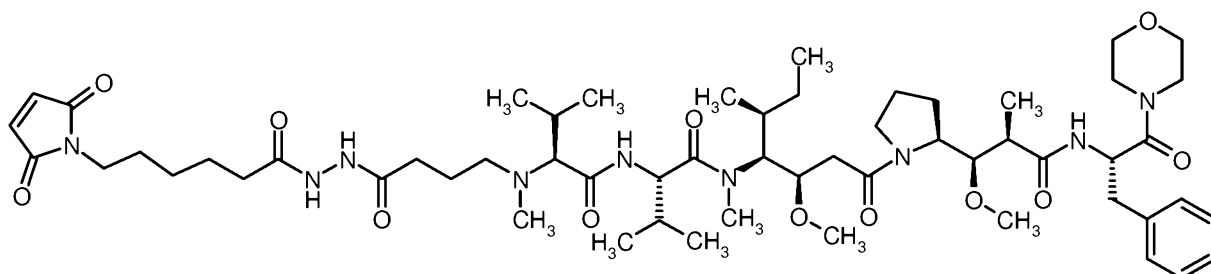
- 20 26.7 mg (24.87 μ mol) of Intermediate 100 were dissolved in 10 ml of methanol and hydrogenated over palladium/activated carbon (5%) under standard hydrogen pressure for 30 min. The catalyst was filtered off and the solvent was evaporated off under reduced pressure. After the residue had been dried under high vacuum, 22.5 mg (96% of theory) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.7$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



This compound was prepared in analogy to the synthesis described in Intermediate 157 from *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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-1*H*-pyrrol-1-yl)hexanehydrazide.

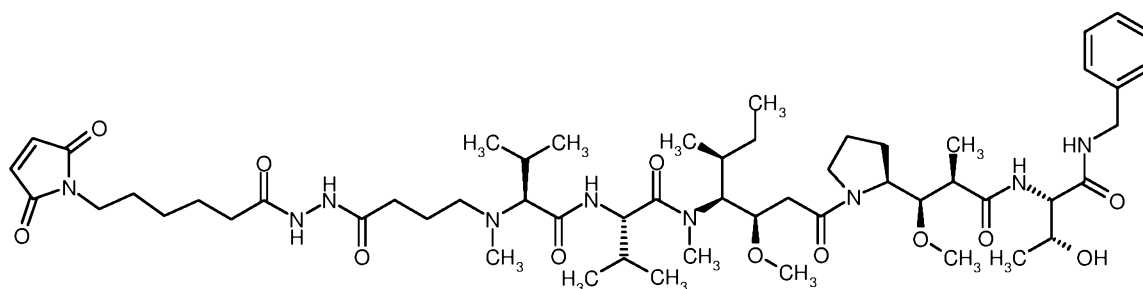
Yield: 8 mg (71% of theory)

HPLC (Method 12): $R_t = 1.9$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*R*)-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



This compound was prepared in analogy to the synthesis described in Intermediate 157 from *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*R*)-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-1*H*-pyrrol-1-yl)hexanehydrazide.

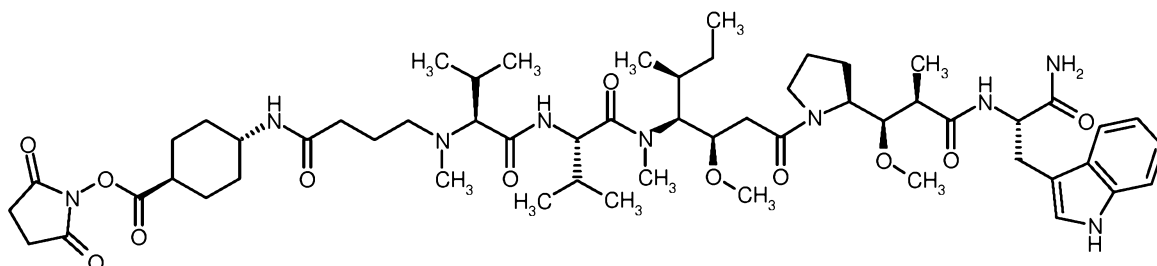
Yield: 3 mg (22% of theory)

HPLC (Method 5): $R_t = 1.6$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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



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.

15 mg (18 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 9 μ l of *N,N*-diisopropylethylamine and with 15 mg (44 μ mol) 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.

HPLC (Method 6): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 0.95$ min; MS (ESIpos): $m/z = 1072$ ($M+H$)⁺.

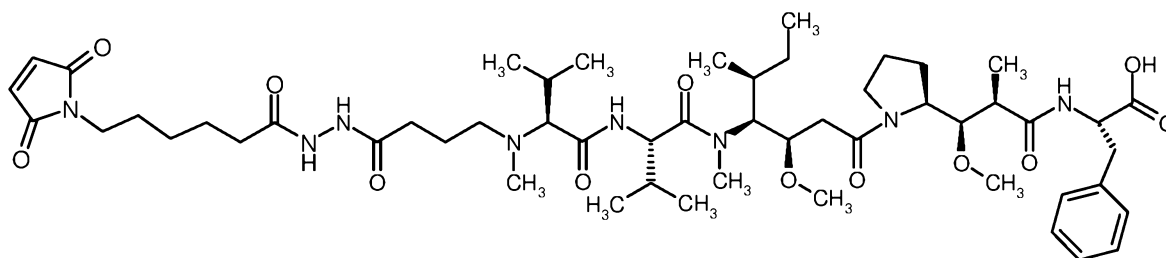
From this protected intermediate, the benzyl ester was first removed by hydrogenolytic means and the free carboxyl component was obtained in quantitative yield. 14 mg (14 μ mol; 1 equiv.) of the deprotected compound were taken up in 5 ml of DMF and admixed with 3.3 mg (29 μ mol; 2.1 equiv.) of *N*-hydroxysuccinimide in the presence of 4.1 mg (21 μ mol; 1.5 equiv.) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 7.5 μ l (44 μ mol; 3.1 equiv.) of *N,N*-diisopropylethylamine and 0.9 mg (7 μ mol; 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.

HPLC (Method 6): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*)-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



This compound was prepared in analogy to the synthesis described in Intermediate 157, proceeding from 4-[[[(2*S*)-1-[[[(2*S*)-1-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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-1*H*-pyrrol-1-yl)hexanohydrazide. The ester intermediate was obtained in 42% yield. In a second step, 6 mg (6

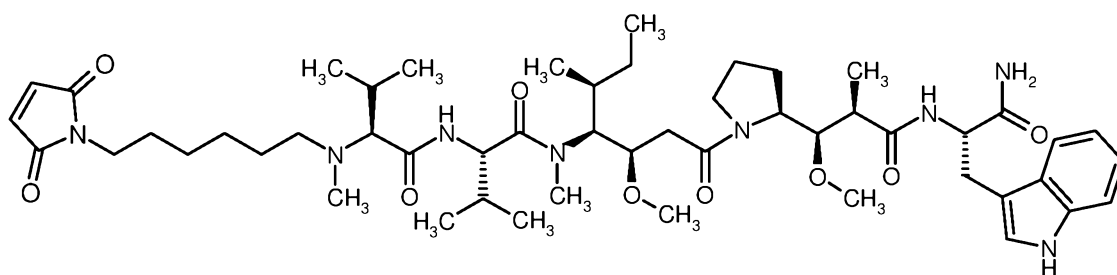
μmol) of this intermediate were cleaved with trifluoroacetic acid the tert-butyl ester. After HPLC purification, 3.4 mg (48% of theory) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.66$ min;

LC-MS (Method 2): $R_t = 1.04$ min; MS (ESIpos): $m/z = 1025$ (M+H)⁺.

5 **Intermediate 106**

N-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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



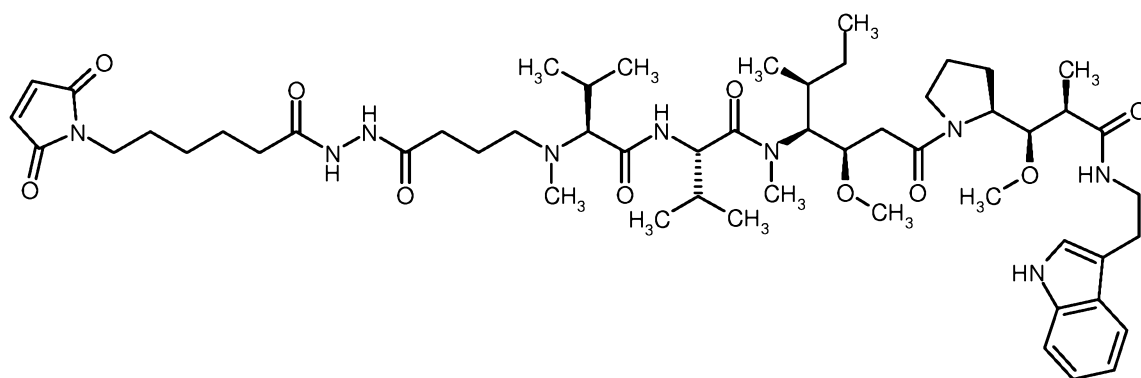
- 10 14 mg (16 μmol) of *N*-(6-aminoheptyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 88) were 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-1*H*-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.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.84$ min; MS (ESIpos): $m/z = 949$ (M+H)⁺.

20 **Intermediate 107**

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-{2-(1*H*-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



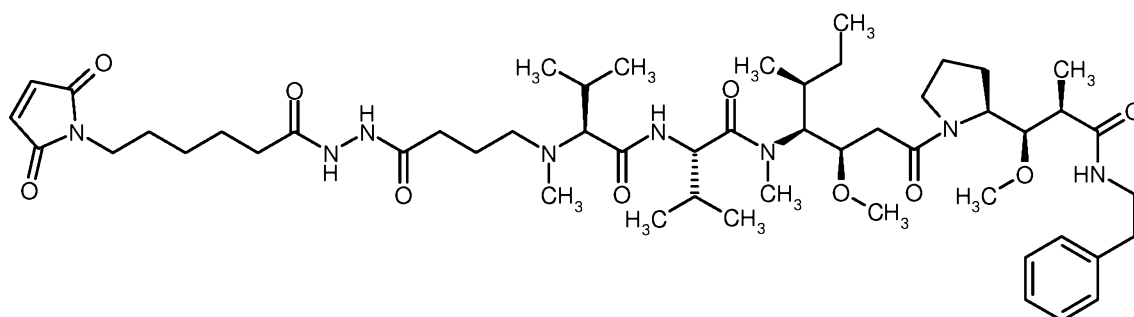
38 mg (47 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 5 {2-(1*H*-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-
 methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 37 ml of DMF and then
 admixed with 71 mg (187 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
 hexafluorophosphate, 33 μ l of *N,N*-diisopropylethylamine and with 37 mg (140 μ mol) of
 commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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
 10 compound were obtained as a colourless foam.

HPLC (Method 5): R_t = 1.6 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-
 15 valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)
 amino]propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



The compound was prepared in analogy to Intermediate 107.

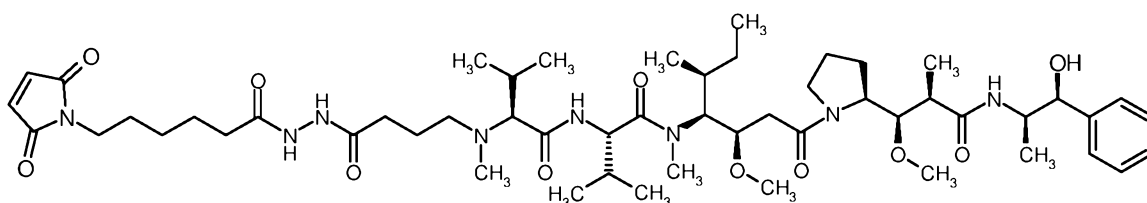
Yield: 2.5 mg (30% of theory)

HPLC (Method 12): $R_t = 1.9$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-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



The compound was prepared in analogy to Intermediate 107 from the compound in Intermediate 92.

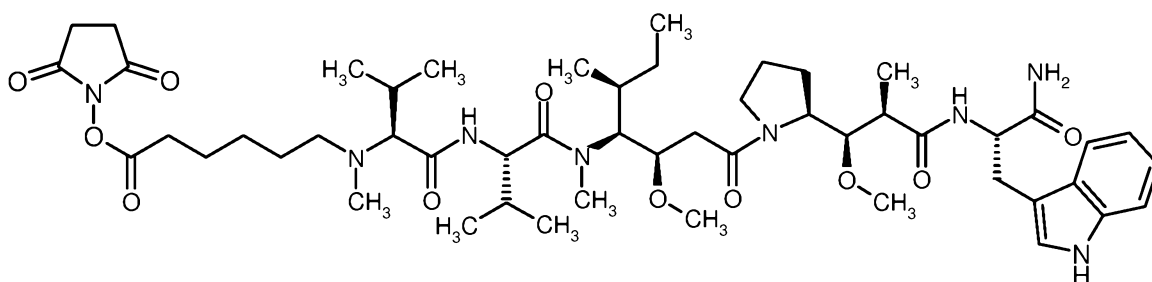
Yield: 35 mg (65% of theory)

HPLC (Method 5): $R_t = 1.9$ min;

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*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-amino-3-(1*H*-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



This compound was prepared in analogy to Intermediate 147 from the compound in Intermediate 83.

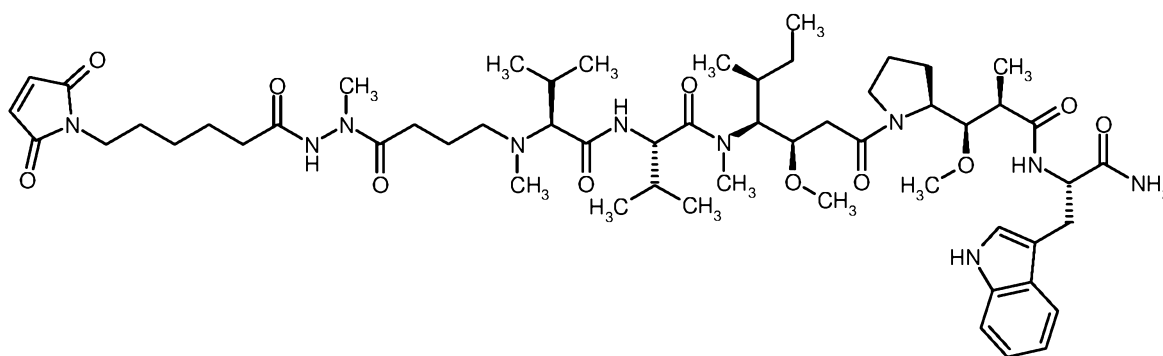
Yield: 2.4 mg (24% of theory)

HPLC (Method 6): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]-1-methylhydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-amino-3-(1*H*-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



10 This compound was prepared in analogy to Intermediate 140 from Intermediate 82 and Intermediate 22.

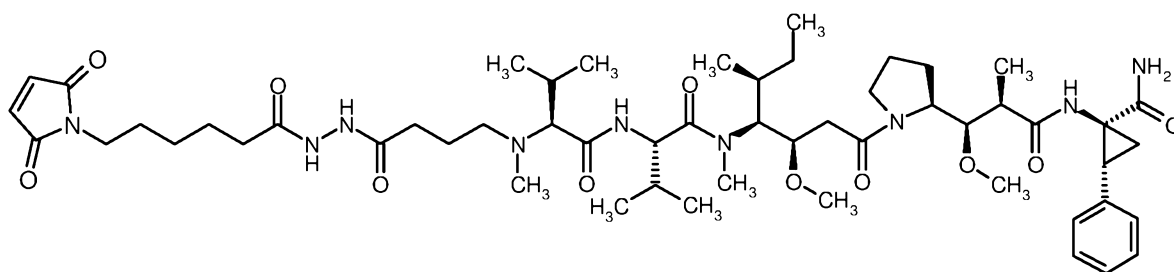
Yield: 6.5 mg (51% of theory)

HPLC (Method 6): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-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



This compound was prepared in analogy to Intermediate 157 from the compound in Intermediate 81.

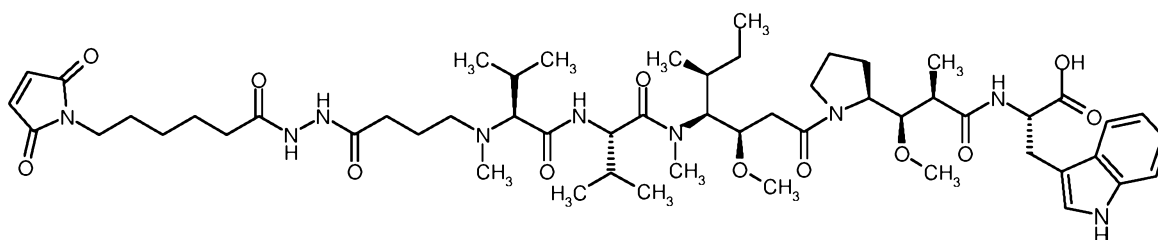
5 Yield: 5.7 mg (57 % of theory)

HPLC (Method 5): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.87$ min; MS (ESIpos): $m/z = 1036$ ($M+H$)⁺.

Intermediate 113

10 *N*-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*)-1-carboxy-2-(1*H*-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



15 95 mg (104 μ mol) of 4-[[[(2*S*)-1-{[(2*S*)-1-{[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-*tert*-butoxy-3-(1*H*-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 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 20 73 μ l of *N,N*-diisopropylethylamine and with 68 mg (261 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 5): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 0.93$ min; MS (ESIpos): $m/z = 1121$ ($M+H$)⁺.

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.

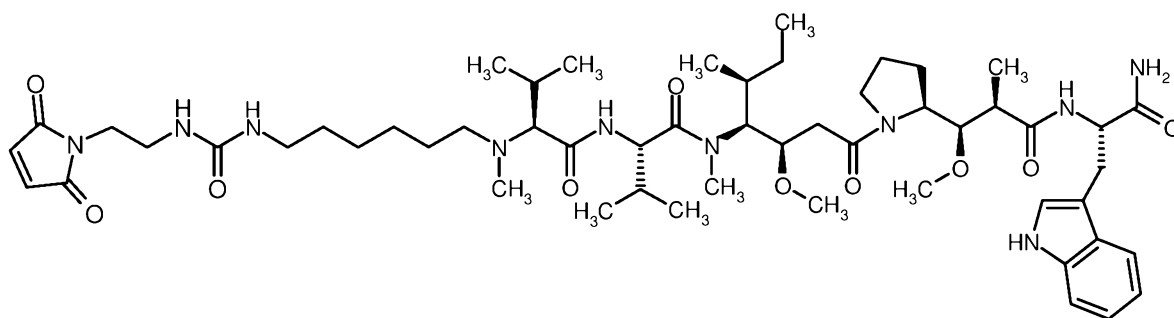
Thus, 61 mg (62 % of theory) of the title compound were obtained as a colourless foam.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 1064$ ($M+H$)⁺.

Intermediate 114

10 *N*-[6-([2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl]carbamoyl)amino]hexyl]-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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



15

5 mg (5 μ mol) of *N*-(6-aminoheptyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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 μ l of DMF and admixed with 5.3 mg (8 μ mol) of 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl carbamate and 2.8 μ l 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.

20

Yield: 0.58 mg (11% of theory) of a colourless foam

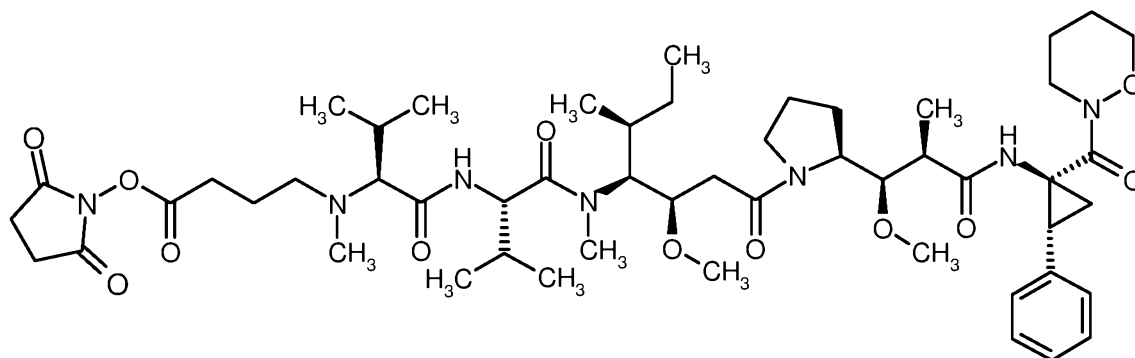
HPLC (Method 5): $R_t = 1.6$ min;

25 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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-

5 valinamide



This compound was prepared in analogy to the compound in Intermediate 147, proceeding from 8 mg (9 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-

10 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.

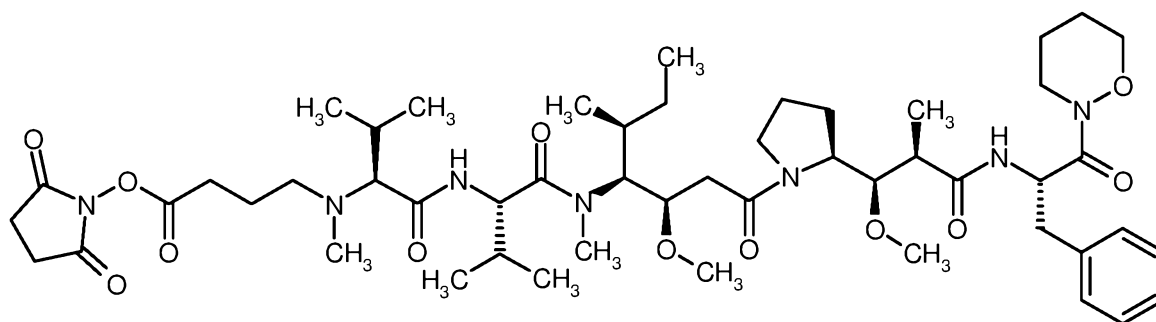
Yield: 3 mg (27% of theory) (hydrolysis-sensitive)

HPLC (Method 5): R_t = 1.7 min;

15 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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



This compound was prepared in analogy to the compound in Intermediate 147, proceeding from 5 mg (6 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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.

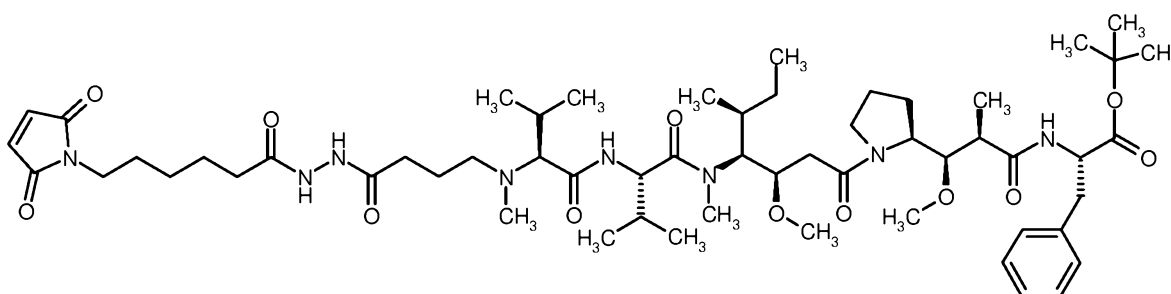
Yield: 3.2 mg (43% of theory) (hydrolysis-sensitive)

10 HPLC (Method 5): $R_t = 1.7$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



This compound was prepared in analogy to Intermediate 157 from the compound in Intermediate 86.

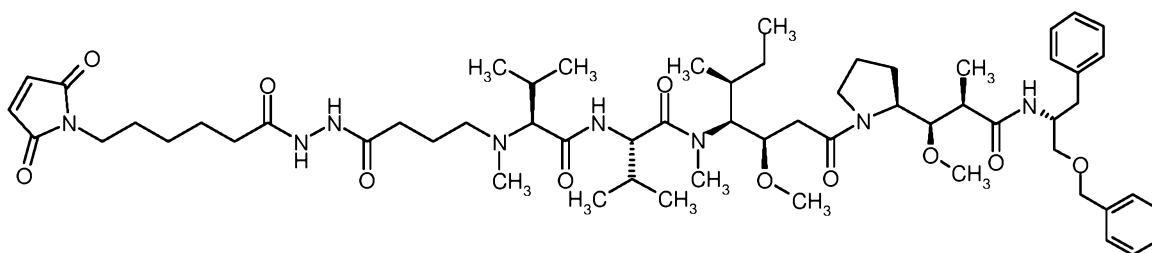
Yield: 7 mg (42% of theory)

HPLC (Method 5): $R_t = 1.6$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*R*)-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

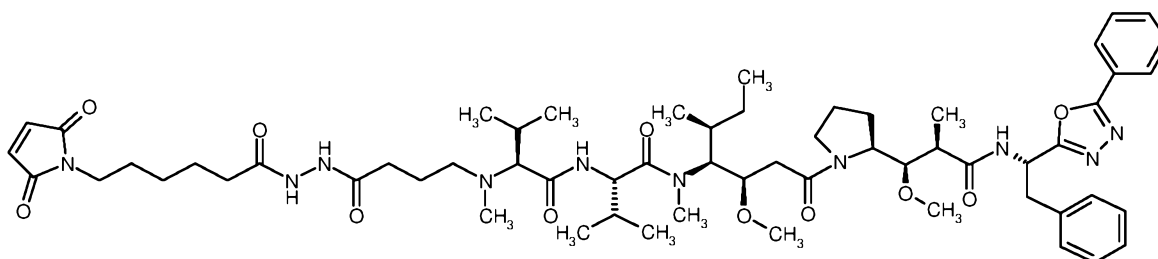


The target compound was prepared analogously to Intermediate 157 from 7 mg (7.8 μ mol) of the compound in Intermediate 68. Yield: 6.3 mg (53% of theory)

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*S*)-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



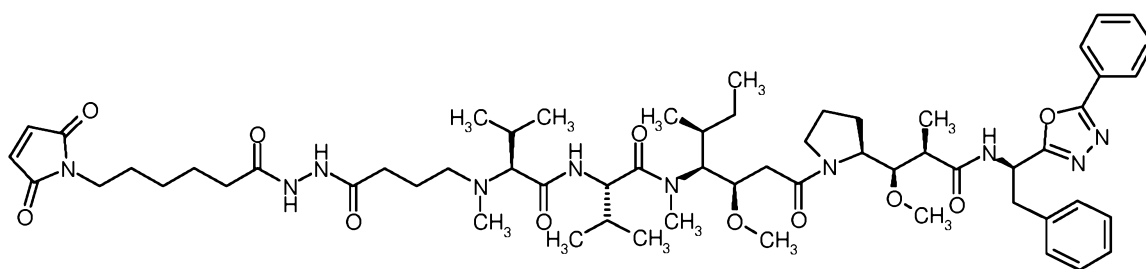
7.4 mg (8.1 mmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*S*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide and 6.3 mg (24.2 mmol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

LC-MS (Method 11): $R_t = 0.89$ min; MS (ESIpos): $m/z = 1126$ ($M+H$)⁺

Intermediate 120

- 5 *N*-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*R*)-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

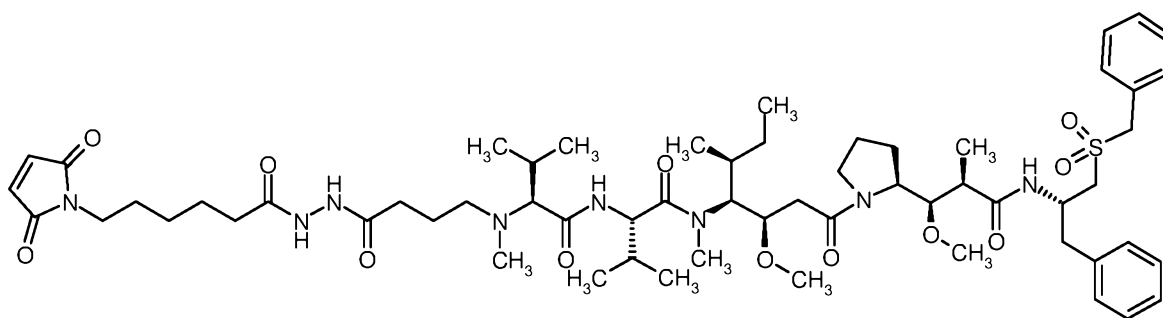


- 10 12.8 mg (13.9 mmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*R*)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide and 10.9 mg (41.8 mmol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanohydrazide 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.
- 15

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-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
- 20

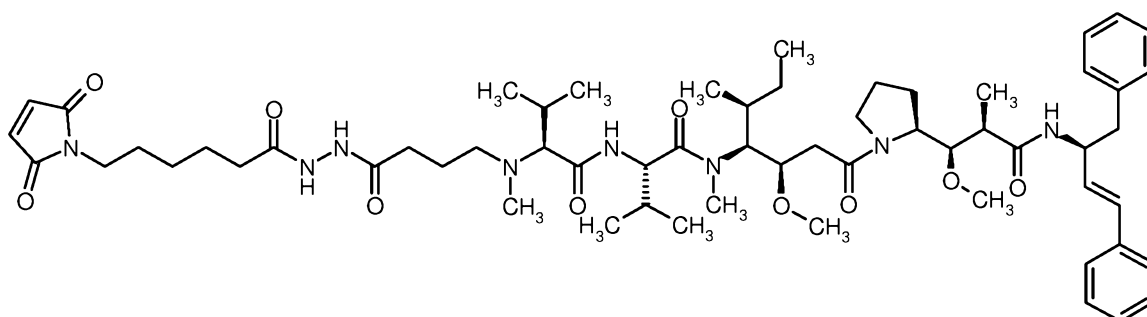


7.4 mg (7.9 mmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 5 {[(2*S*)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide and
 6.2 mg (23.5 mmol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

LC-MS (Method 11): $R_t = 0.87$ min; MS (ESIpos): $m/z = 1150$ ($M+H$)⁺

10 **Intermediate 122**

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*E*)-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



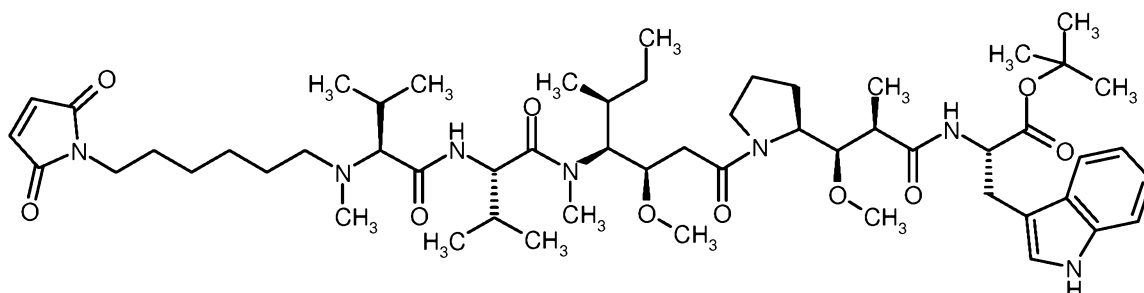
15

8 mg (9.1 mmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 {[(2*S*,3*E*)-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-1*H*-pyrrol-1-yl)hexanehydrazide hydrochloride were coupled and worked up in
 20 analogy to Intermediate 157. 8.2 mg (82% of theory) of the title compound were obtained as a
 white solid.

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-1*H*-pyrrol-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[[2*S*)-1-*tert*-butoxy-3-(1*H*-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



5

30 mg (30 μ mol) 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 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1*H*-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.

10

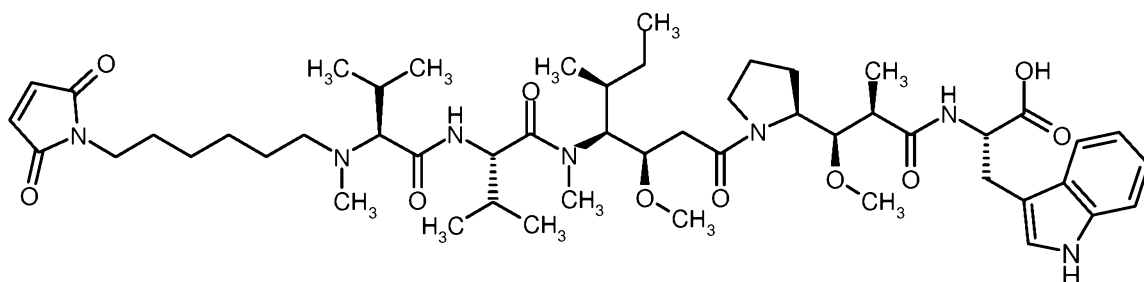
HPLC (Method 5): R_t = 2.2 min;

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-1*H*-pyrrol-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*)-1-carboxy-2-(1*H*-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

15



20

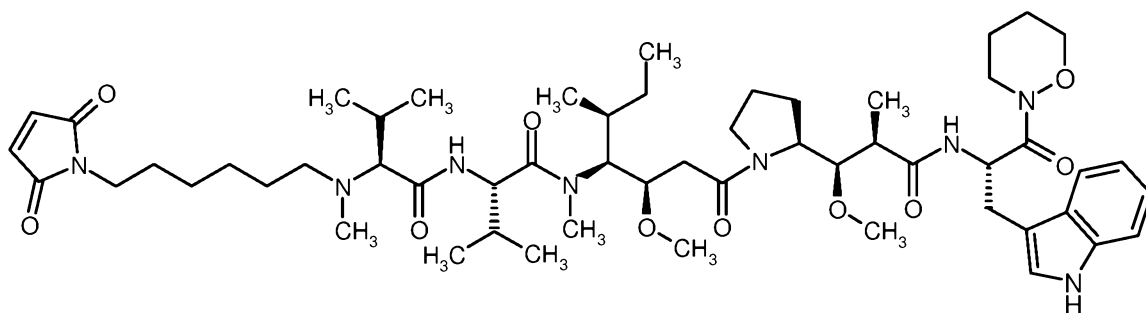
22 mg (20 μ mol) of Intermediate 123 were reacted with 4 ml of trifluoroacetic acid in 8 ml of dichloromethane at RT for 1 h. Thereafter, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 11 mg (54% of theory) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-
5 [(1*R*,2*R*)-3-[(2*S*)-3-(1*H*-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



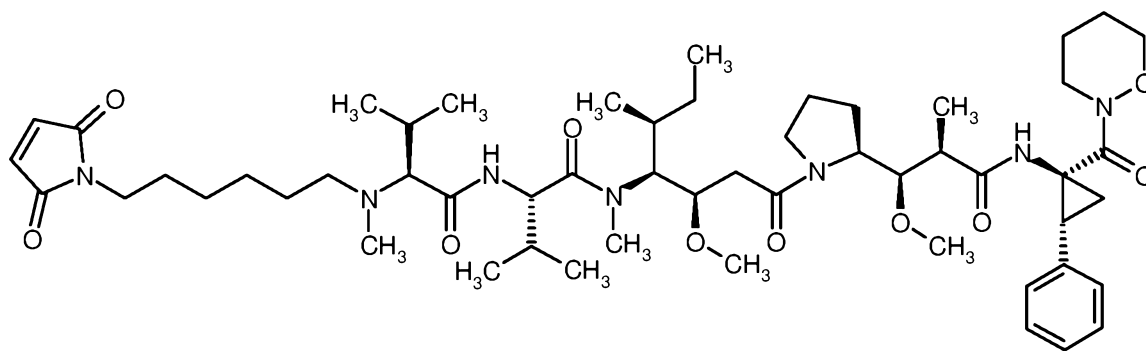
22.5 mg (20 μ mol) of Intermediate 101 were taken up in 2 ml of 1:1 dioxane/water and then
10 admixed with 5.6 mg (40 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate and
with 0.25 ml of saturated sodium hydrogencarbonate solution. The reaction mixture was stirred at
RT for 30 min. Then 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
15 lyophilization, 12.8 mg (50% of theory) of the title compound were obtained as a colourless foam.

HPLC (Method 5): $R_t = 1.9$ min;

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-1*H*-pyrrol-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-
20 {(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-yl)carbonyl)-2-
phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-
valinamide



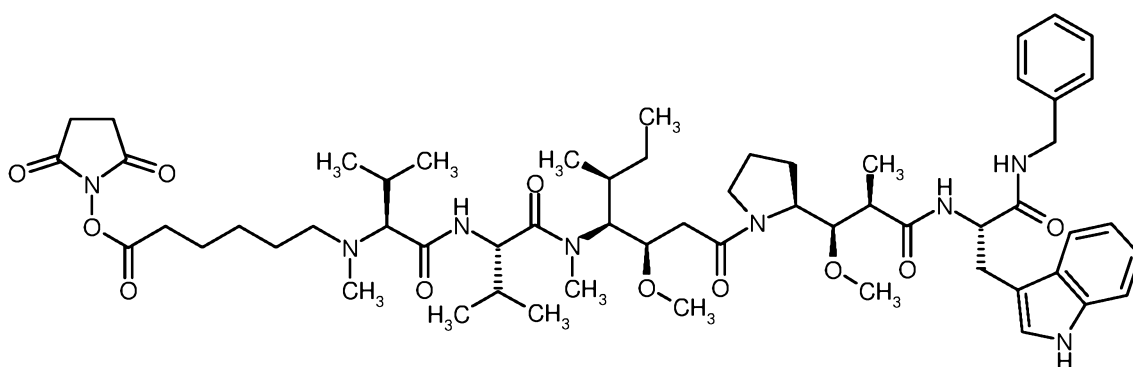
64 mg (70 μ mol) of *N*-(6-aminoheptyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-((2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino)-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 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 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 1 h and then concentrated under reduced pressure. Then another 8 mg (55 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1*H*-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 μ l 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.

HPLC (Method 5): R_t = 1.96 min;

LC-MS (Method 1): R_t = 0.97 min; MS (ESIpos): m/z = 992 ($M+H$)⁺.

Intermediate 127

20 *N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-((2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzylamino)-3-(1*H*-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



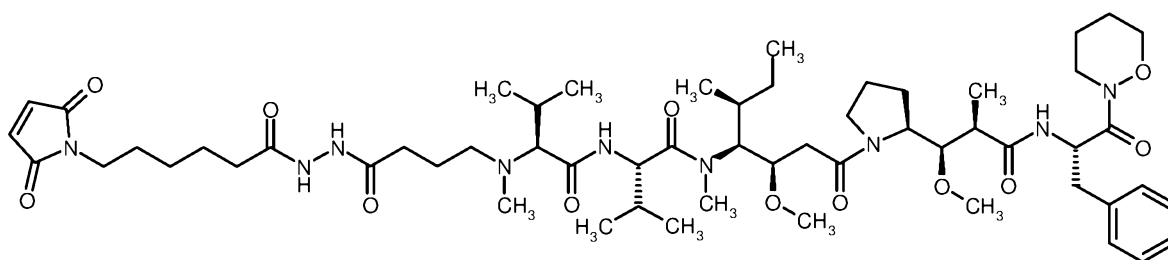
17 mg (18 μ mol) of *N*-(5-carboxypentyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 5 {[(2*S*)-1-(benzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-
 oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide
 (Intermediate 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 μ mol) of 1-(3-
 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.21 mg (0.17 μ mol) 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%
 10 of theory) of the title compound were obtained.

HPLC (Method 5): R_t = 2.0 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-
 15 valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



20 5 mg (5.6 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-
 [(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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

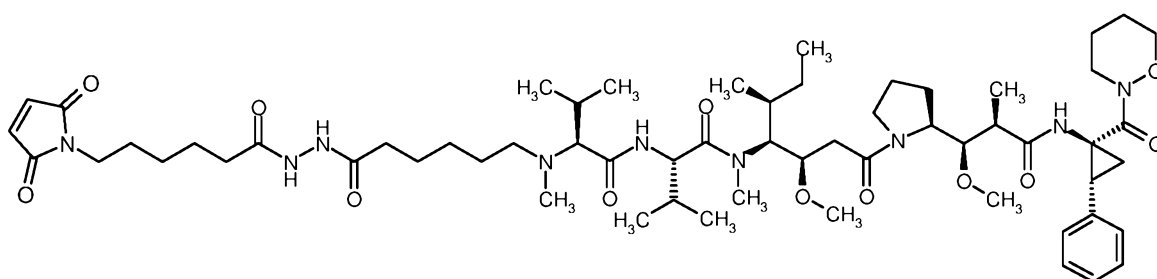
in 845 μl of DMF and then admixed with 3.2 mg (17 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.6 mg (17 μmol) of 1-hydroxy-1*H*-benzotriazole hydrate, 1.96 μl of *N,N*-diisopropylethylamine and with 5.9 mg (22.5 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and
 5 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.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.88$ min; MS (ESIpos): $m/z = 1094$ ($M+H$)⁺.

Intermediate 129

10 *N*-(6-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-6-oxohexyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



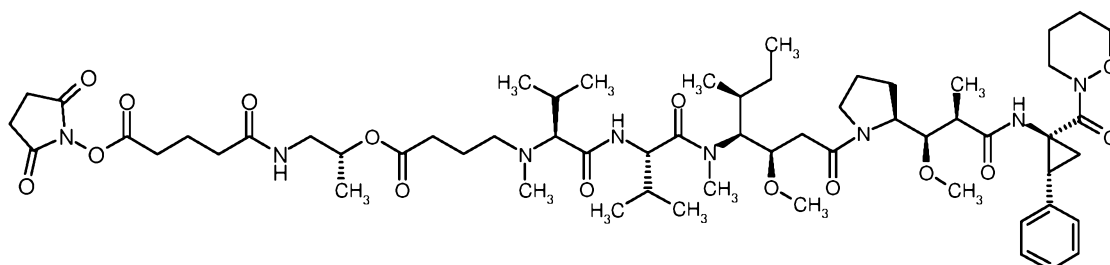
15 4 mg (4.3 μmol) of *N*-(5-carboxypentyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 646 μl of DMF and then admixed with 2.5 mg (13 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.0 mg (13 μmol) of 1-hydroxy-1*H*-
 20 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-1*H*-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.

25 HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 9): $R_t = 4.9$ min; MS (ESIpos): $m/z = 1134$ ($M+H$)⁺.

Intermediate 130

N-(4-{[(2*R*)-1-({5-[(2,5-dioxopyrrolidin-1-yl)oxy]-5-oxopentanoyl}amino)propan-2-yl]oxy}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



10.5 mg (11.7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.7 mg (5.8 μ mol) of 4-dimethylaminopyridine and with 8.2 mg (47 μ mol) of commercially available *tert*-butyl (2*R*)-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.

HPLC (Method 5): R_t = 2.0 min;

LC-MS (Method 1): R_t = 1.03 min; MS (ESIpos): m/z = 1056 ($M+H$)⁺.

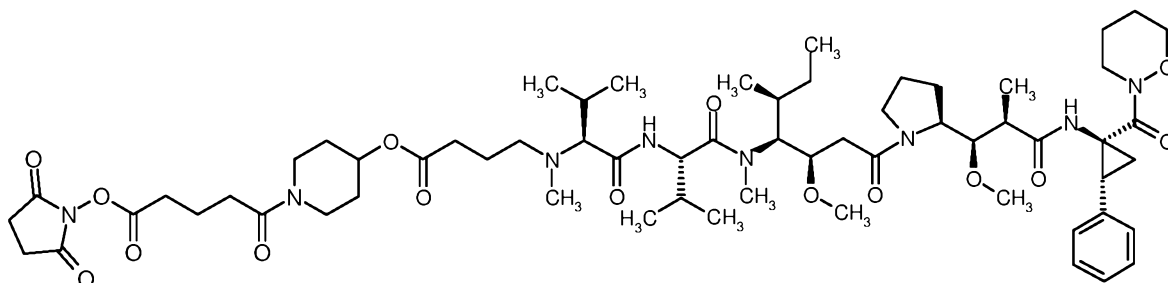
Subsequently, the Boc protecting group was detached with trifluoroacetic acid. 4.9 mg (0.005 mmol) of the deprotected crude product were then, without further purification, taken up in 1.8 ml of dichloromethane and admixed with 3.7 mg (0.011 mmol) of 1,1'-[(1,5-dioxopentane-1,5-diyl)bis(oxy)]dipyrrolidine-2,5-dione, 2.4 μ l (0.014 mmol) of *N,N*-diisopropylethylamine and 0.6 mg (5 μ mol) 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.

HPLC (Method 5): R_t = 1.8 min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-*L*-valinamide



10 mg (11 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(1*S*,2*R*)-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 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.88 mg (6 μ mol) of 4-dimethylaminopyridine and with 5.2 mg (22 μ mol) 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.

HPLC (Method 5): R_t = 2.1 min;

LC-MS (Method 1): R_t = 1.04 min; MS (ESIpos): m/z = 1116 ($M+H$)⁺.

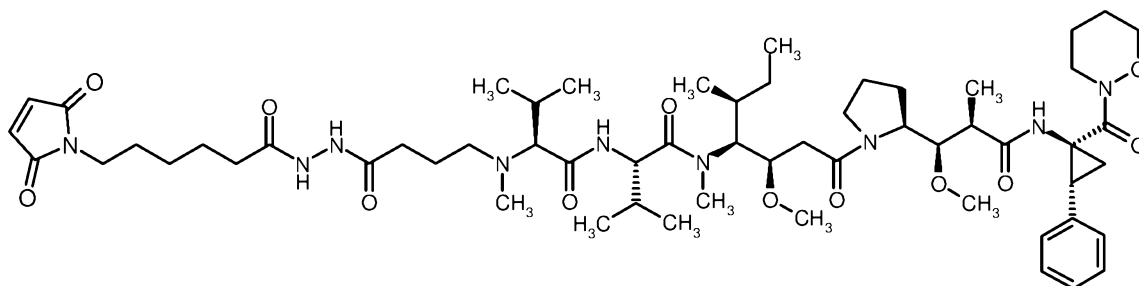
Subsequently, the *Z* protecting group was detached by hydrogenolytic means in ethanol over palladium/activated carbon. 4.6 mg (0.005 mmol) of the deprotected crude product were then, without further purification, taken up in 1.8 ml of dichloromethane and admixed with 3.8 mg (0.012 mmol) of 1,1'-[(1,5-dioxopentane-1,5-diyl)bis(oxy)]dipyrrolidine-2,5-dione, 0.8 μ l (0.005 mmol) of *N,N*-diisopropylethylamine and 0.6 mg (5 μ mol) 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.

HPLC (Method 5): R_t = 1.8 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazinyl}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



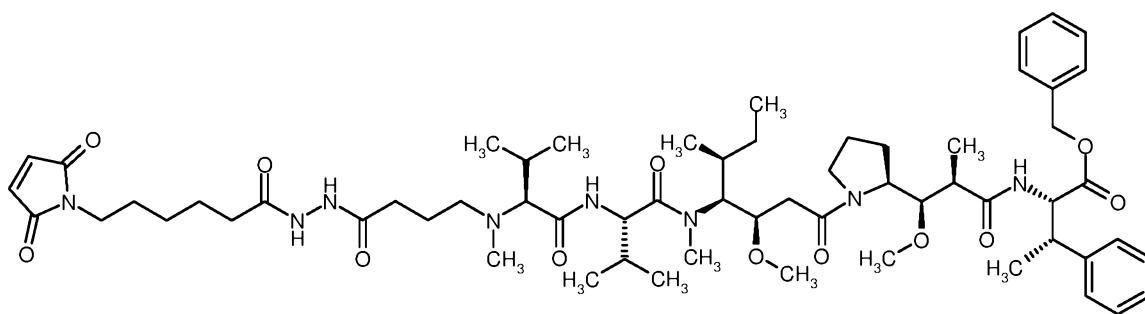
15 mg (16.7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 2500 μ l of DMF and then admixed with 9.6 mg (50 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 7.6 mg (50 μ mol) of 1-hydroxy-1*H*-benzotriazole hydrate, 5.8 μ l of *N,N*-diisopropylethylamine and with 17.4 mg (67 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 5): R_t = 1.7 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazinyl}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*,3*S*)-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



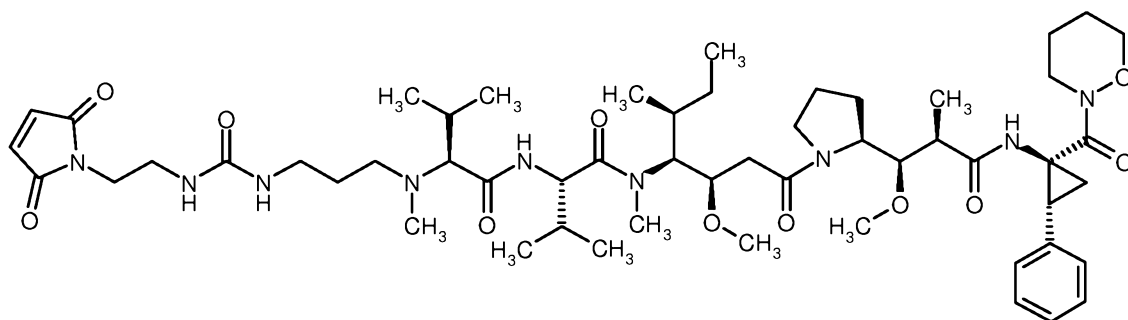
5.8 mg (6.3 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-
 5 {[(2*S*,3*S*)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 943 μ l of DMF and then admixed with 3.6 mg (19 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.9 mg (19 μ mol) of 1-hydroxy-1*H*-benzotriazole hydrate, 2.2 μ l of *N,N*-diisopropylethylamine and with 6.6 mg (25 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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
 10 obtained as a colourless foam.

HPLC (Method 5): R_t = 2.0 min;

LC-MS (Method 1): R_t = 1.03 min; MS (ESIpos): m/z = 1129 ($M+H$)⁺.

Intermediate 134

15 *N*-[3-({[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl]carbamoyl}amino)propyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



First, 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl carbamate was prepared under standard conditions, proceeding from commercially available 1-(2-aminoethyl)-1*H*-pyrrole-2,5-dione trifluoroacetate and 4-nitrophenyl chlorocarbonate.

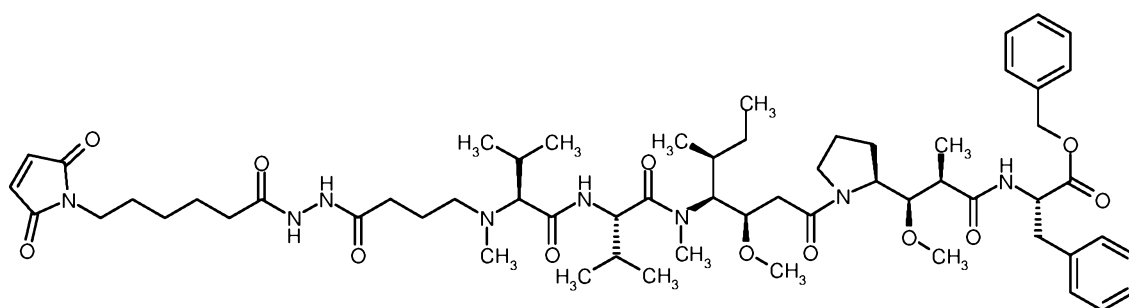
5 mg (6 μ mol) of *N*-(3-aminopropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 1000 μ l of DMF and then admixed with 2 μ l of *N,N*-diisopropylethylamine and with 2.2 mg (9 μ mol) of 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 5): R_t = 1.7 min;

LC-MS (Method 2): R_t = 1.09 min; MS (ESIpos): m/z = 1036 ($M+H$)⁺.

Intermediate 135

15 *N*-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



20 10 mg (11 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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 μ l of DMF and then admixed with 6.3 mg (33 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4.5 mg (33 μ mol) of 1-hydroxy-1*H*-benzotriazole hydrate, 5.7 μ l of *N,N*-diisopropylethylamine and with 11.5 mg (44 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was

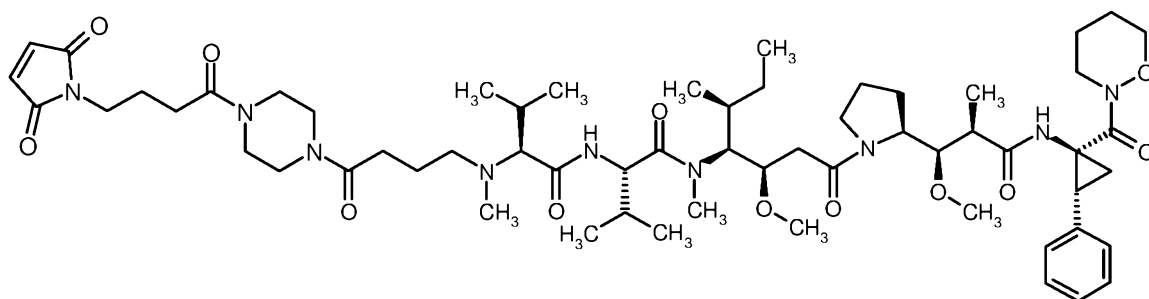
purified by means of preparative HPLC. Thus, 2.6 mg (14% of theory) of the title compound were obtained as a colourless foam.

HPLC (Method 6): $R_t = 2.1$ min;

LC-MS (Method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 1115$ ($M+H$)⁺.

5 Intermediate 136

N-(4-{4-[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoyl]piperazin-1-yl}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



First, 1-[4-oxo-4-(piperazin-1-yl)butyl]-1*H*-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-1*H*-pyrrol-1-yl)butanoic acid over 2 stages.

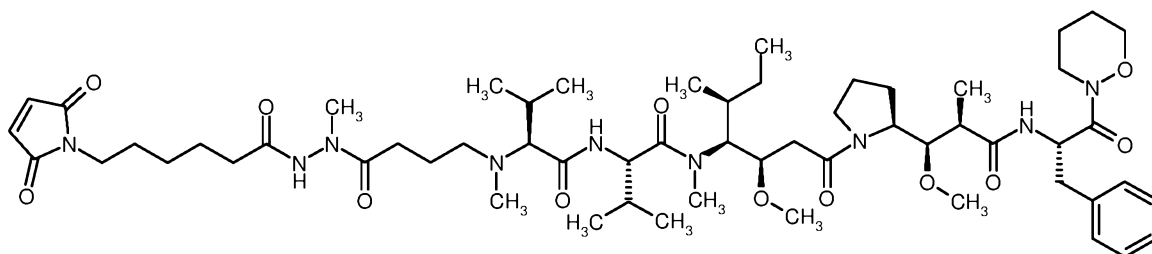
5 mg (5.6 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-
15 [(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]
amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were
dissolved in 1000 μ l of DMF and then admixed with 2.1 mg (11 μ mol) of 1-(3-
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.7 mg (11 μ mol) of 1-hydroxy-1*H*-
benzotriazole hydrate, 2 μ l of *N,N*-diisopropylethylamine and with 3.5 mg (5.6 μ mol) of 1-[4-oxo-
20 4-(piperazin-1-yl)butyl]-1*H*-pyrrole-2,5-dione trifluoroacetate. The mixture was stirred at RT
overnight. Then 2.1 mg (5.6 μ mol) 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
25 lyophilization from water, 0.6 mg (10% of theory) of the title compound was obtained as a
colourless foam.

HPLC (Method 6): $R_t = 1.9$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]-1-methylhydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(2*S*)-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



First, 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N'*-methylhexanehydrazide trifluoroacetate was prepared under standard conditions, proceeding from commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoic acid and *tert*-butyl 1-methylhydrazinecarboxylate over 2 stages.

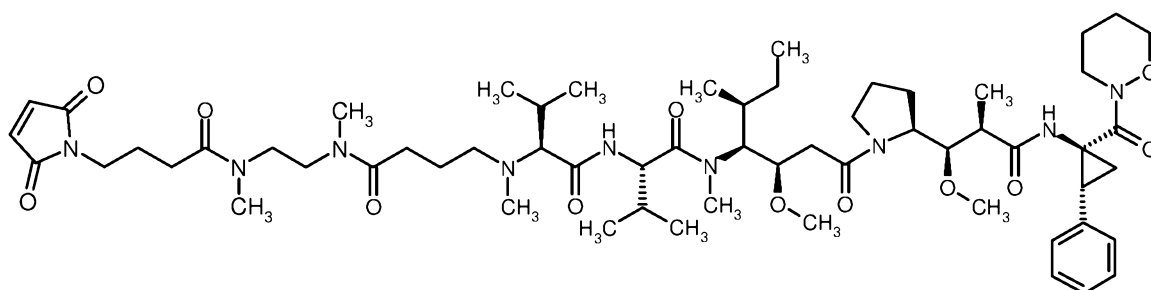
6.9 mg (8 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 2540 μ l of DMF and then admixed with 3.6 mg (9 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 3 μ l of *N,N*-diisopropylethylamine and with 4.1 mg (12 μ mol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 5): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)butanoyl](methyl)amino}ethyl)(methyl)amino]-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



Proceeding from *tert*-butylmethyl 2-(methylamino)ethyl carbamate and 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid, over 2 stages, 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*-methyl-*N*-[2-(methylamino)ethyl]butanamide trifluoroacetate was first prepared by.

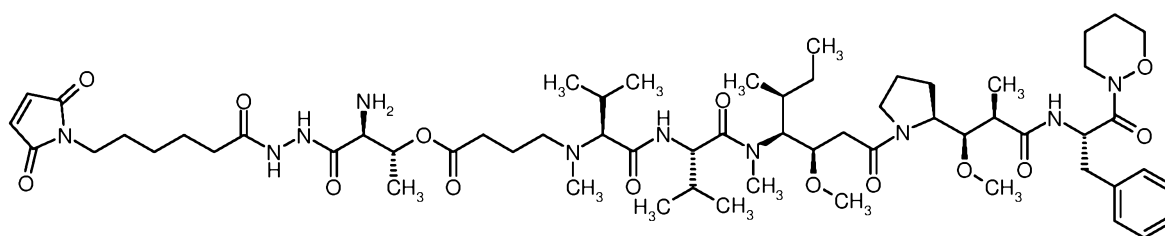
- 5 6.6 mg (7.3 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 2000 μ l of DMF and then admixed with 5.6 mg (14.7 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 2.6 μ l of *N,N*-diisopropylethylamine and with 4.1 mg (9 μ mol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-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%
- 10 of theory) of the title compound were obtained as a colourless foam.
- 15

HPLC (Method 6): R_t = 2.0 min;

LC-MS (Method 1): R_t = 0.91 min; MS (ESIpos): m/z = 1134 ($M+H$)⁺.

Intermediate 139

- (2*R*,3*S*)-3-amino-4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3*R*,4*S*,7*S*,10*S*)-4-[(2*S*)-butan-2-yl]-7,10-diisopropyl-3-(2-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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
- 20



13 mg (14.7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-
 [(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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
 5 in 10 ml of dichloromethane and then admixed with 8.4 mg (44 μ mol) of 1-(3-
 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5.4 mg (44 μ mol) of 4-
 dimethylaminopyridine and with 9 mg (29.3 μ mol) of commercially available benzyl *N*-(*tert*-
 butoxycarbonyl)-L-threoninate. The mixture was stirred at RT for 5 h. Subsequently, the reaction
 10 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.

HPLC (Method 12): R_t = 2.3 min;

15 LC-MS (Method 1): R_t = 1.13 min; MS (ESIpos): m/z = 1178 ($M+H$)⁺.

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 μ mol) of 1-
 (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4 mg (26.2 μ mol) of 1-hydroxy-1*H*-
 20 benzotriazole hydrate, 54.6 μ l of *N,N*-diisopropylethylamine and with 9.1 mg (34.9 μ mol) of
 commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

25 HPLC (Method 12): R_t = 2.1 min;

LC-MS (Method 1): R_t = 0.97 min; MS (ESIpos): m/z = 1295 ($M+H$)⁺.

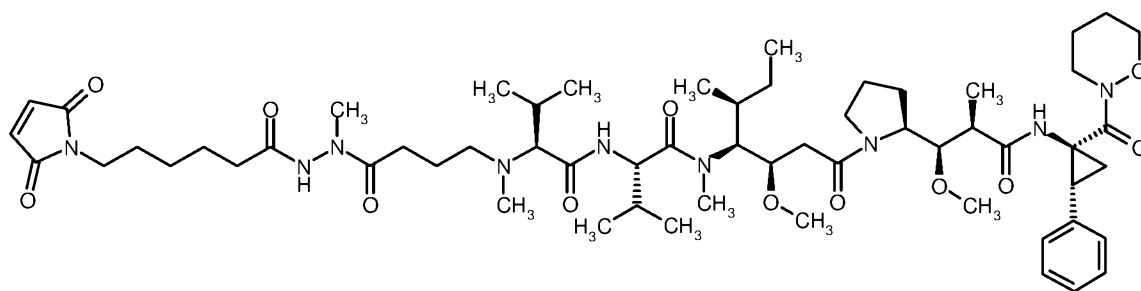
Subsequently, 9.5 mg (7.3 μ mol) were deprotected with 0.5 ml of trifluoroacetic acid in 2 ml of
 dichloromethane of the Boc-protected intermediate and, after lyophilization from dioxane, 9 mg
 (82% of theory) of the title compound were obtained as a colourless foam.

HPLC (Method 12): $R_t = 2.1$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]-1-methylhydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



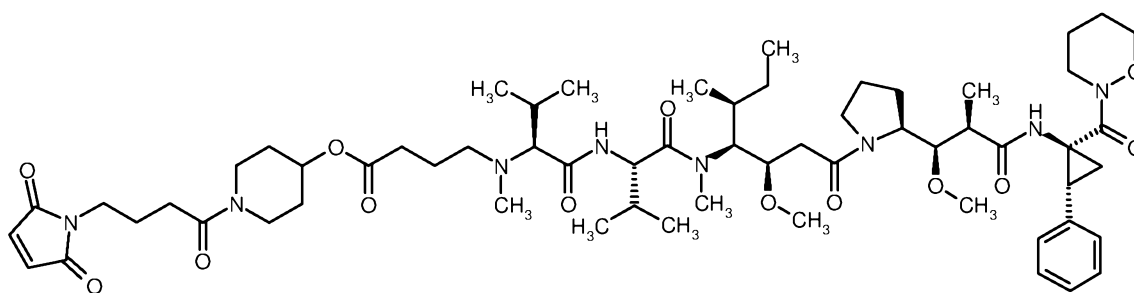
4.1 mg (12 μ mol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*-methylhexanehydrazide trifluoroacetate (Intermediate 22) were dissolved together with 6.9 mg (8 μ mol) of the compound from Intermediate 61 in 2.5 ml of DMF and then admixed with 3.5 mg (9 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 3 μ l 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.

HPLC (Method 5): $R_t = 1.8$ min;

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-1*H*-pyrrol-1-yl)butanoyl]piperidin-4-yl}oxy)-4-oxobutyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



44 mg (49 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.8 mg (24 μ mol) of 4-dimethylaminopyridine and with 23 mg (98 μ mol) 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.

HPLC (Method 5): R_t = 2.1 min;

LC-MS (Method 1): R_t = 1.04 min; MS (ESIpos): m/z = 1116 ($M+H$)⁺.

Subsequently, the *Z* protecting group was detached by hydrogenolytic means in ethanol over palladium/activated carbon.

19 mg (19 μ mol) of the deprotected crude product were then, without further purification, taken up in 4 ml of DMF and admixed with 7 mg (39 μ mol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid, 11 mg (29 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 5 μ l 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.

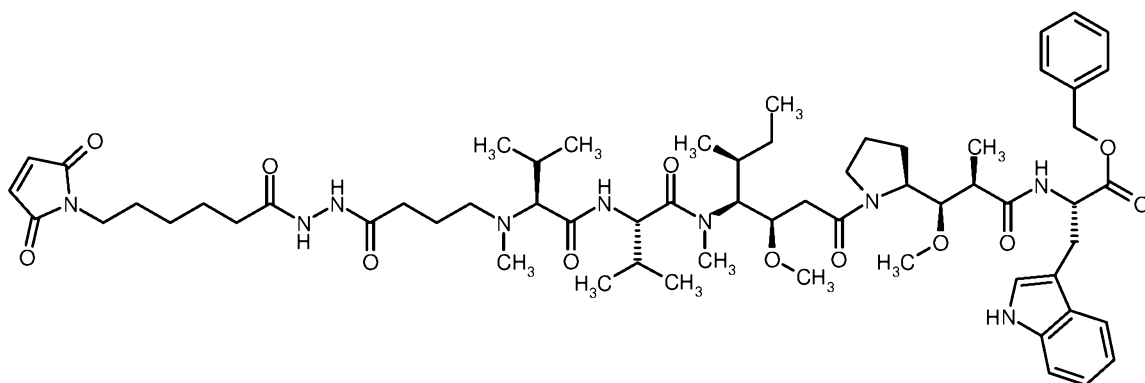
HPLC (Method 5): R_t = 1.8 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-(benzyloxy)-3-(1*H*-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



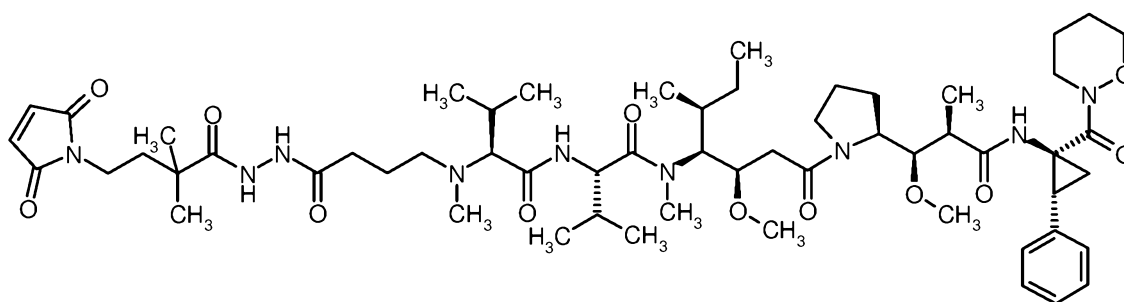
9 mg (9.5 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 5 {[(2*S*)-1-(benzyloxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 72) were dissolved in 1000 μ l of DMF and then admixed with 10 mg (38 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide, 7.2 mg (19 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 8 μ l
 10 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.

HPLC (Method 5): R_t = 1.9 min;

15 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-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-
 20 methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



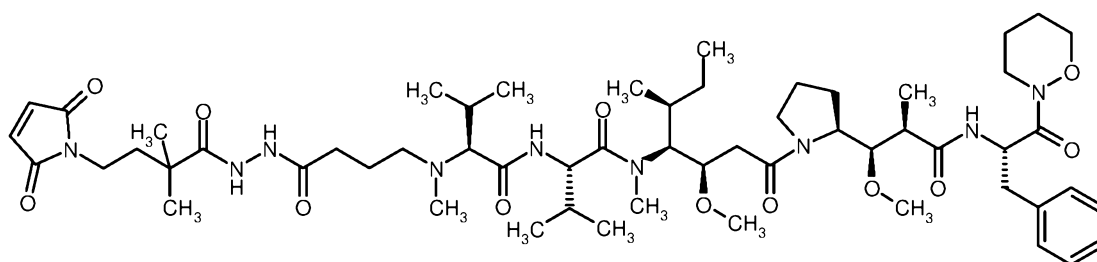
- 6 mg (6.7 μmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide
- 5 (Intermediate 61) were reacted with 3 mg (8.7 μmol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate in analogy to Intermediate 142 to give 2 mg (27% of theory) of the title compound.

HPLC (Method 12): $R_t = 2.1$ min;

LC-MS (Method 3): $R_t = 1.92$ min; MS (ESIpos): $m/z = 1106$ ($M+H$)⁺.

10 **Intermediate 144**

N-(4-{2-[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



15

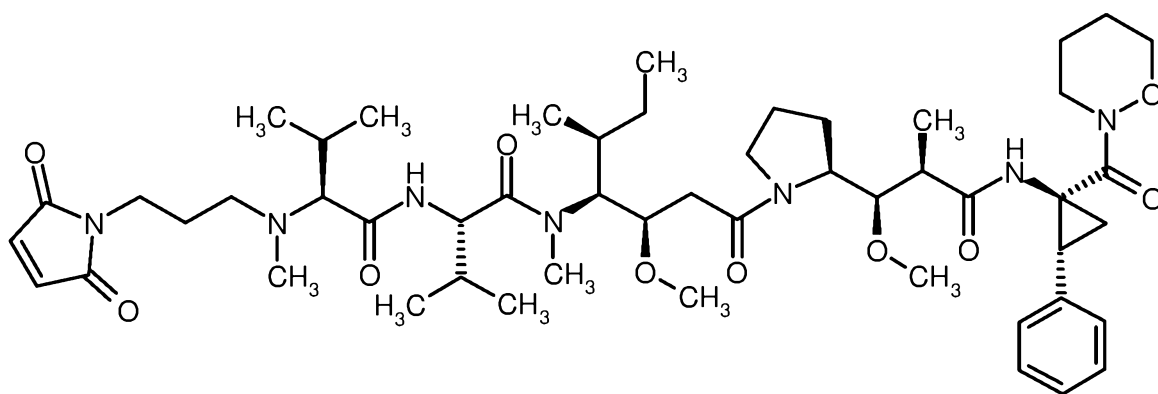
- To a solution of 5 mg (5.6 μmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide in 1 ml of DMF were added 7.65 mg (22.5 μmol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-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-1*H*-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate was added. After stirring overnight, the
- 20

reaction mixture was concentrated and purified by preparative HPLC. 3.5 mg (85% purity, 48% of theory) of the title compound were obtained.

LC-MS (Method 3): $R_t = 1.86$ min; $m/z = 1094$ ($M+H$)⁺.

Intermediate 145

5 *N*-[3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-
 {(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[[(1*S*,2*R*)-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



10

12 mg (14 μ mol) of *N*-(3-aminopropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 μ l of dioxane and admixed with 1.5 ml of saturated sodium hydrogencarbonate solution and then with 3.2 mg (21 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1*H*-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.

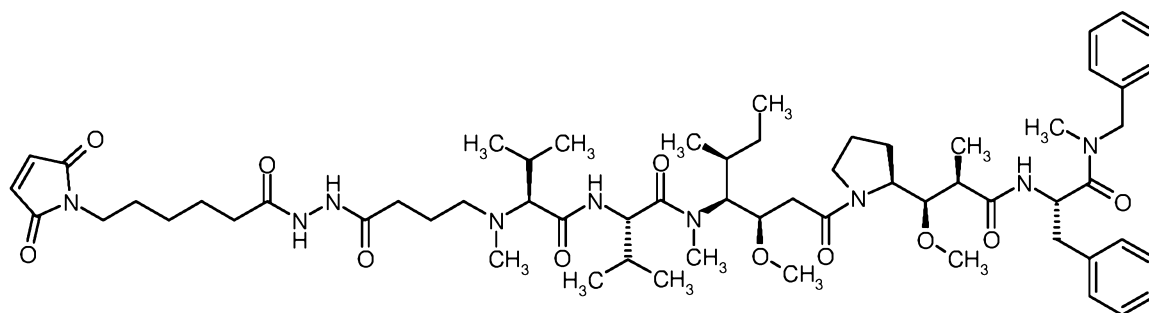
HPLC (Method 5): $R_t = 1.7$ min;

20 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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



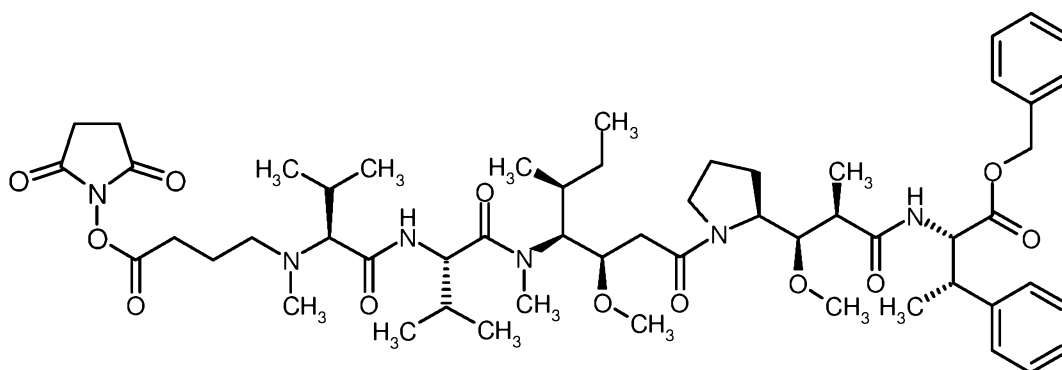
9 mg (9.8 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
5 {[(2*S*)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl] amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide (Intermediate 73) were reacted in analogy to Intermediate 133 with 10 mg (39 μ mol) of 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide to give 1.8 mg (15% of theory) of the title compound.

10 HPLC (Method 12): R_t = 2.2 min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-
15 {[(2*S*,3*S*)-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



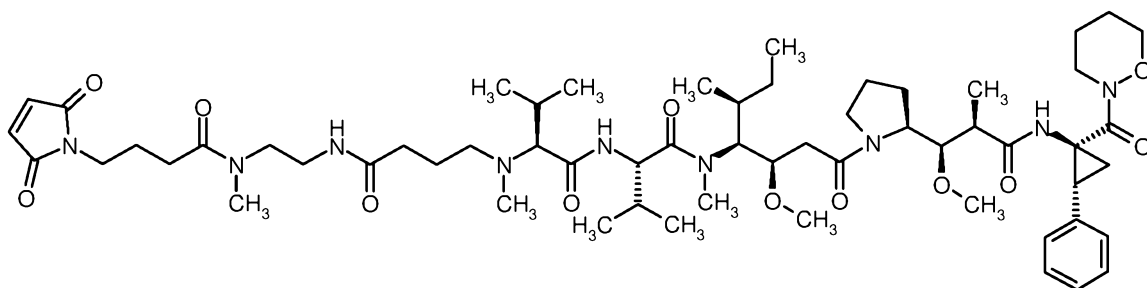
16 mg (17 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
{[(2*S*,3*S*)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl] amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide

(Intermediate 70) were dissolved in 2 ml of dichloromethane and admixed with 2.6 mg (23 μ mol) of 1-hydroxypyrrolidine-2,5-dione and then with 4 mg (21 μ mol) 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.

HPLC (Method 5): R_t = 2.0 min;

Intermediate 148

10 *N*-{4-[(2-{[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoyl](methyl)amino}ethyl)amino]-4-oxobutyl}-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



15 6 mg (7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 μ mol) of *N*-(2-aminoethyl)-4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*-methylbutanamide trifluoroacetate, 10.1 mg (27 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 5 μ l of *N,N*-diisopropylethylamine in 2 ml of DMF and stirred at RT overnight. Then another 5 mg (23.5 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 3 μ l 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.

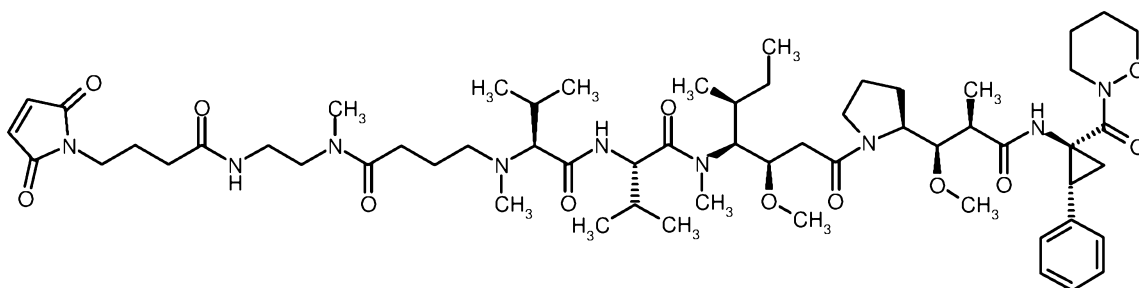
25 The corresponding fractions were concentrated and, by lyophilization from dioxane, 1.3 mg (15% of theory) of the title compound were obtained.

HPLC (Method 12): R_t = 2.1 min;

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-1*H*-pyrrol-1-yl)butanoyl]amino}ethyl)(methyl)amino]-4-oxobutyl}-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-
5 {[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



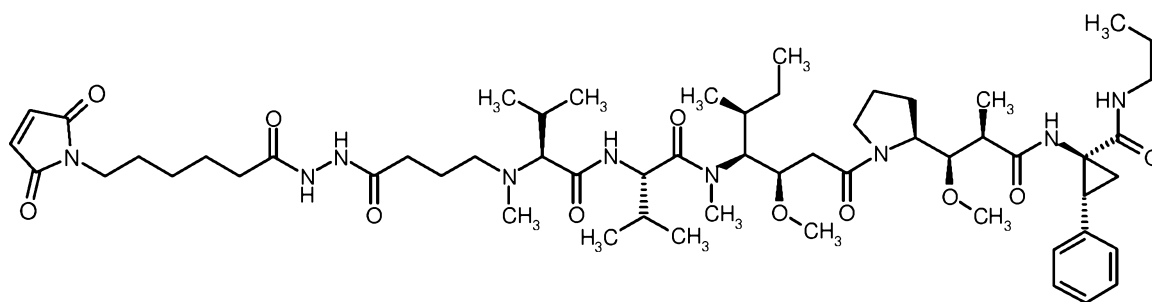
6 mg (7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-
10 [(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]
amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide
(Intermediate 61) were combined with 3.1 mg (9 μ mol) of 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-
yl)-*N*-[2-(methylamino)ethyl]butanamide trifluoroacetate, 10.1 mg (27 μ mol) of O-(7-
azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 5 μ l of *N,N*-
diisopropylethylamine in 2 ml of DMF, and the mixture was stirred at RT for 4 h. Then the solvent
15 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.

HPLC (Method 12): $R_t = 2.1$ min;

LC-MS (Method 1): $R_t = 0.89$ min; MS (ESIpos): $m/z = 1121$ ($M+H$)⁺.

20 Intermediate 150

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-
valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[[1*S*,2*R*)-2-
phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-
yl]-*N*-methyl-L-valinamide



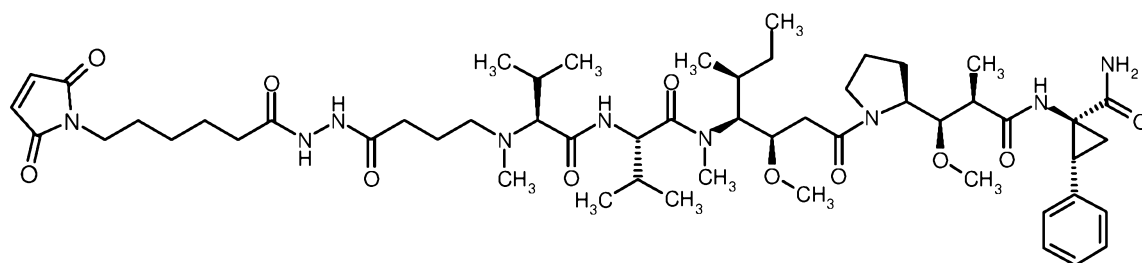
7.9 mg (9 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-[(1*S*,2*R*)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino]propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 3 ml of DMF and then admixed with 10.4 mg (54 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 8.3 mg (54 μ mol) of 1-hydroxy-1*H*-benzotriazole hydrate, 9 μ l of *N,N*-diisopropylethylamine and with 9.5 mg (36 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 6): R_t = 1.9 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*,2*R*)-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



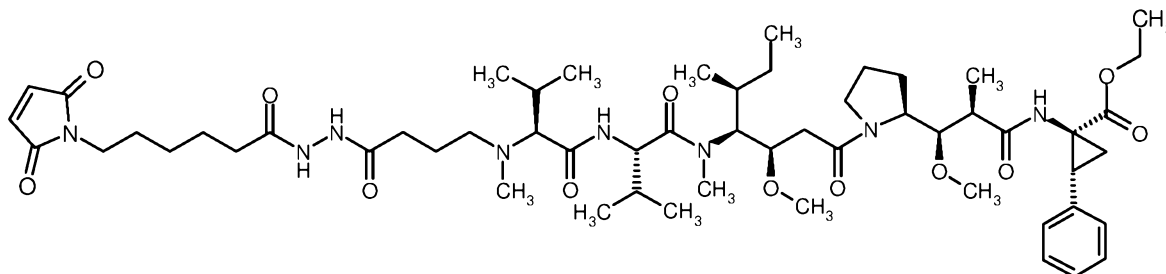
The compound was prepared analogously to Intermediate 150, proceeding from the compound in Intermediate 81.

HPLC (Method 5): R_t = 1.7 min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-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



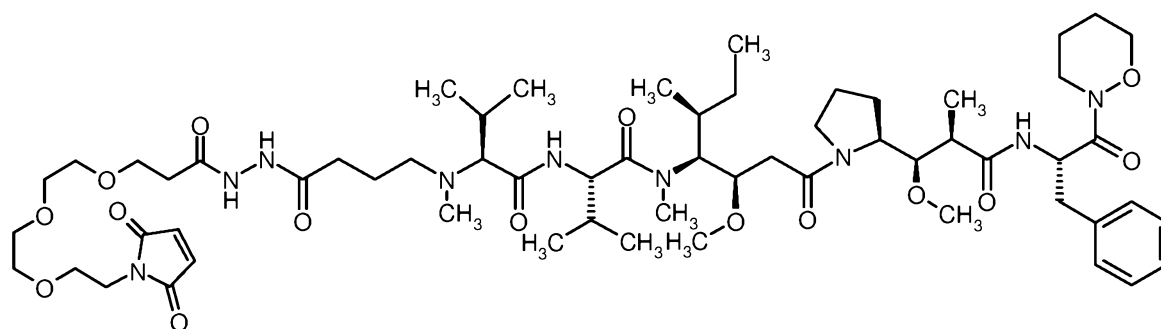
10 mg (12 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-1-(ethoxycarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide were dissolved in 3 ml of DMF and then admixed with 8.9 mg (23 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 10 μ l of *N,N*-diisopropylethylamine and with 12 mg (47 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-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.

HPLC (Method 6): $R_t = 2.0$ min;

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-1*H*-pyrrol-1-yl)-12,15-dioxo-3,6,9-trioxa-13,14-diazaoctadecan-18-yl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(2*S*)-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



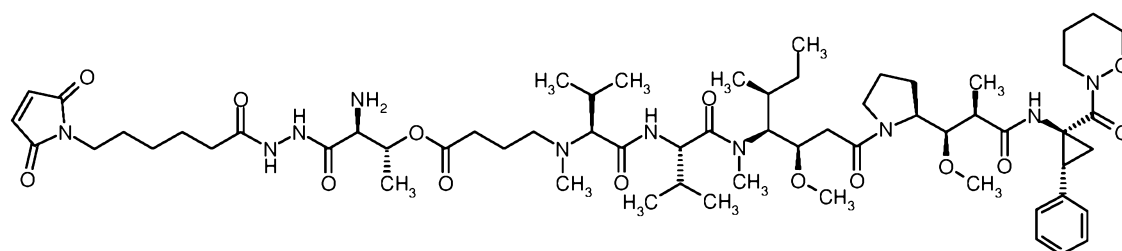
To a solution of 5 mg (5.6 μmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide in 1 ml of DMF were added 9.7 mg (22.5 μmol) of 3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1*H*-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-1*H*-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanehydrazide trifluoroacetate were added. The reaction mixture was stirred at RT overnight and then purified by preparative HPLC.

3.6 mg (51% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.90 min; m/z = 1185 ($M+H$)⁺.

Intermediate 154

(2*R*,3*S*)-3-amino-4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3*R*,4*S*,7*S*,10*S*)-4-[(2*S*)-butan-2-yl]-7,10-diisopropyl-3-(2-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-yl)carbonyl]-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl]-2-oxoethyl)-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate



20

15 mg (17 μmol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*)-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 μ mol) of 4-dimethylaminopyridine and with 10.3 mg (33 μ mol) 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.

HPLC (Method 12): $R_t = 2.5$ min;

LC-MS (Method 1): $R_t = 1.13$ min; MS (ESIpos): $m/z = 1190$ ($M+H$)⁺.

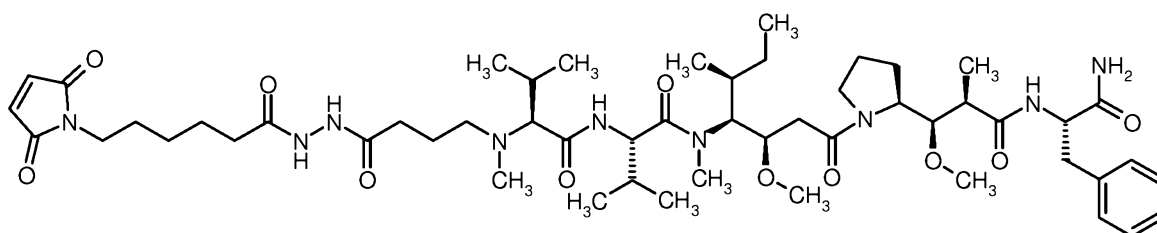
Subsequently, the benzyl ester protecting group was removed by hydrogenation under standard hydrogen pressure in methanol over 10% palladium/activated carbon, and the acid thus obtained, as described in Intermediate 151, was joined to 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide. In a last 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.

HPLC (Method 12): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 0.81$ min; MS (ESIpos): $m/z = 1207$ ($M+H$)⁺.

20 **Intermediate 155**

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



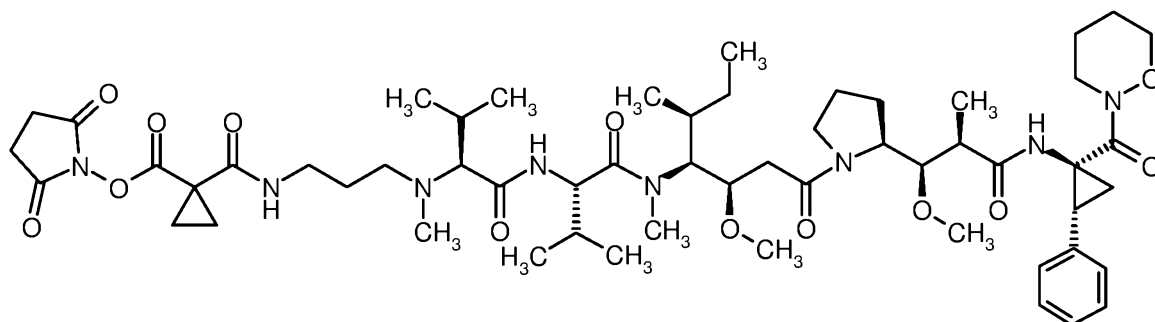
This compound was prepared in analogy to the synthesis described in Intermediate 152, from *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanehydrazide.

HPLC (Method 5): $R_t = 1.6$ min;

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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



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*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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.

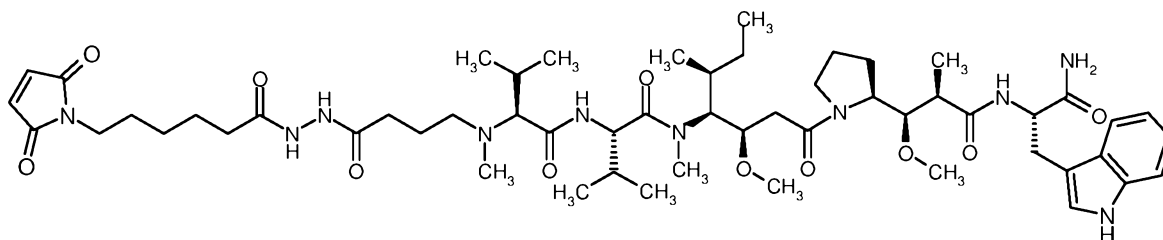
HPLC (Method 12): $R_t = 2.0$ min;

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-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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



15 mg (18 μ mol) of (*N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 5 {[(2*S*)-1-amino-3-(1*H*-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 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 12 μ l of *N,N*-diisopropylethylamine and with 14 mg (53 μ mol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-
 10 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.

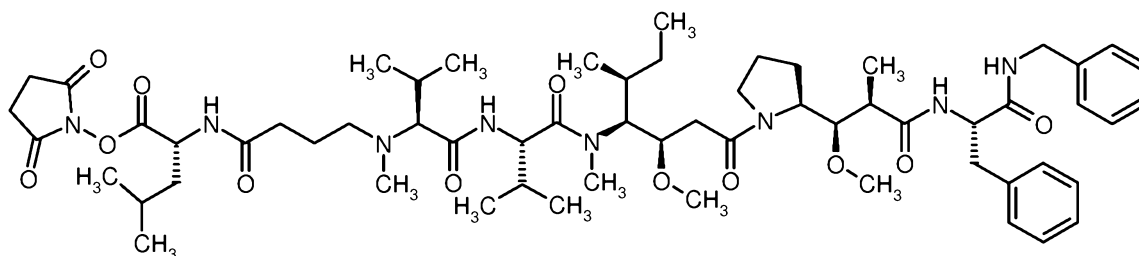
HPLC (Method 5): R_t = 1.6 min;

15 LC-MS (Method 1): R_t = 0.85 min; MS (ESIpos): m/z = 1063 ($M+H$)⁺.

¹H-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).

20 **Intermediate 158**

N-[4-({(2*R*)-1-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-methyl-1-oxopentan-2-yl}amino)-4-oxobutyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



13 mg (14.7 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-
 {[(2*S*)-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 μ mol) of *O*-(7-
 5 azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 6 μ l of *N,N*-
 diisopropylethylamine and with 7 mg (31 μ mol) 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
 10 colourless foam.

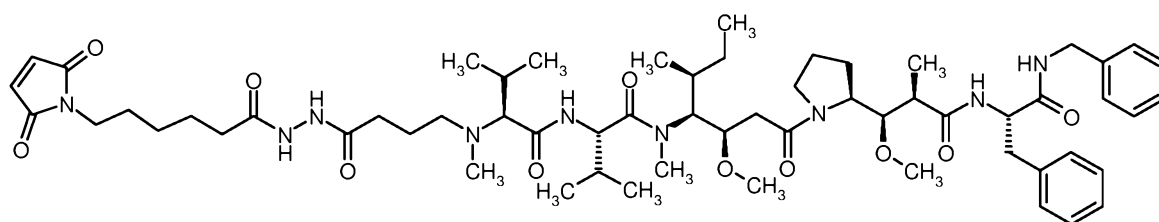
HPLC (Method 5): R_t = 2.2 min;

LC-MS (Method 1): R_t = 1.21 min; MS (ESIpos): m/z = 1076 ($M+H$)⁺.

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
 15 μ mol) of this intermediate were taken up in 1.5 ml of dichloromethane and reacted with 0.8 mg (7
 μ mol) of *N*-hydroxysuccinimide in the presence of 1.2 mg (6 μ mol) of 1-(3-dimethylaminopropyl)-
 3-ethylcarbodiimide hydrochloride and 0.16 mg (1 μ mol) 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.

20 Intermediate 159

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-
 valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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



25 This compound was prepared in analogy to the synthesis described in Intermediate 157, from *N*-(3-
 carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-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-
 30 dihydro-1*H*-pyrrol-1-yl)hexanehydrazide.

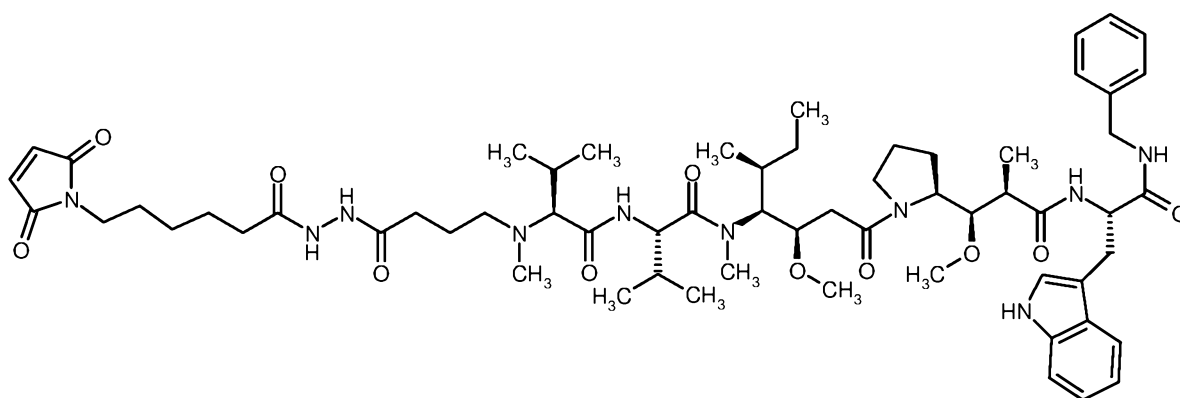
Yield: 6 mg (53% of theory)

HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.94$ min; MS (ESIpos): $m/z = 1114$ ($M+H$)⁺.

Intermediate 160

- 5 *N*-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-(benzylamino)-3-(1*H*-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



- 10 This compound was prepared in analogy to the synthesis described in Intermediate 157, from 20 mg (21 μ mol) of *N*-(3-carboxypropyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-(benzylamino)-3-(1*H*-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-1*H*-pyrrol-1-yl)hexanehydrazide.

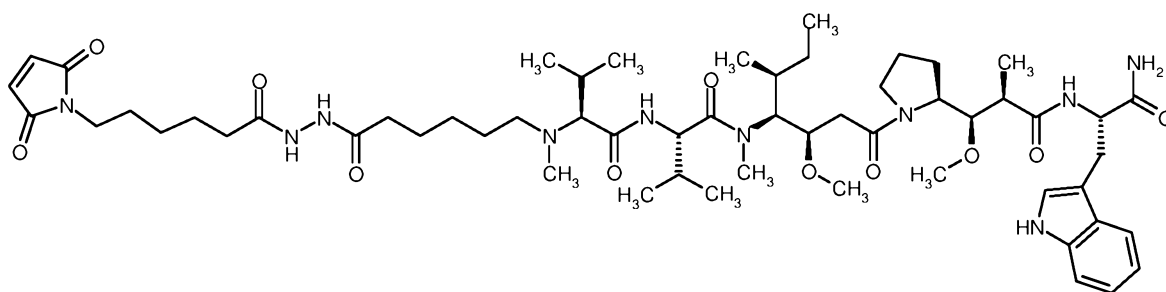
- 15 Yield: 13 mg (52% of theory)

HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.92$ min; MS (ESIpos): $m/z = 1153$ ($M+H$)⁺.

Intermediate 161

- 20 *N*-(6-{2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]hydrazino}-6-oxohexyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-amino-3-(1*H*-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



This compound was prepared in analogy to the synthesis described in Intermediate 157, from *N*-(5-carboxypentyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[(2*S*)-1-amino-3-(1*H*-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-1*H*-pyrrol-1-yl)hexanehydrazide.

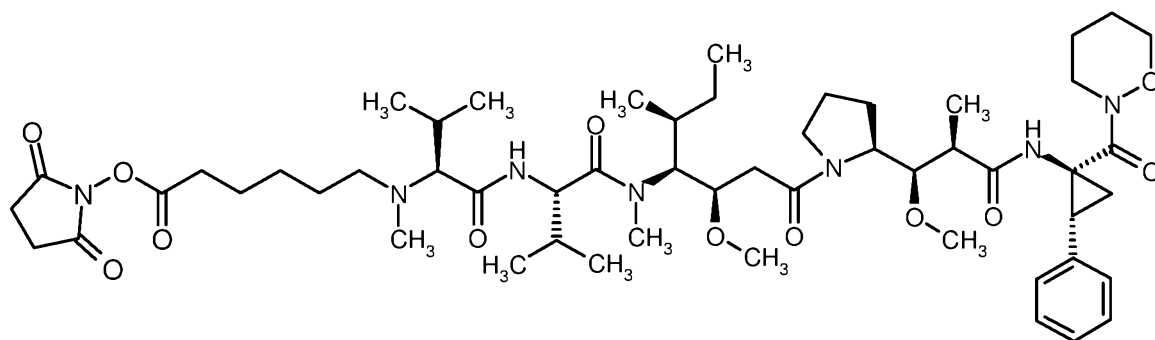
Yield: 0.8 mg (16% of theory)

HPLC (Method 5): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.78$ min; MS (ESIpos): $m/z = 1092$ ($M+H$)⁺.

10 **Intermediate 162**

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino]-3-oxopropyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide



15

18 mg (20 μ mol) of *N*-(5-carboxypentyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(1*S*,2*R*)-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 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.24 mg (0.17 μ mol) of DMAP. After stirring at RT for 2 h, another 22 mg (190 mmol) of 1-hydroxypyrrolidine-2,5-dione, 11 mg

20

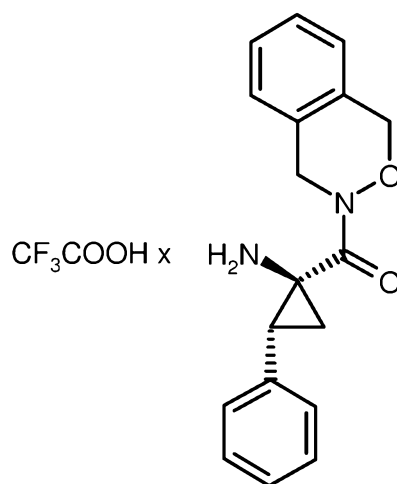
(60 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.24 mg (0.17 μ mol) of DMAP were added and the reaction mixture was stirred at RT for a further hour. This was followed by concentration under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 8.2 mg (41% of theory) of the title compound were obtained.

HPLC (Method 5): R_t = 2.0 min;

LC-MS (Method 11): R_t = 0.9 min; MS (ESIpos): m/z = 1024 ($M+H$)⁺.

Intermediate 163

[(1*S*,2*R*)-1-amino-2-phenylcyclopropyl](1,4-dihydro-3*H*-2,3-benzoxazin-3-yl)methanone trifluoroacetate



First, proceeding from 265 mg (0.82 mmol) of *tert*-butyl (1*S*,2*R*)-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 (1*S*,2*R*)-1-(1,4-dihydro-3*H*-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl carbamate intermediate was prepared.

Yield: 108 mg (34% of theory)

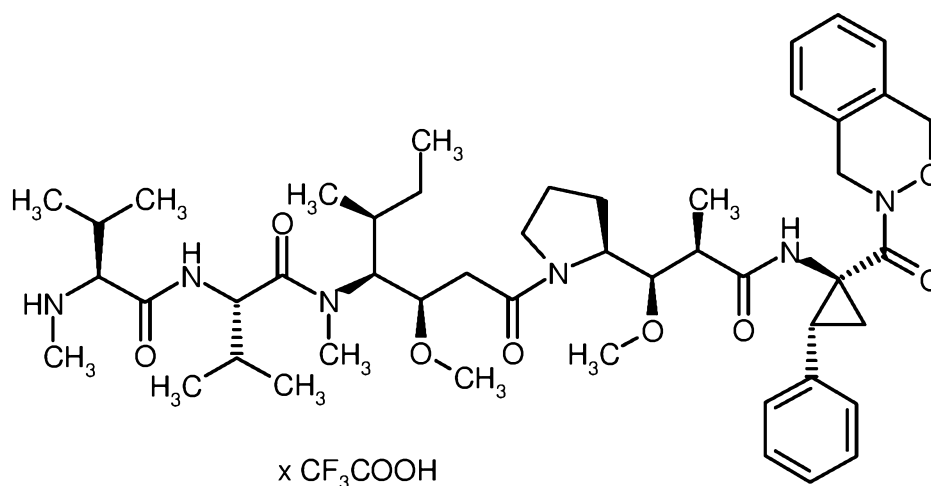
LC-MS (Method 2): R_t = 1.3 min; MS (ESIpos): m/z = 395 ($M+H$)⁺.

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.

LC-MS (Method 1): $R_t = 0.7$ min; MS (ESIpos): $m/z = 295$ ($M+H$)⁺.

Intermediate 164

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-1-(1,4-dihydro-3*H*-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



166 mg (0.196 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-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 [(1*S*,2*R*)-1-amino-2-phenylcyclopropyl](1,4-dihydro-3*H*-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 μ l (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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-1-(1,4-dihydro-3*H*-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.

HPLC (Method 5): $R_t = 1.68$ min;

LC-MS (Method 1): $R_t = 1.51$ min; MS (ESIpos): $m/z = 1083$ ($M+H$)⁺.

19 mg (0.015 mmol) of this intermediate were dissolved in 4 ml of DMF. After 817 μ l 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).

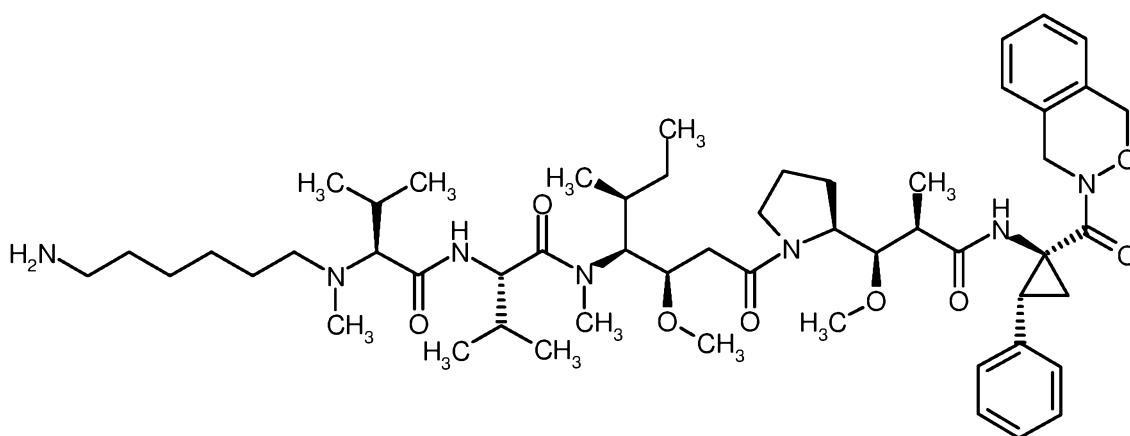
- 5 The corresponding fractions were combined, the solvent was removed under reduced pressure and then the residue was lyophilized from dioxane/water. 12 mg (92% of theory) of the title compound were obtained as a colourless foam.

HPLC (Method 6): R_t = 2.0 min;

LC-MS (Method 1): R_t = 0.94 min; MS (ESIpos): m/z = 861 (M+H)⁺.

10 **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



- 15 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.

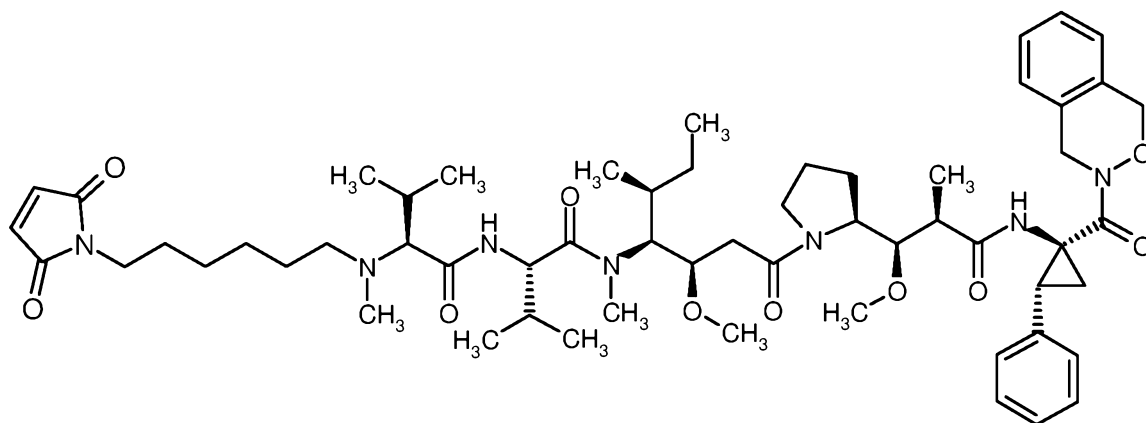
Yield: 4.5 mg (23% of theory over 2 stages)

- 20 HPLC (Method 12): R_t = 1.9 min;

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-
 5 methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide



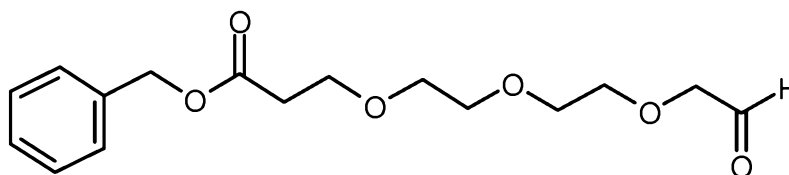
4.4 mg (4.5 μ mol) of Intermediate 165 were taken up in 1 ml of 1:1 dioxane/water and then
 admixed with 1 mg (6.8 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate and with
 50 μ l of saturated aqueous sodium hydrogencarbonate solution. The reaction mixture was stirred at
 10 RT for 30 min. Then another 50 μ l 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.

HPLC (Method 12): $R_t = 2.1$ min;

15 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



The title compound was prepared from 6 g (21.55 mmol) of commercially available 3-{2-[2-(2-
 20 hydroxyethoxy)ethoxy]ethoxy}propanoic acid under standard conditions, first by esterification

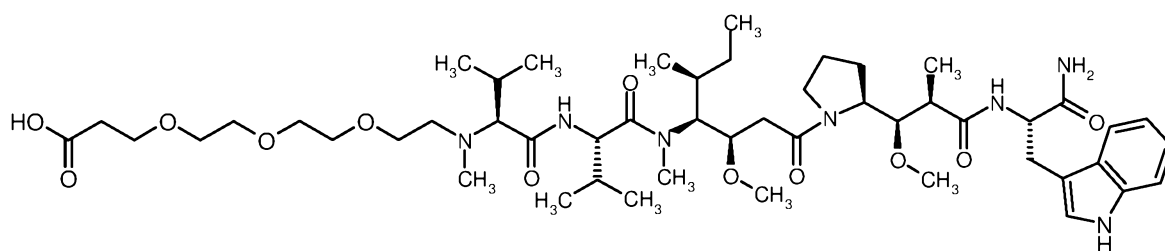
with benzyl chloride and caesium carbonate and subsequent oxidation with sulphur trioxide-pyridine complex.

Yield: 611 mg (10% of theory over 2 stages)

LC-MS (Method 2): $R_t = 1.69$ min; MS (ESIpos): $m/z = 311$ ($M+H$)⁺.

5 **Intermediate 168**

N-(2-{2-[2-(2-carboxyethoxy)ethoxy]ethoxy}ethyl)-*N*-methyl-*L*-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-amino-3-(1*H*-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



10

First, in analogy to the synthesis described in Intermediate 69, by coupling of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-*L*-valyl-*N*-[(2*R*,3*S*,4*S*)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-*N*-methyl-*L*-valinamide (Intermediate 4) and *N*^α-[(2*R*,3*R*)-3-methoxy-2-methyl-3-[(2*S*)-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*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-1-amino-3-(1*H*-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.

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.

HPLC (Method 12): $R_t = 2.04$ min;

LC-MS (Method 1): $R_t = 0.97$ min; MS (ESIpos): $m/z = 1064$ (M+H)⁺.

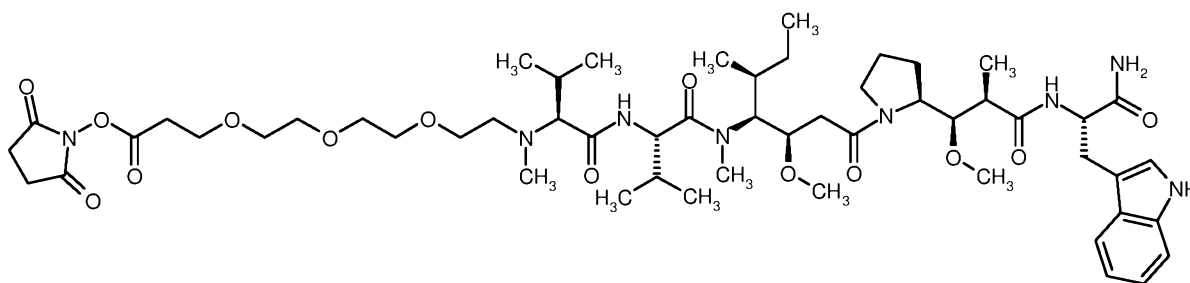
25 mg (0.024 mmol) of this intermediate were taken up in 10 ml of methanol and hydrogenated over 10% palladium on activated carbon under standard hydrogen pressure at RT for 45 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. After lyophilization from dioxane, 19.7 mg (85% of theory) of the title compound were obtained.

HPLC (Method 12): $R_t = 1.8$ min;

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



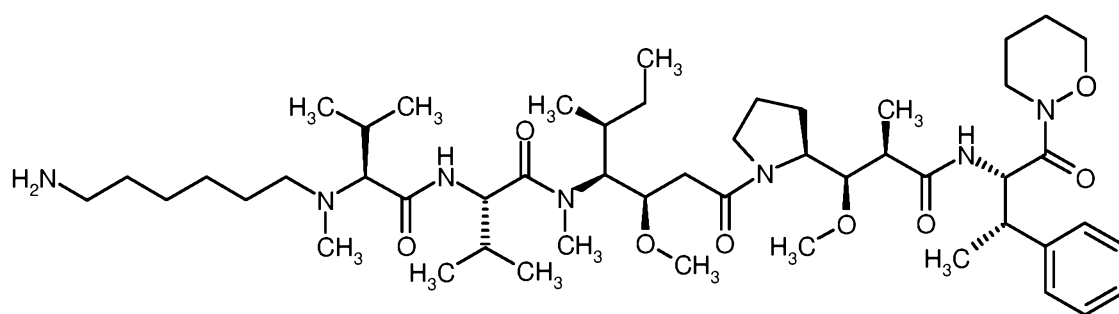
10 mg (10 μ mol) of Intermediate 168 were dissolved in 3 ml of DMF and admixed with 3.5 mg (30 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 2.4 mg (10 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 5 μ l of N,N-diisopropylethylamine. After stirring at RT for 20 h, 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.

HPLC (Method 12): $R_t = 1.9$ min;

LC-MS (Method 11): $R_t = 0.81$ min; MS (ESIpos): $m/z = 1071$ (M+H)⁺.

Intermediate 170

N-(6-aminoheptyl)-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



This compound was prepared in analogy to Intermediate 101 over 2 stages, proceeding from 26 mg (0.028 mmol) of Intermediate 15.

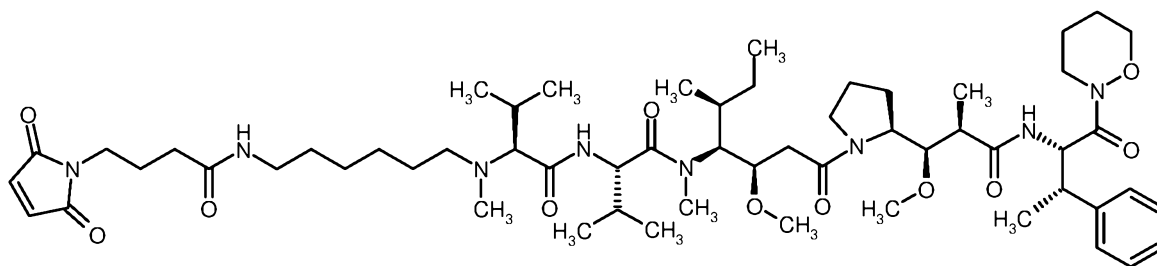
Yield: 16.7 mg (63% of theory over 2 stages)

5 HPLC (Method 12): $R_t = 1.9$ min;

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



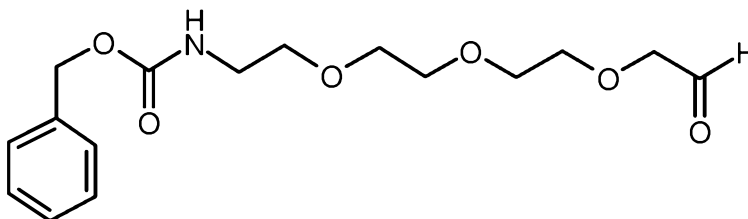
6.7 mg (7.3 μ mol) of the compound formed from Intermediate 170 and 3 mg (14.7 μ mol) of
 15 commercially available 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid were taken up in 2
 ml of DMF and admixed with 5.6 mg (14.7 μ mol) of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-
 tetramethyluronium hexafluorophosphate (HATU) and 2 μ l 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
 20 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.

HPLC (Method 12): $R_t = 2.0$ min;

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



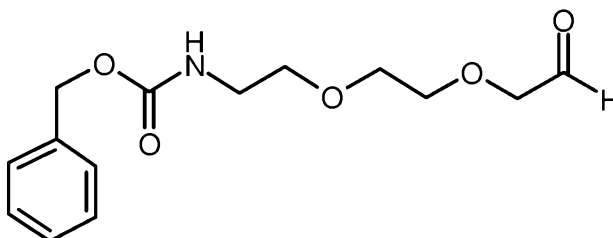
- 5 The title compound was prepared from commercially available 2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethanol under standard conditions, by first introducing the Z protecting group and then oxidizing with sulphur trioxide-pyridine complex.

HPLC (Method 12): $R_t = 1.4$ min;

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



- 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.
- 15

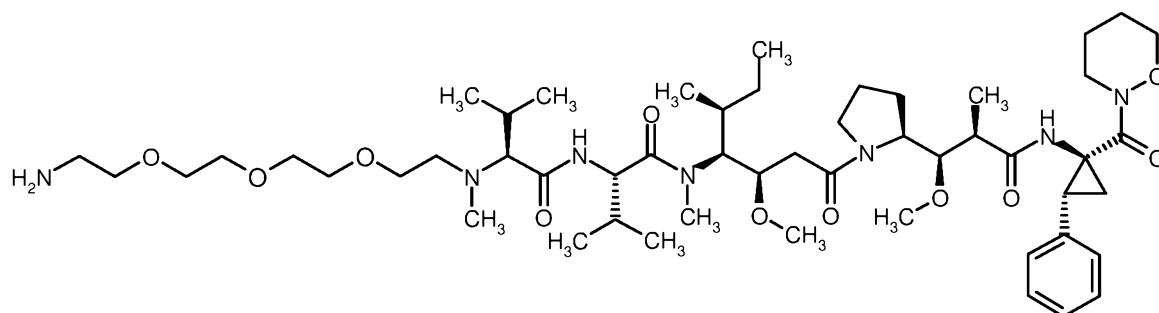
HPLC (Method 12): $R_t = 1.3$ min;

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-
 20 {(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



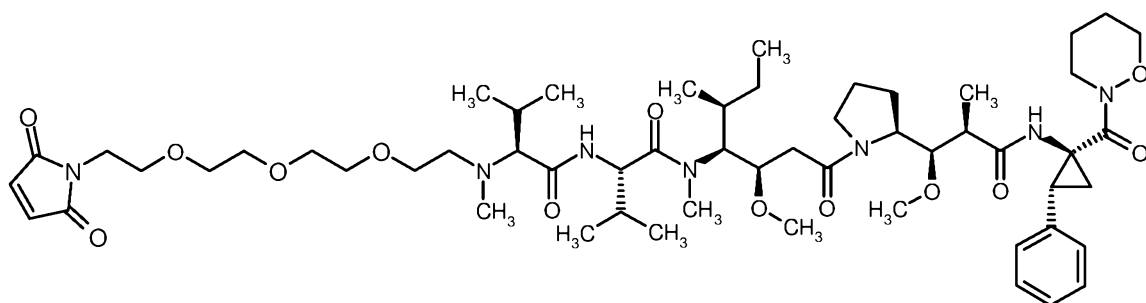
47 mg (0.05 mmol) of Intermediate 16 were reductively aminated in analogy to the preparation of
 5 Intermediate 167 with benzyl 2-{2-[2-(2-oxoethoxy)ethoxy]ethoxy}ethyl carbamate in the presence of borane-pyridine complex. Subsequently, the Z protecting group was removed by hydrogenolytic means with 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.

HPLC (Method 5): $R_t = 1.7$ min;

10 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



The preparation was effected in analogy zu Intermediate 166, proceeding from 34 mg (0.03 mmol) of Intermediate 174.

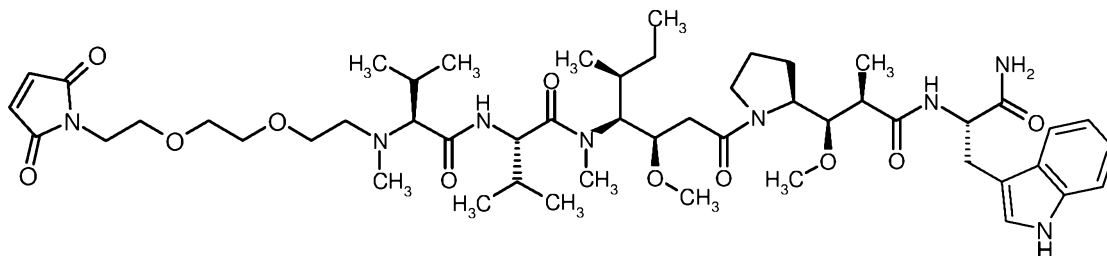
Yield: 8.3 mg (23% of theory)

20 HPLC (Method 5): $R_t = 1.9$ min;

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-
 5 methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-
 L-valinamide



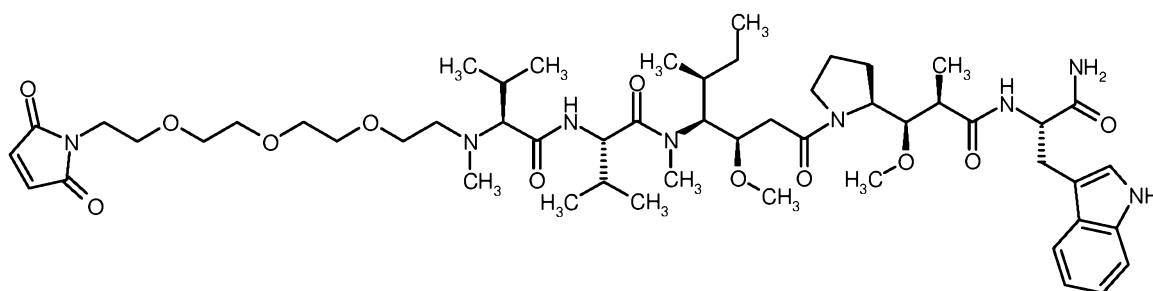
The preparation was effected in analogy to Intermediates 174 and 175, commencing with the
 reductive amination of Intermediate 16 with Intermediate 173, subsequent deprotection and
 10 formation of the maleimide.

HPLC (Method 12): $R_t = 1.8$ min;

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-
 15 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



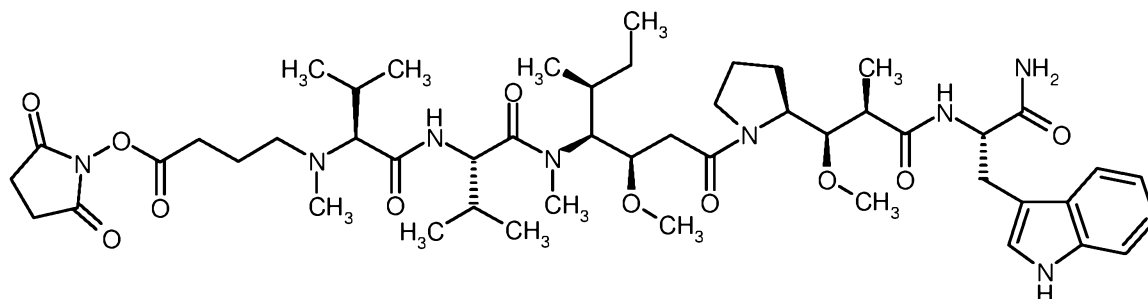
The preparation was effected in analogy to Intermediates 174 and 175, commencing with the
 20 reductive amination of Intermediate 16 with Intermediate 172, subsequent deprotection and
 formation of the maleimide.

HPLC (Method 12): $R_t = 1.9$ min;

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-
5 [(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

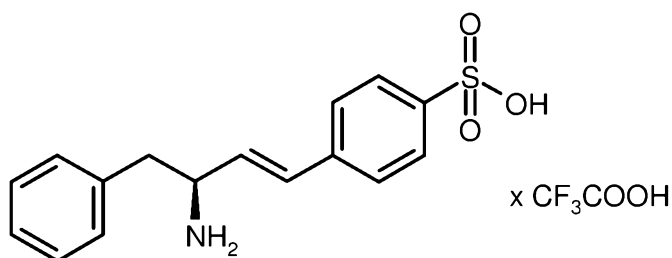


The preparation was effected in analogy to Intermediates 162, proceeding from 6 mg of Intermediate 82.

10 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



A mixture of 13.6 mg (0.06 mmol) of palladium(II) acetate, 469 mg (1.46 mmol) of potassium 4-
15 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.

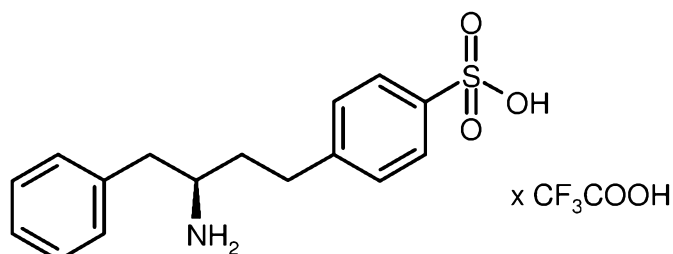
20 This mixture was subsequently taken up in 30 ml of dichloromethane, admixed with 1 ml of trifluoroacetic acid and stirred at RT for 20 h. After concentrating under reduced pressure, the

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.

LC-MS (Method 11): $R_t = 0.44$ min; MS (ESIpos): $m/z = 304$ ($M+H$)⁺.

Intermediate 180

5 4-[(3R)-3-amino-4-phenylbutyl]benzenesulphonic acid



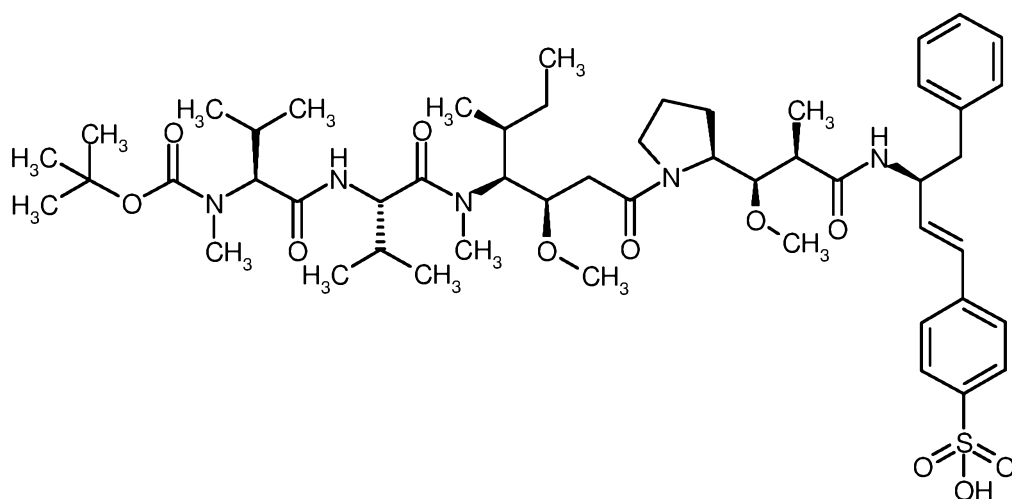
100 mg (0.25 mmol) of 4-[(1E,3S)-3-amino-4-phenylbut-1-en-1-yl]benzenesulphonic acid trifluoroacetate were suspended in 10 ml of acetic acid and a few drops of DMF and water, admixed with 70 mg (0.07 mmol) of palladium on charcoal (10%) and hydrogenated at hydrogen
10 pressure 2.2 bar for 24 h. The solution was filtered and the filtrate purified by prep. HPLC.

29 mg (76% purity, 21% of theory) of product were obtained.

LC-MS (Method 1): $R_t = 0.46$ min; MS (ESIpos): $m/z = 306$ ($M+H$)⁺.

Intermediate 181

15 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

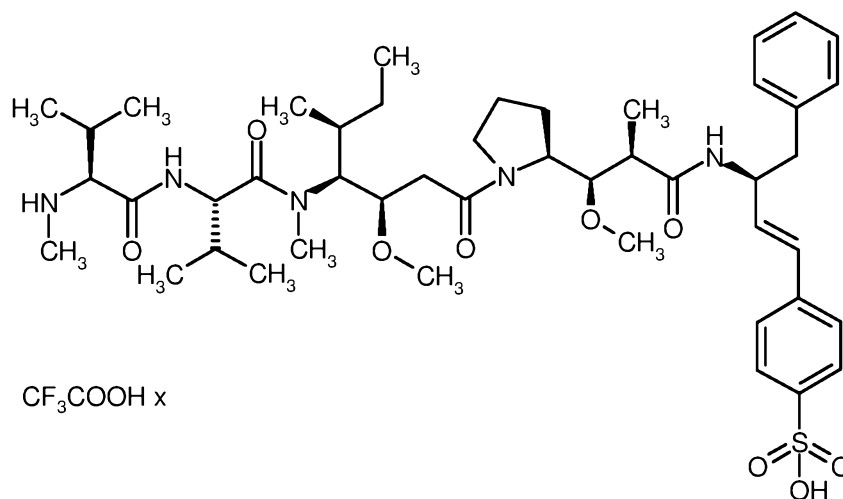


To a solution of 90 mg (0.13 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 4 ml of DMF were added 60 mg (0.16 mmol) of HATU and 69 μ l of (0.39 mmol) Hünig's base. 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.

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



15

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.

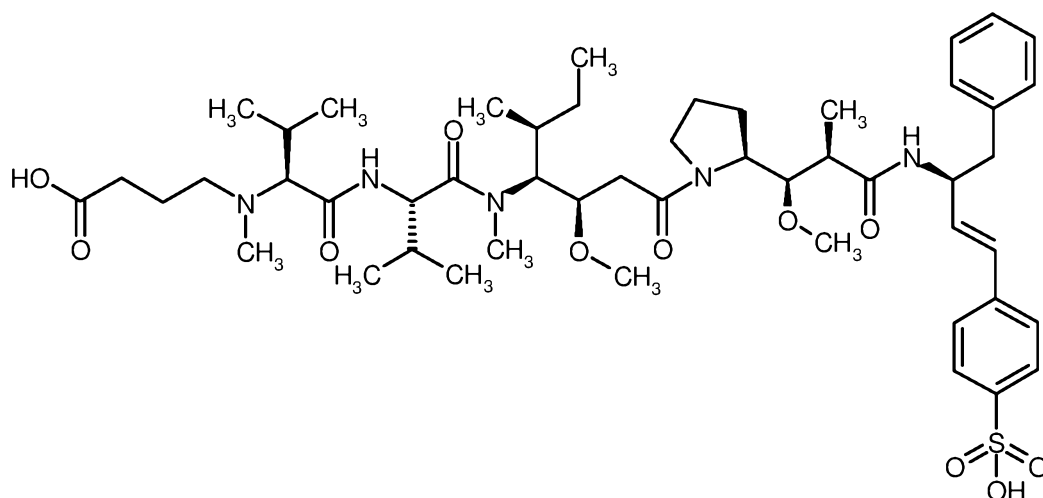
91 mg (98% of theory) of the target compound were obtained.

LC-MS (Method 1): $R_t = 0.85$ min; MS (ESIpos): $m/z = 871$ ($M+H$)⁺

20

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



5

16.7 μ l (0.03 mmol) of a 15% aqueous succinaldehyde solution were initially charged in 943 μ l 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-[(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

10 trifluoroacetate (Intermediate 181) and 1.1 μ l (0.02 mmol) of acetic acid. The reaction mixture was stirred for 5 min at RT and then 2.9 μ l (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.

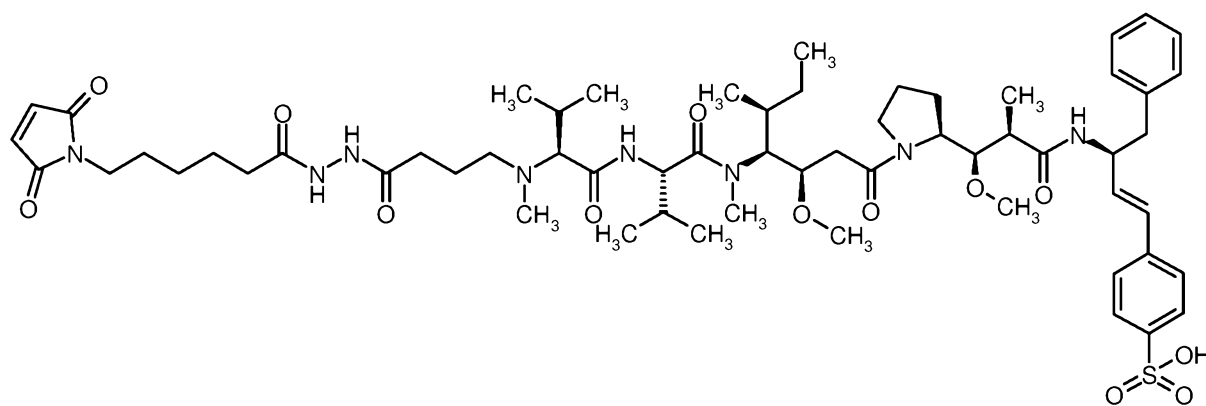
15 This gave 20 mg (83% purity, 80% of theory) of the title compound.

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

20



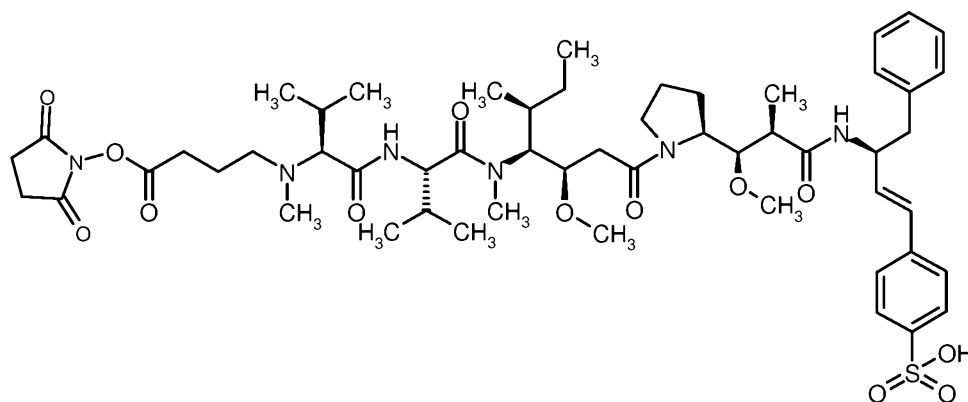
8 mg (7.5 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-((2S)-2-
 [(1R,2R)-1-methoxy-2-methyl-3-oxo-3-((2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-
 5 yl)amino)propyl]pyrrolidin-1-yl)-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, 2.8 mg (8.2
 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide 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.

3 mg (31% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.90 min; MS (ESIpos): m/z = 1164 ($M+H$)⁺

10 **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



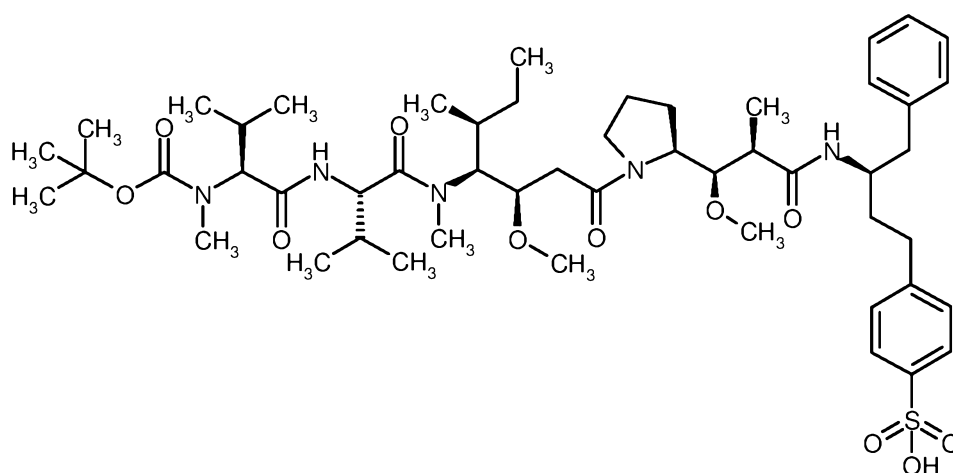
15 To a solution of 8 mg (7.5 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-
 methoxy-1-((2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2S,3E)-1-phenyl-4-(4-
 sulphophenyl)but-3-en-2-yl]amino)propyl]pyrrolidin-1-yl)-5-methyl-1-oxoheptan-4-yl]-N-methyl-
 L-valinamide in 2 ml of DMF were 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.

LC-MS (Method 1): $R_t = 0.89$ min; MS (ESIpos): $m/z = 1054$ ($M+H$)⁺

5 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

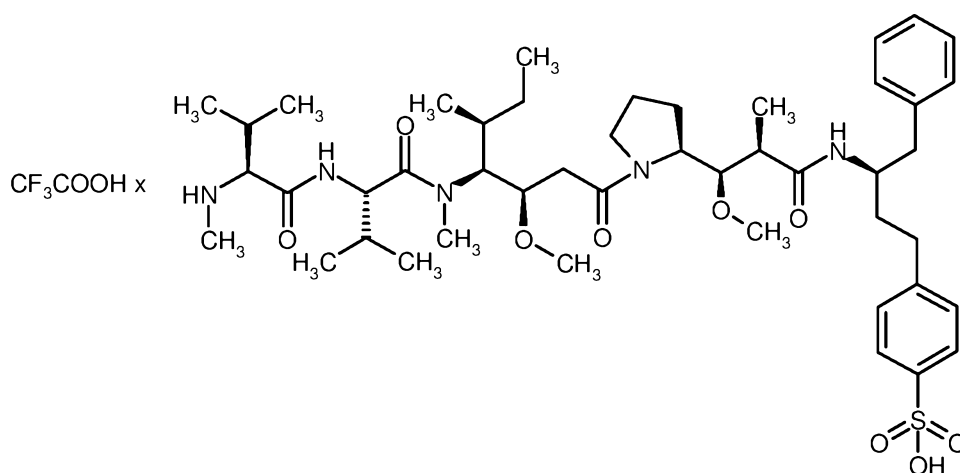


- 10 To a solution of 43 mg (0.06 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1.9 ml of DMF were added 29 mg (0.07 mmol) of HATU and 33 μl (0.19 mmol) of Hünig's 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.
- 15 This gave 58 mg of a 45:55 mixture of the title compound and of the already deprotected amine.

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

- 20 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



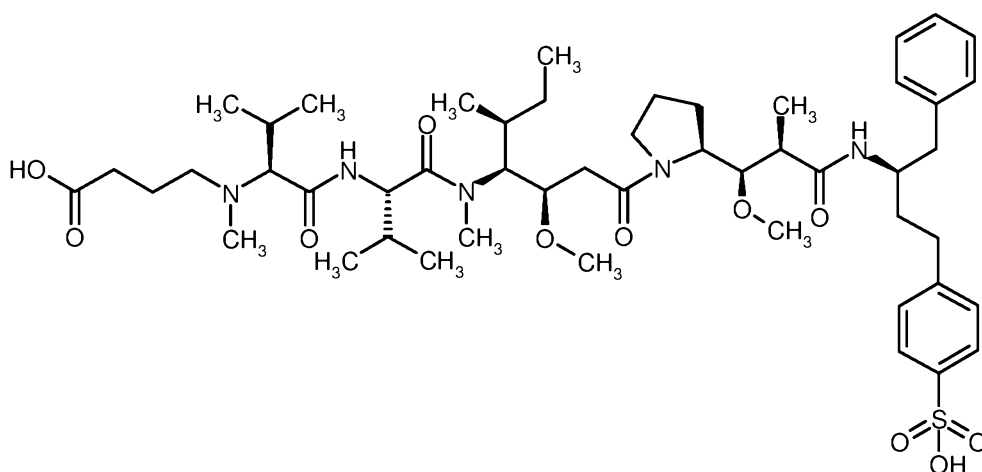
58 mg of Intermediate 186 were dissolved in 4.1 ml of dichloromethane, 0.41 ml of trifluoroacetic acid was added and the mixture was stirred at RT for 30 min. After concentration under reduced pressure, the crude product was purified by prep. HPLC.

5 50 mg (90% purity, 85% of theory) of the title compound were obtained.

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



171 μ l (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 μ l (0.2 mmol) of acetic acid. The reaction mixture was stirred for 5 min at

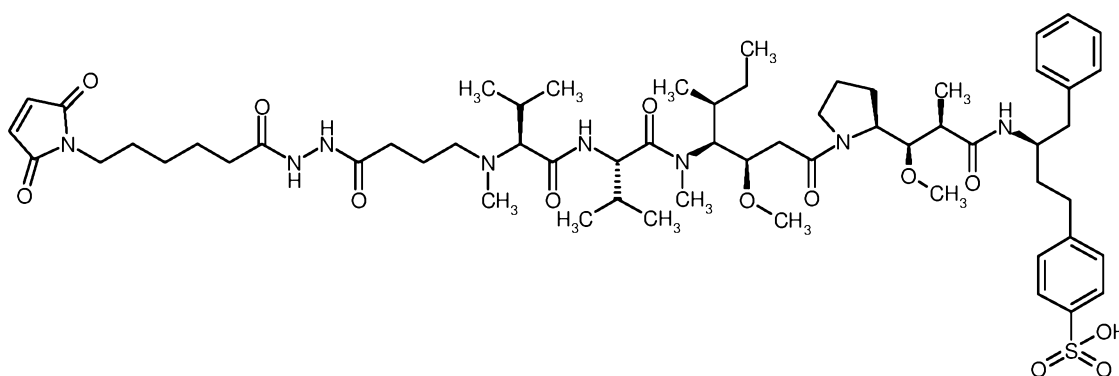
RT and then 30 μ l (0.24 mmol) of borane-pyridine complex were added. After stirring for 24 hours, a further equivalent of borane-pyridine complex was added and the mixture was stirred for a further 2 h. The reaction mixture was then purified by prep. HPLC.

40 mg (90% purity, 66% of theory) of the title compound were obtained.

- 5 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



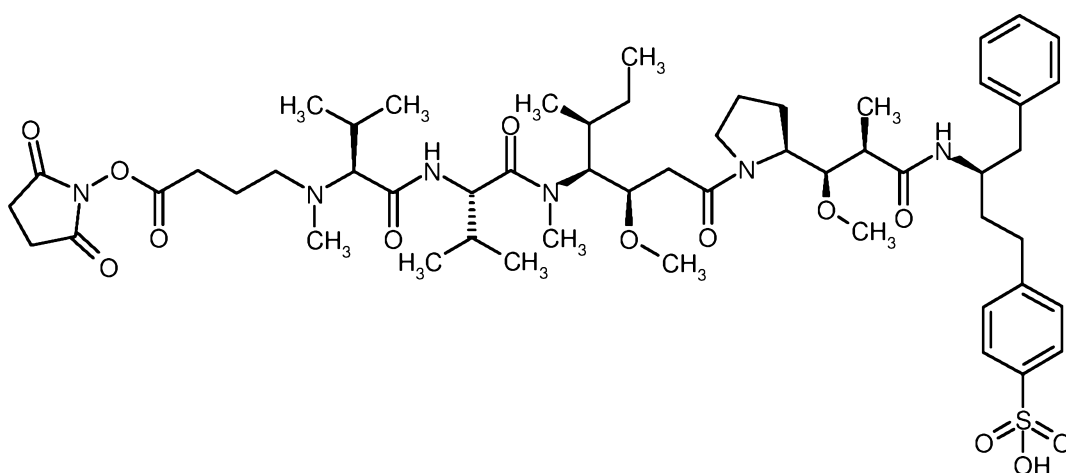
- 10 mg (9.3 μ mol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, 3.5 mg (10.3 μ mol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide trifluoroacetate, 4.3 mg (11.2 μ mol) of HATU and 4.9 μ l (28 μ mol) 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.

4.2 mg (92% purity, 33% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.91 min; MS (ESIpos): m/z = 1166 ($M+H$)⁺

- 20 **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



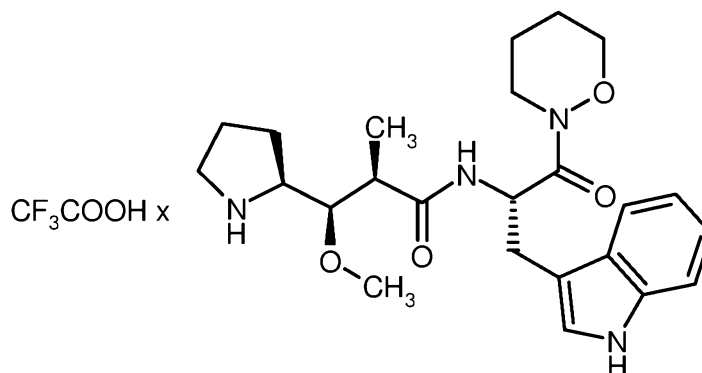
To a solution of 10 mg (9.3 μ mol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino]propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 2.5 ml of DMF were added 10.7 mg (93 μ mol) of N-hydroxysuccinimide, 10.6 mg (28 μ mol) of EDCI and 0.12 mg (0.9 μ mol) of DMAP. The reaction mixture was stirred at RT for 20 h and then purified by prep. HPLC.

3.8 mg (72% purity, 25% of theory) of the title compound were obtained.

LC-MS (Method 1): R_t = 0.90 min; MS (ESIpos): m/z = 1055 ($M+H$)⁺

10 **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



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).

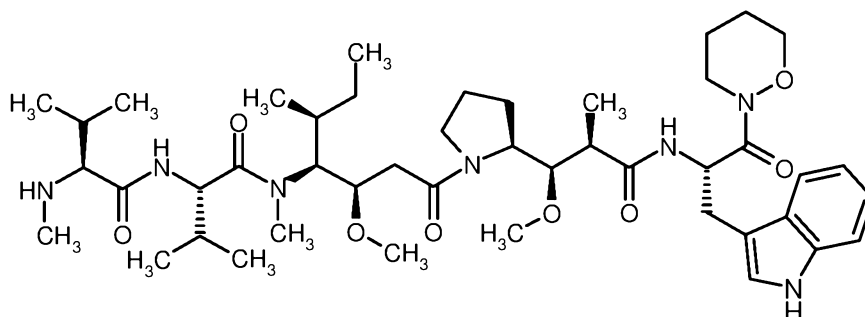
Yield over 2 stages: 62 mg (67% of theory)

HPLC (Method 6): $R_t = 1.65$ min;

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



1015 mg (1.59 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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 (2*R*,3*R*)-*N*-[(2*S*)-3-(1*H*-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]-3-methoxy-2-methyl-3-[(2*S*)-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.

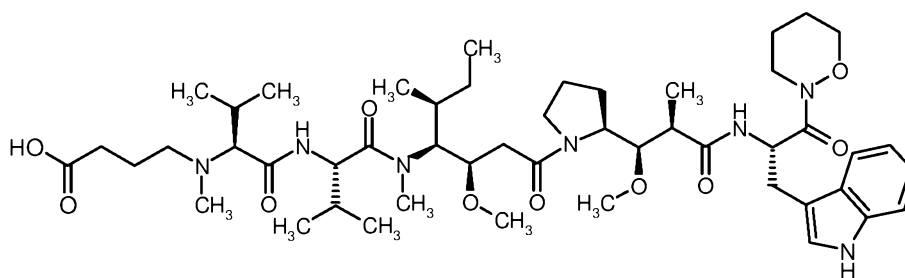
HPLC (Method 12): $R_t = 1.8$ min;

LC-MS (Method 1): $R_t = 0.84$ min; MS (ESIpos): $m/z = 840$ ($M+H$)⁺.

¹H NMR (500 MHz, DMSO-*d*₆): $\delta = 10.8$ (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 H₂O 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



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 μ l 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 μ l 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.

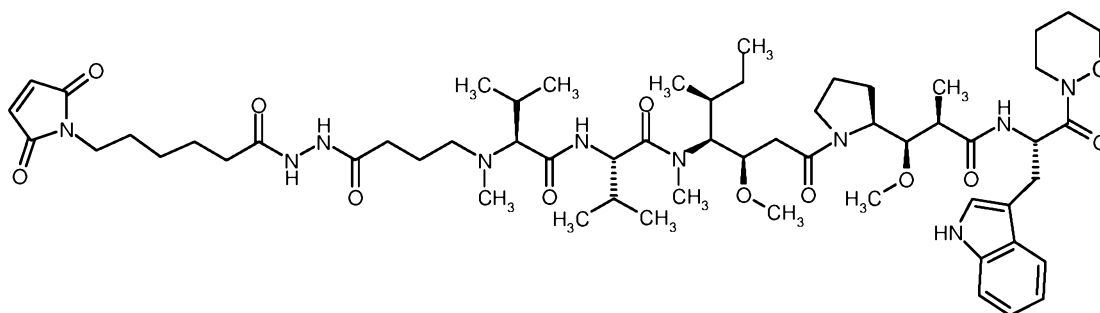
HPLC (Method 5): $R_t = 1.7$ min;

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



This compound was prepared in analogy to the synthesis described in Intermediate 157 from 10 mg (11 μ mol) 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-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.

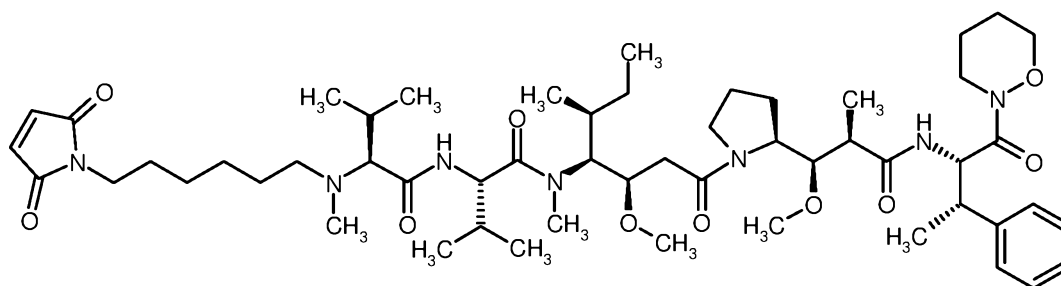
Yield: 4.4 mg (35% of theory)

HPLC (Method 5): R_t = 1.8 min;

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



This compound was prepared in analogy to Intermediate 166, proceeding from 9 mg (0.010 mmol) of Intermediate 170.

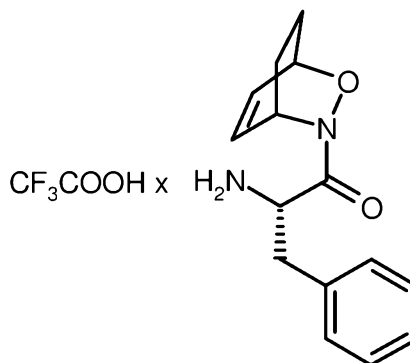
Yield: 1.1 mg (10% of theory)

HPLC (Method 12): R_t = 2.0 min;

LC-MS (Method 1): $R_t = 0.99$ min; MS (ESIpos): $m/z = 994$ (M+H)⁺.

Intermediate 196

(2*S*)-2-amino-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-3-phenylpropan-1-one trifluoroacetate



- 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 μ l (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 (2*S*)-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.

LC-MS (Method 1): $R_t = 1.1$ min; MS (ESIpos): $m/z = 359$ (M+H)⁺.

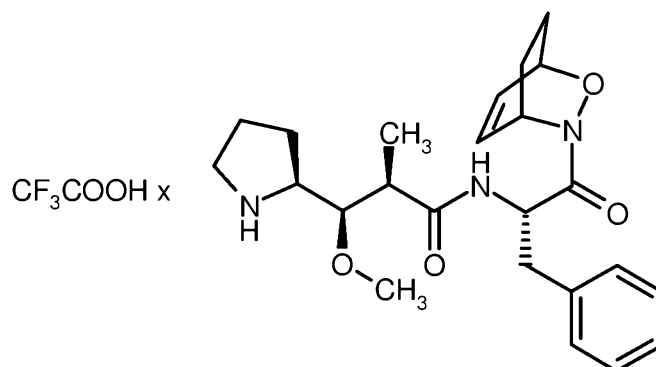
- 64 mg (0.18 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 1 ml of trifluoroacetic acid was added, and the mixture was stirred at RT for 30 min. This was followed by concentration under reduced pressure and lyophilization of the remaining residue from water/dioxane. In this way, 66 mg (quant.) of the title compound were obtained as a foam.

HPLC (Method 6): $R_t = 1.45$ min;

LC-MS (Method 3): $R_t = 1.12$ min; MS (ESIpos): $m/z = 259$ (M+H)⁺.

Intermediate 197

(2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(2*S*)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2*S*)-pyrrolidin-2-yl]propanamide trifluoroacetate



- 5 First, (2*R*,3*R*)-3-[(2*S*)-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 66 mg (0.18 mmol) of (2*S*)-
- 10 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 μ l (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)
- 15 of the Boc-protected intermediate *tert*-butyl (2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-{[(2*S*)-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.

HPLC (Method 6): R_t = 2.13 min;

LC-MS (Method 1): R_t = 1.13 min; MS (ESIpos): m/z = 528 ($M+H$)⁺.

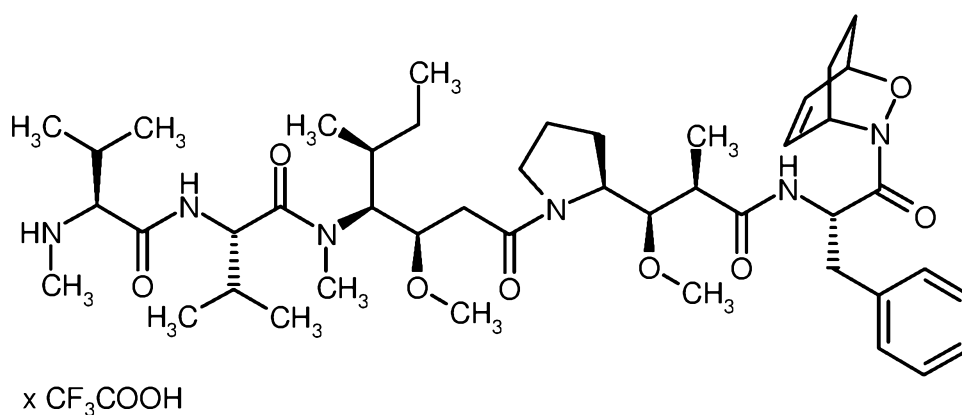
- 20 52 mg (0.1 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 1 ml of trifluoroacetic acid was added, and the mixture was stirred at RT for 20 min. This was followed by concentration under reduced pressure and stirring of the remaining residue with 20 ml of diethyl ether. After 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.

- 25 HPLC (Method 6): R_t = 1.62 min;

LC-MS (Method 1): $R_t = 0.68$ min; MS (ESIpos): $m/z = 428$ ($M+H$)⁺.

Intermediate 198

N-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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



44.5 mg (0.071 mmol) of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(2*R*,3*S*,4*S*)-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 (2*R*,3*R*)-3-methoxy-2-methyl-*N*-[(2*S*)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2*S*)-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 μ l (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*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*)-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.

HPLC (Method 6): $R_t = 2.78$ min;

LC-MS (Method 3): $R_t = 2.96$ min; MS (ESIpos): $m/z = 1047$ ($M+H$)⁺.

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.

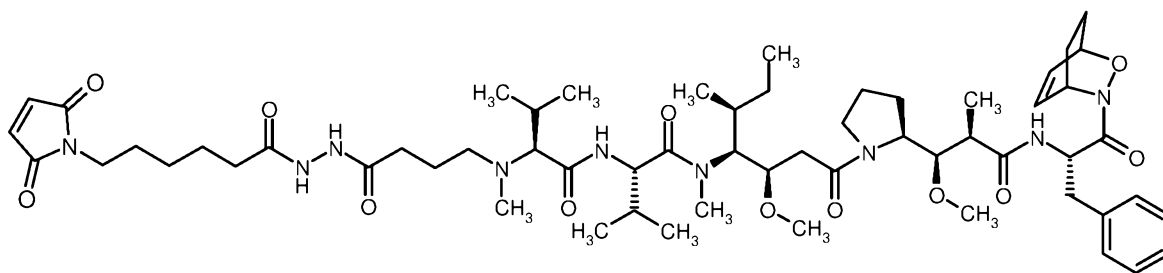
HPLC (Method 6): $R_t = 1.94$ min;

5 LC-MS (Method 3): $R_t = 1.71$ min; MS (ESIpos): $m/z = 825$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 8.9$ -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 H₂O peak].

10 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



15 The title compound was prepared in analogy to Intermediates 193 and 194, proceeding from 23 mg (24 μ mol) 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-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
20 (Intermediate 198).

HPLC (Method 12): $R_t = 1.9$ min;

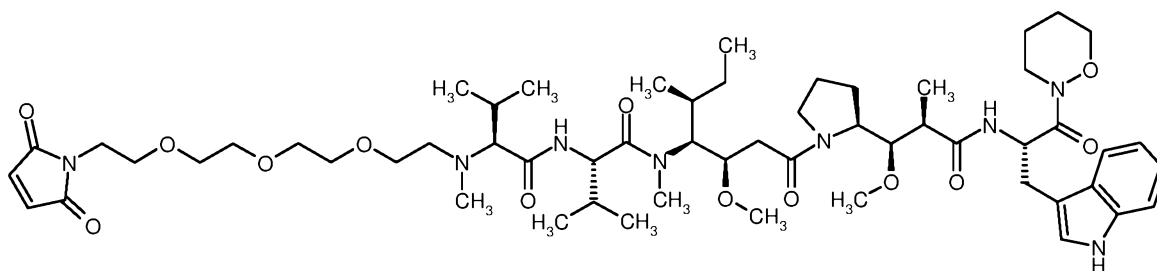
LC-MS (Method 2): $R_t = 2.1$ min; MS (ESIpos): $m/z = 1118$ ($M+H$)⁺.

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-

25

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



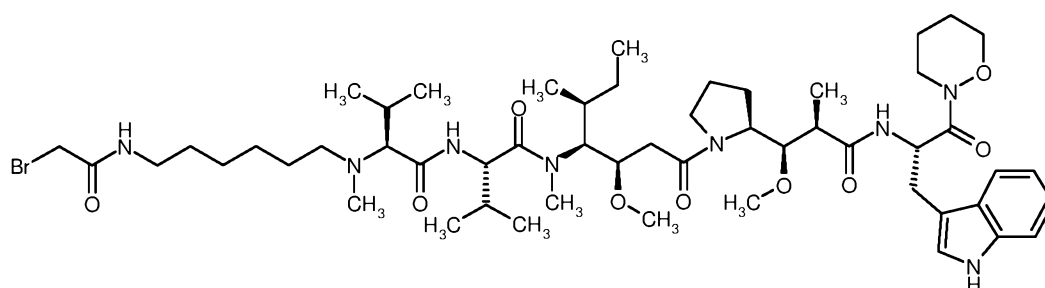
- 5 The preparation was effected in analogy to Intermediates 174 and 175, commencing with the reductive alkylation of Intermediate 192 with Intermediate 172, subsequent deprotection and formation of the maleimide.

HPLC (Method 12): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 1025$ (M+H)+.

10 **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



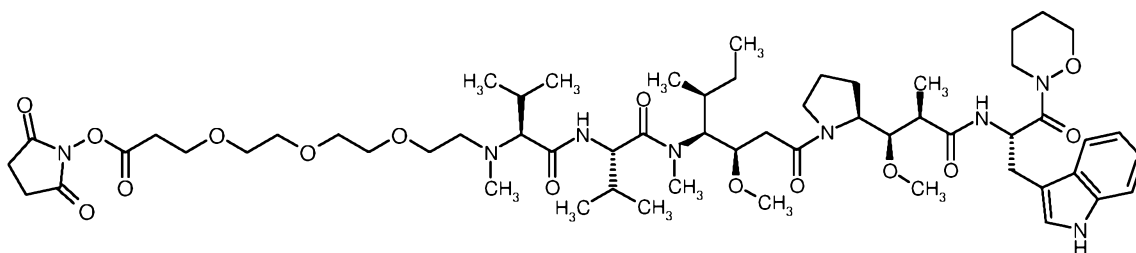
- 15 22 mg (0.023 mmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-3-[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 101) were dissolved in 9.5 ml of THF and admixed at 0°C with 4.2 μ l 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.
- 20

HPLC (Method 5): $R_t = 1.8$ min;

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



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.

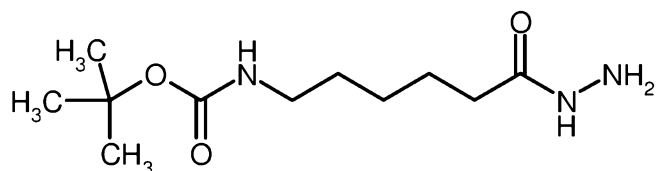
13 mg (10 μ mol) of this intermediate were dissolved in 5 ml of DMF and admixed with 2.1 mg (20 mmol) of 1-hydroxypyrrolidine-2,5-dione, 6.5 μ l of *N,N*-diisopropylethylamine and 7.1 mg (0.02 mmol) of HATU. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. 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.

HPLC (Method 12): $R_t = 2.0$ min;

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

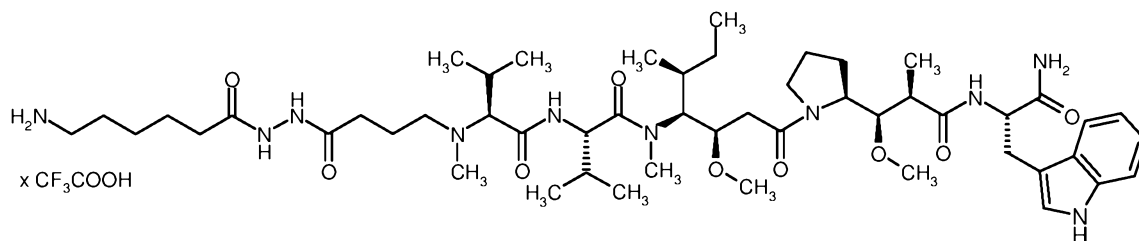


This compound was prepared by standard peptide chemistry methods, by coupling of 6-[(*tert*-butoxycarbonyl)amino]hexanoic acid with benzyl hydrazinecarboxylate in the presence of EDCI and HOBT, and subsequent hydrogenolytic cleavage of the benzyloxycarbonyl protecting group.

- 5 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
- 10 trifluoroacetate



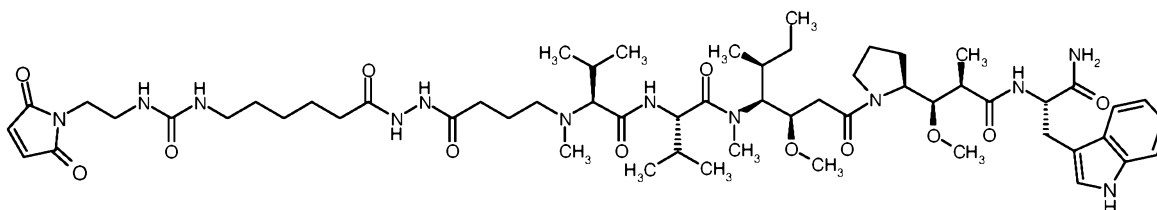
- 146 mg (50 μ mol) of (N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were
- 15 dissolved in 5 ml of DMF and then admixed with 30.6 mg (80 μ mol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 19 μ l of N,N-diisopropylethylamine and with 22.4 mg (60 μ mol) 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
- 20 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.

HPLC (Method 12): $R_t = 1.6$ min;

- 25 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



This compound was prepared in analogy to Intermediate 114, proceeding from Intermediates 50 and 204.

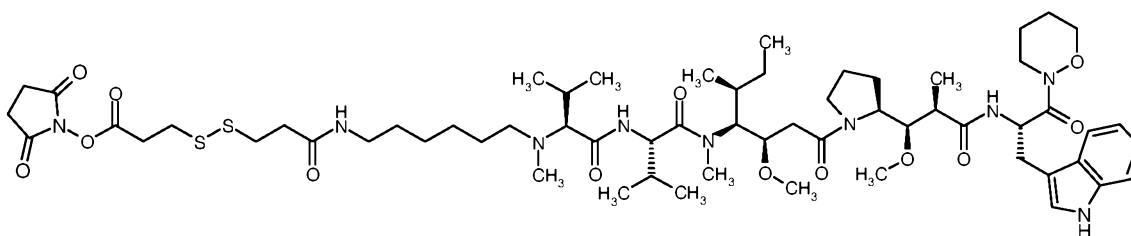
Yield: 4 mg (78% of theory)

HPLC (Method 12): $R_t = 1.7$ min;

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



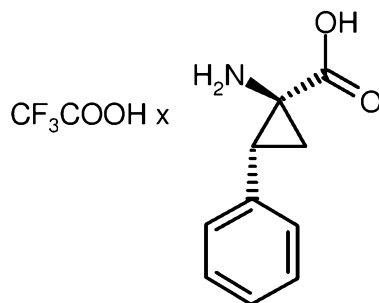
8 mg (10 μ mol) of Intermediate 101 were dissolved in 2 ml of DMF and admixed with 8.6 mg (20 μ mol) of 1,1'-{disulphanediylbis[(1-oxopropane-3,1-diyl)oxy]}dipyrrolidine-2,5-dione and 3.7 μ l of *N,N*-diisopropylethylamine. The reaction mixture was stirred at RT for 2 h and then the solvent was evaporated off under reduced pressure and the residue was purified by preparative HPLC. 7.2 mg (68% of theory) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 11): $R_t = 0.94$ min; MS (ESIpos): $m/z = 615$ [$\frac{1}{2}(M+2H^+)$]

Intermediate 207

(1S,2R)-1-amino-2-phenylcyclopropanecarboxylic acid trifluoroacetate



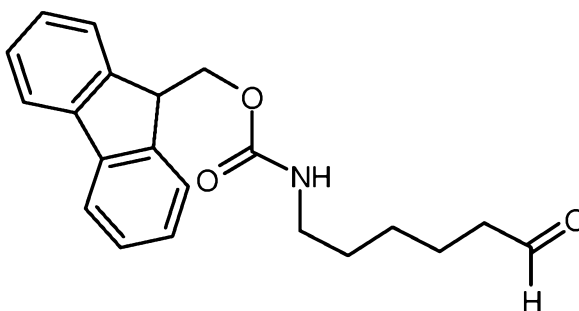
5

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.

LC-MS (Method 1): $R_t = 0.23$ min; MS (ESIpos): $m/z = 178$ ($M+H$) $^+$.

10 **Intermediate 208**

9H-fluoren-9-ylmethyl 6-oxohexyl carbamate



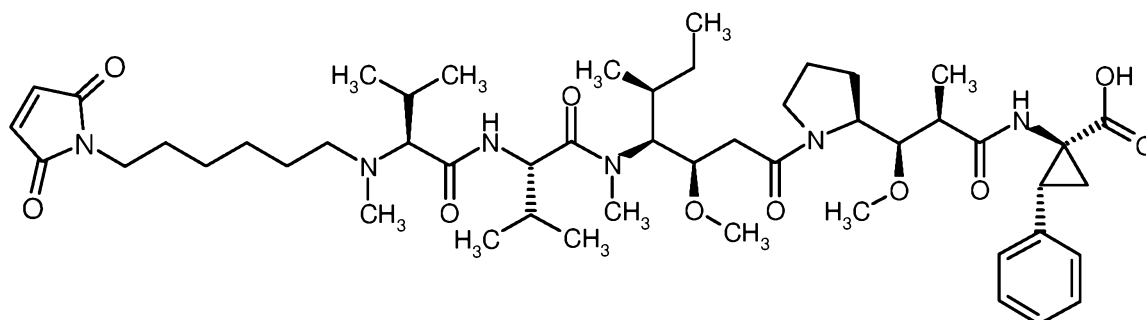
15 The title compound was prepared from 1 g (2.95 mmol) of commercially available 9H-fluoren-9-ylmethyl 6-hydroxyhexyl carbamate under standard conditions, by oxidation with sulphur trioxide-pyridine complex. 840 mg (85% of theory) of the title compound were obtained.

HPLC (Method 12): $R_t = 2.0$ min;

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



5

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.

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.

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.

HPLC (Method 12): $R_t = 1.7$ min;

LC-MS (Method 11): $R_t = 0.7$ min; MS (ESIpos): $m/z = 843$ ($M+H$)⁺.

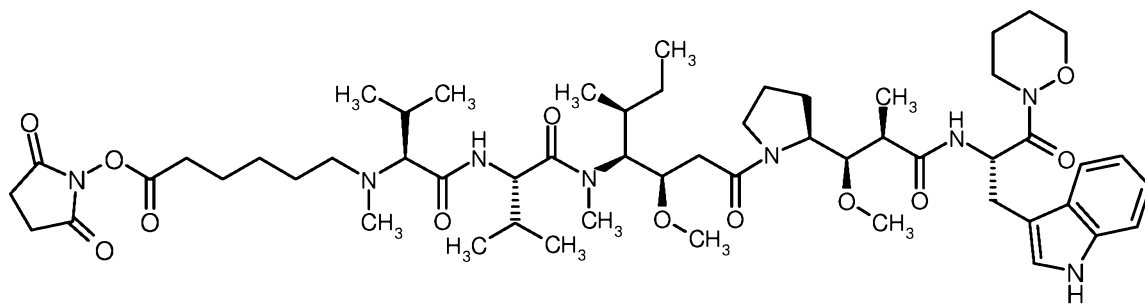
6 mg (7.12 μ mol) of this intermediate were taken up in 1 ml of dioxane and then admixed with 6.6 mg (42.7 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate and with 5 μ l of saturated aqueous sodium hydrogencarbonate solution. The reaction mixture was stirred at RT for 1 h. Then another 3 portions each of 50 μ l 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.

HPLC (Method 12): $R_t = 1.9$ min;

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



First, 6-oxohexanoic acid was prepared by a literature method (J. Org. Chem. 58, 1993, 2196-2200).

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 μ l 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.

HPLC (Method 12): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.87$ min; MS (ESIpos): $m/z = 955$ ($M+H$)⁺.

¹H NMR (500 MHz, DMSO-d₆, characteristic signals): $\delta = 12.0$ (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).

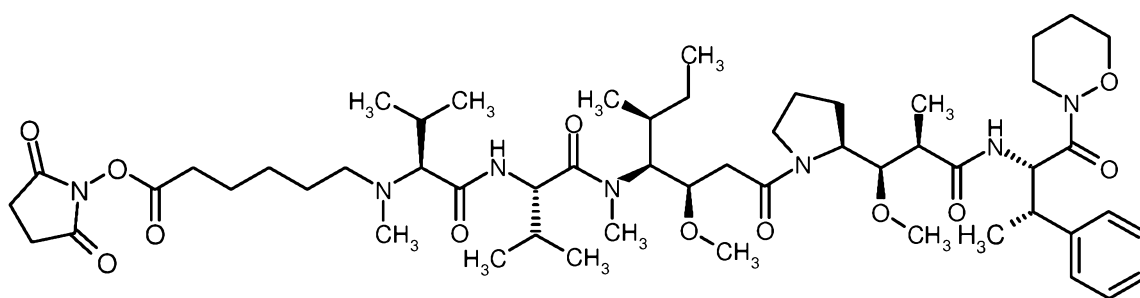
22 mg (23 μ mol) of this intermediate were dissolved in 1.8 ml of dichloromethane and admixed with 13.2 mg (70 μ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 26.5 mg (230 μ mol) of 1-hydroxypyrrolidine-2,5-dione and 0.28 mg (2 μ mol) of dimethylaminopyridine, and the reaction 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.

HPLC (Method 12): $R_t = 1.9$ min;

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



15 mg (20 μ mol) of *N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*,3*S*)-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.

Yield: 9.2 mg (61% of theory)

HPLC (Method 12): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.87$ min; MS (ESIpos): $m/z = 929$ ($M+H$)⁺.

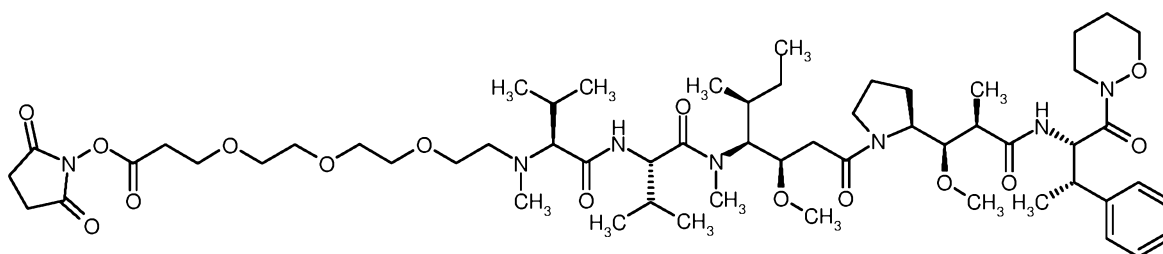
9 mg (10 μ mol) of this intermediate were dissolved in 3 ml of DMF and admixed with 5.6 mg (48 μ mol) of 1-hydroxypyrrolidine-2,5-dione, 5 μ l of *N,N*-diisopropylethylamine and 5.5 mg (0.015 mmol) of HATU, and the reaction mixture was treated in an ultrasound bath for 6 h. In the course of this, 5.5 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.

HPLC (Method 12): $R_t = 2.0$ min;

LC-MS (Method 1): $R_t = 0.95$ min; MS (ESIpos): $m/z = 1027$ ($M+H$)⁺.

Intermediate 212

20 N-{2-[2-(2-{3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropoxy}ethoxy)ethoxy]ethyl}-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-[(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-[(2*S*,3*S*)-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



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
 5 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.

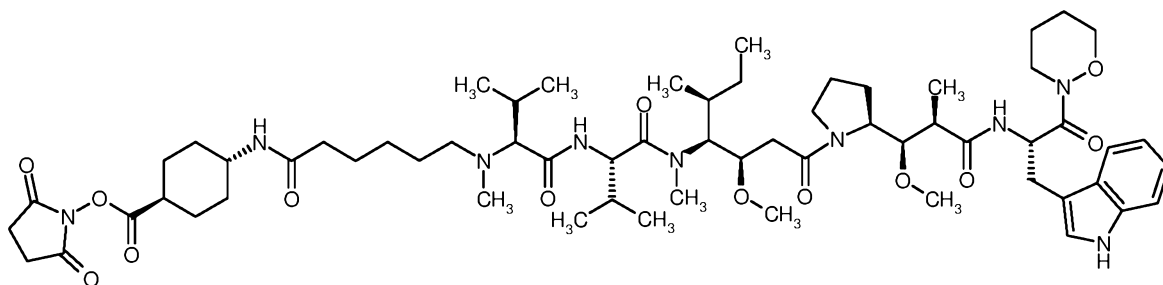
8.4 mg (8 μ mol) of this intermediate were dissolved in 3 ml of DMF and admixed with 9.5 mg (80
 10 μ mol) of 1-hydroxypyrrolidine-2,5-dione, 10 μ l of *N,N*-diisopropylethylamine and 9.4 mg (25 μ mol) of HATU, and the reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. 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
 15 preparative HPLC. After lyophilization from acetonitrile/water, 4 mg (32% of theory) of the title compound were obtained.

HPLC (Method 12): R_t = 2.0 min;

LC-MS (Method 1): R_t = 0.96 min; MS (ESIpos): m/z = 1117 ($M+H$)⁺.

Intermediate 213

20 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



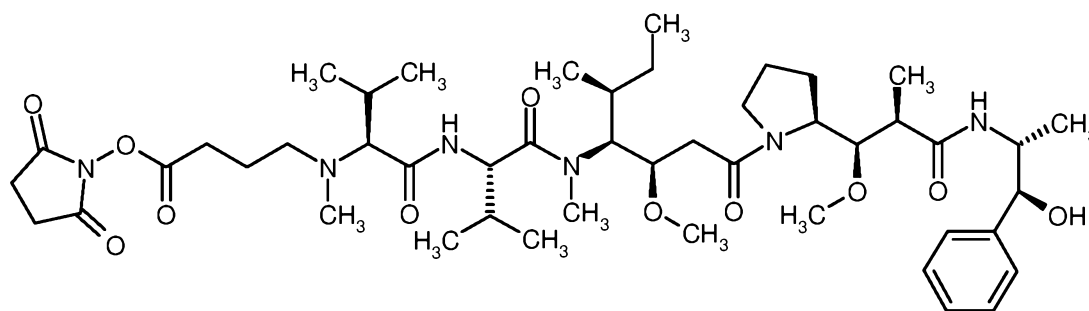
This compound was prepared in analogy to Intermediate 104, proceeding from N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, the synthesis of which was described under Intermediate 210. 9.3 mg of the title compound (37% of theory over 3 stages) were obtained.

HPLC (Method 12): $R_t = 1.9$ min;

10 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



15

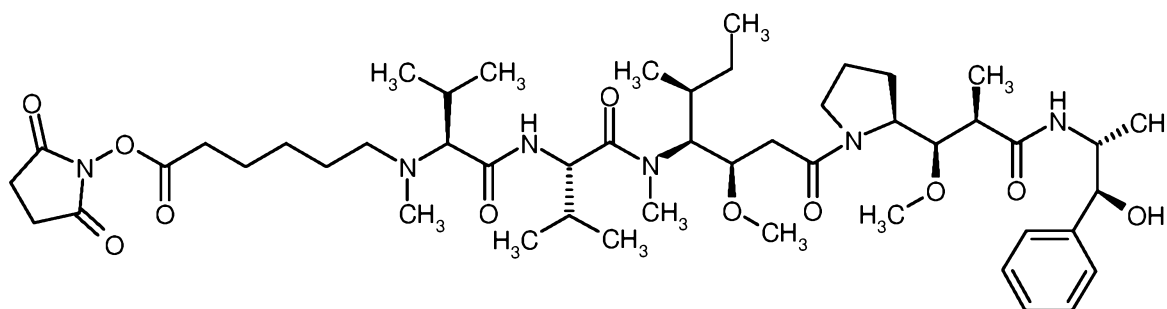
This compound was prepared in analogy to Intermediate 210, by conversion of Intermediate 92 to the active ester.

HPLC (Method 5): $R_t = 1.6$ min;

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



5

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.

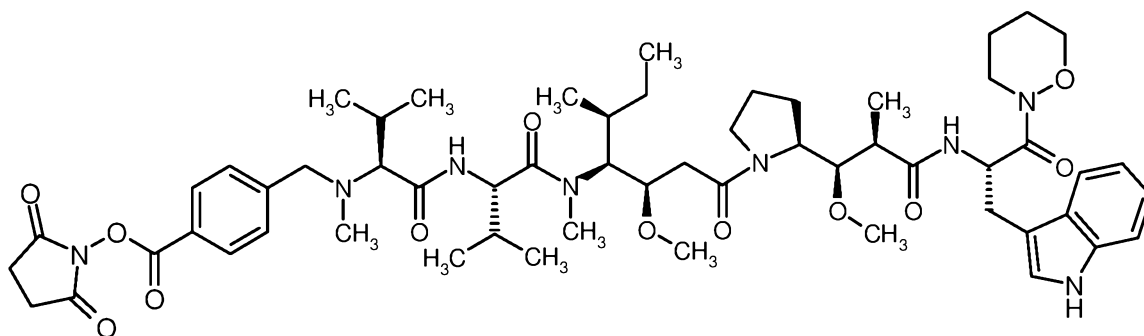
10

HPLC (Method 5): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.85$ min; MS (ESIpos): $m/z = 930$ ($M+H$)⁺.

15 **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



20

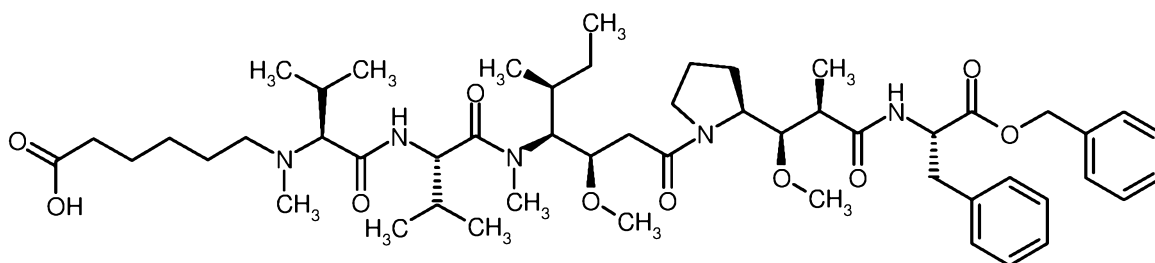
First, in analogy to the preparation of Intermediate 183, Intermediate 192 was reacted with 4-formylbenzoic acid with borane-pyridine complex to give N-(4-carboxybenzyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-3-[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino]-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-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.

HPLC (Method 5): $R_t = 1.8$ min;

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



53 mg (84 μ mol) 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 μ mol) 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 μ l of N,N-diisopropylethylamine, 14 mg (92 μ mol) of HOBt and 17.6 mg (92 μ mol) 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.

LC-MS (Method 1): $R_t = 1.55$ min; $m/z = 1044$ (M+H)⁺.

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-

{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-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.

HPLC (Method 5): $R_t = 1.9$ min;

- 5 LC-MS (Method 1): $R_t = 1.01$ min; $m/z = 822$ ($M+H$)⁺.

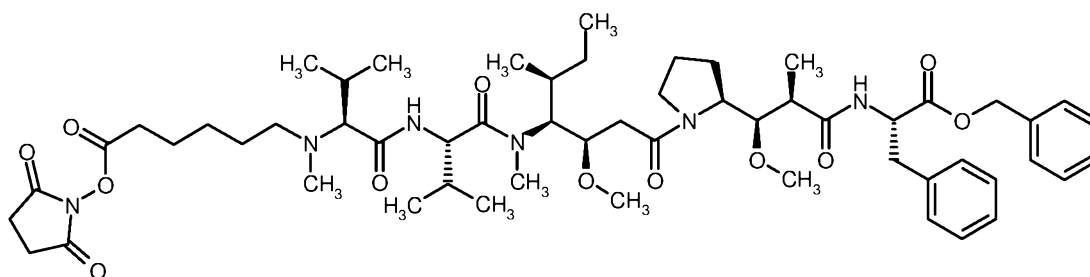
60 mg (0.06 mmol) of this intermediate were reacted, in analogy to Intermediate 210, with 6-oxohexanoic acid in the presence of borane-pyridine complex. 45 mg (75% of theory) of the title compound were obtained as a foam.

HPLC (Method 5): $R_t = 1.9$ min;

- 10 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*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(2*S*)-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



15

This compound was prepared by conversion of 42 mg (0.05 mmol) of Intermediate 217 to the active ester.

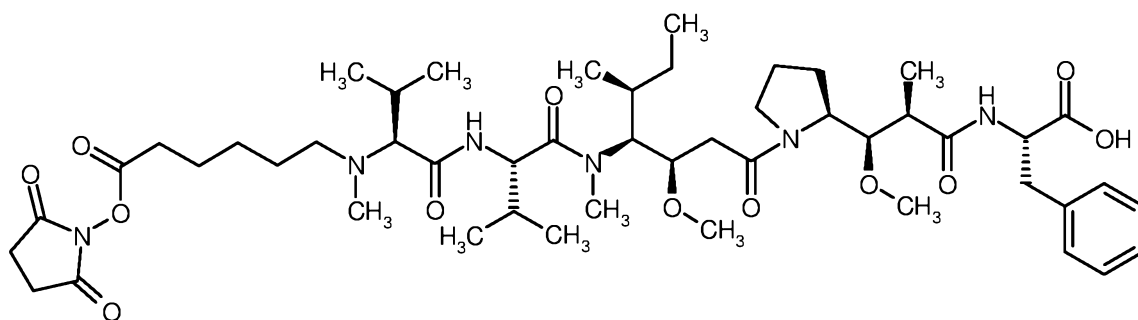
Yield: 26 mg (54%)

HPLC (Method 5): $R_t = 2.1$ min;

- 20 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*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-[(1*S*)-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



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.

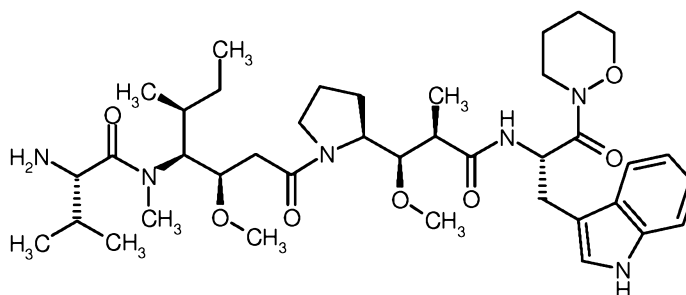
5 The residue was lyophilized from 1:1 acetonitrile/water. This gave 14 mg (92% of theory) of the title compound as a colourless foam.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos): m/z = 944 (M+H)⁺.

Intermediate 220

10 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



0.5 g (1.01 mmol) of Intermediate 1 in 10 ml of dichloromethane were admixed with 1 ml of
15 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.

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 μ l (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.

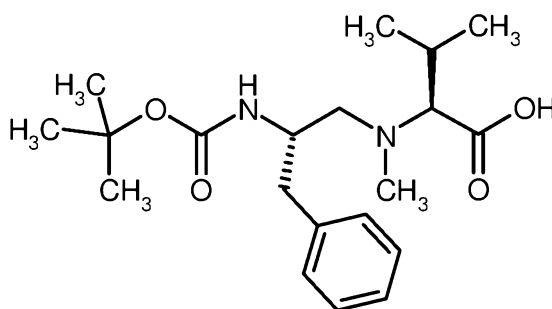
562 mg (0.57 mmol) of this intermediate were taken up in 50 ml of methanol and hydrogenated with 155 mg of 10% palladium on activated carbon under standard hydrogen pressure at RT for 20 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. The residue was purified 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.

HPLC (Method 5): double peak with $R_t = 1.75$ and 1.86 min;

LC-MS (Method 1): double peak at $R_t = 0.84$ min and 0.91 min with the same mass; MS (ESIpos): $m/z = 944$ ($M+H$)⁺.

15 Intermediate 221

N-{(2S)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropyl}-N-methyl-L-valine



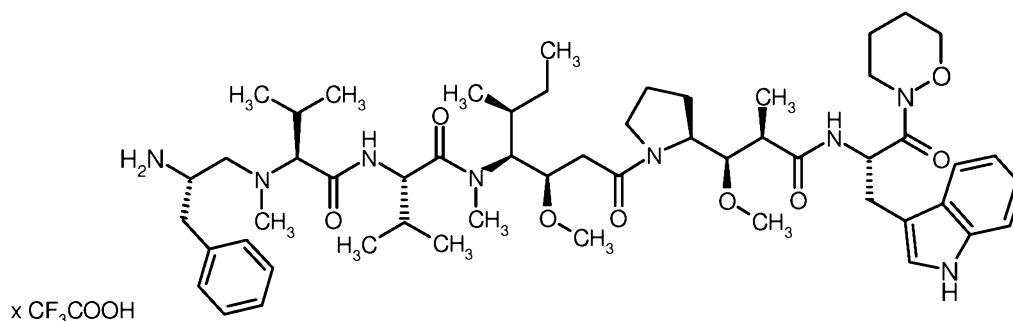
100 mg (0.76 mmol) of commercially available N-methyl-L-valine and 285 mg (1.14 mmol) of commercially available *tert*-butyl (2S)-1-oxo-3-phenylpropan-2-yl carbamate were combined in 22 ml of methanol and admixed with 340 mg (3.66 mmol) of borane-pyridine complex and 70 μ l of acetic acid. The reaction 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.

HPLC (Method 12): $R_t = 1.6$ min;

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
 5 trifluoroacetate



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 μ l (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
 10 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.

HPLC (Method 12): $R_t = 2.2$ min;

20 LC-MS (Method 1): $R_t = 1.17$ min; MS (ESIpos): $m/z = 1073$ ($M+H$)⁺.

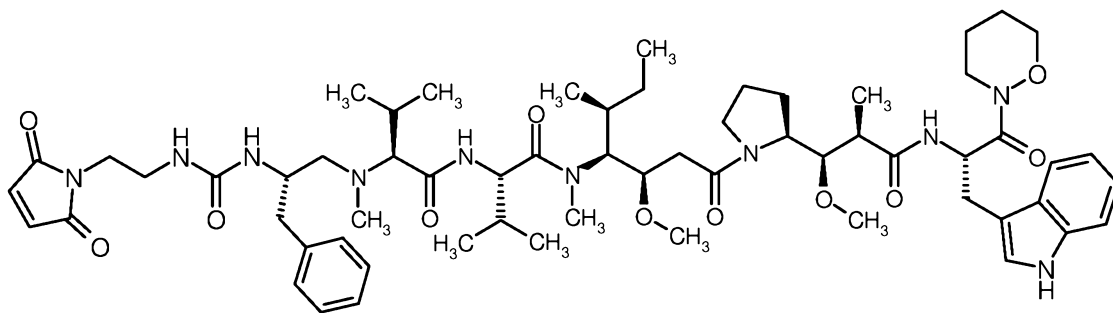
60 mg (0.05 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 2 ml of trifluoroacetic acid were added, and the reaction mixture was stirred at RT for 1.5 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were combined, the solvent
 25 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.

HPLC (Method 12): $R_t = 1.9$ min;

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-
5 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



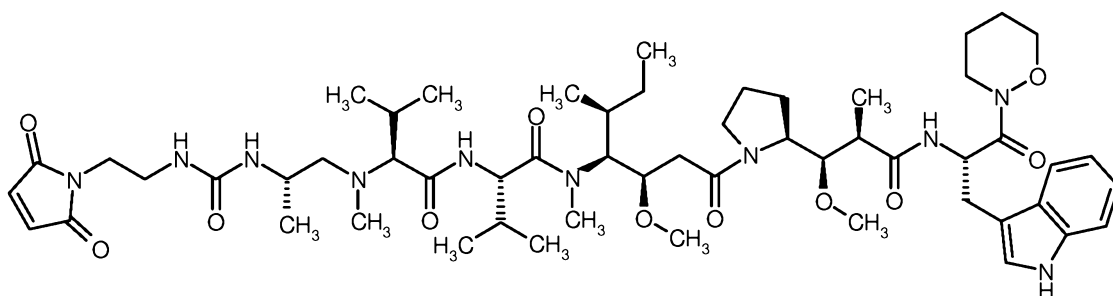
The preparation was effected in analogy to Intermediate 134, proceeding from 5 mg (4.6 μ mol) of Intermediate 222. 3.4 mg (65% of theory) of the title compound were obtained.

10 HPLC (Method 12): $R_t = 2.0$ min;

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-
15 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



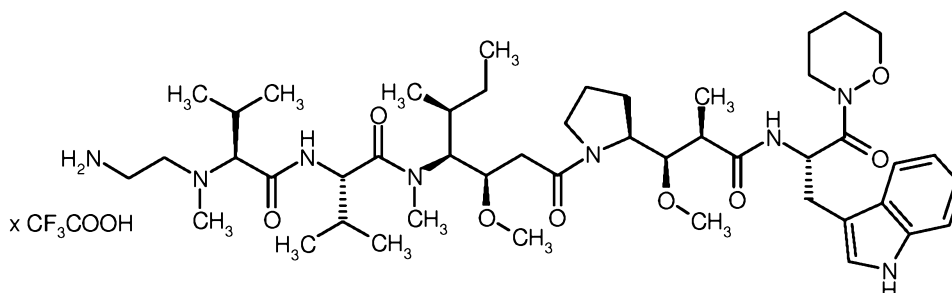
The preparation was effected in analogy to the synthesis of Intermediate 223.

HPLC (Method 12): $R_t = 1.9$ min;

20 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



5

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 μ l 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.

15 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 hexafluorophosphate (HATU) and 37 μ l (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.

25

HPLC (Method 12): R_t = 2.0 min;

LC-MS (Method 1): R_t = 1.02 min; MS (ESIpos): m/z = 984 ($M+H$)⁺.

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.

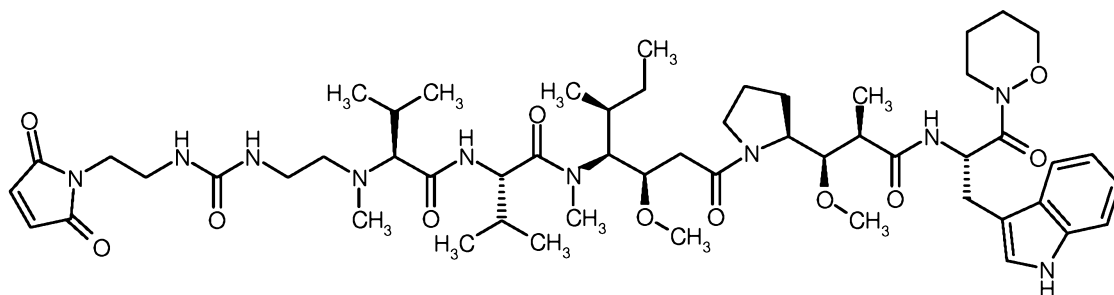
Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were combined, the solvent was removed under reduced pressure and the residue was lyophilized from dioxane/water. In this way, 21 mg (40% of theory) of the title compound were obtained in 65%
 5 purity.

HPLC (Method 12): $R_t = 1.7$ min;

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-
 10 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



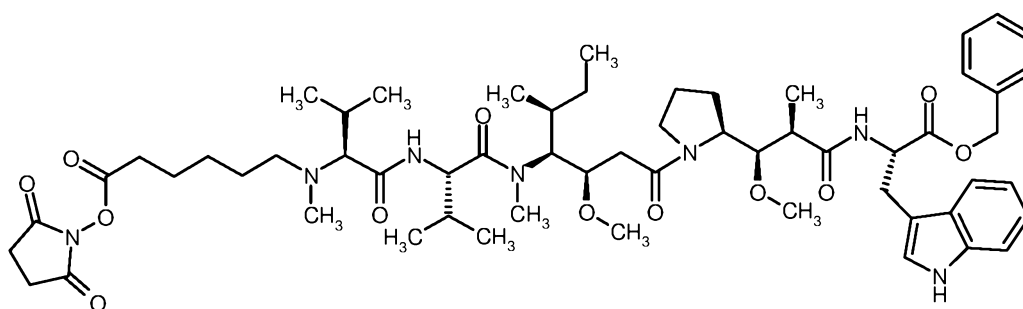
The preparation was effected proceeding from Intermediate 225, in analogy to the synthesis of
 15 Intermediate 134. 11.6 mg (59% of theory) of the title compound were obtained.

HPLC (Method 12): $R_t = 1.9$ min;

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-
 20 [(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



This compound was prepared analogously to Intermediate 218, by conversion to the active ester.

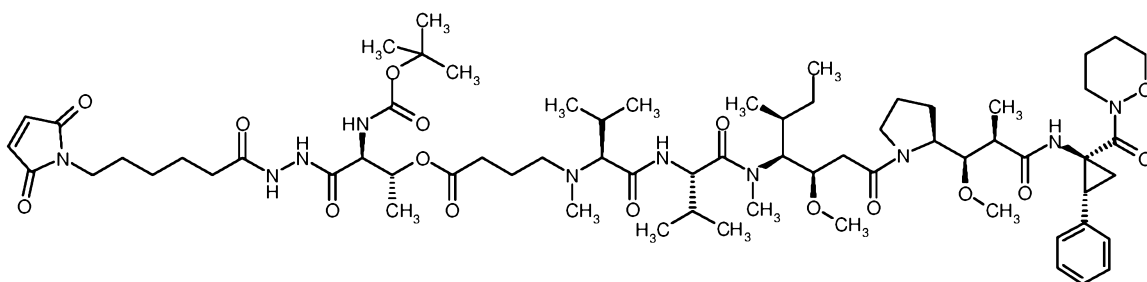
Yield: 18 mg (51% of theory)

HPLC (Method 5): $R_t = 2.1$ min;

- 5 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



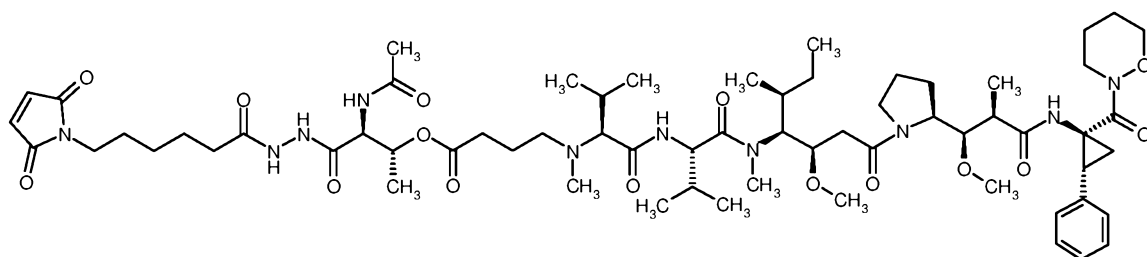
- The title compound was prepared by coupling the Boc-protected intermediate obtained in the synthesis of Intermediate 154 with commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanhydrazide.

HPLC (Method 12): $R_t = 2.1$ min;

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



The title compound was prepared from 7.5 mg (2.5 μ mol) of Intermediate 154 by acetylation with 2.3 μ l of acetic anhydride in 1 ml of DMF in the presence of 0.4 μ l of *N,N*-diisopropylethylamine.

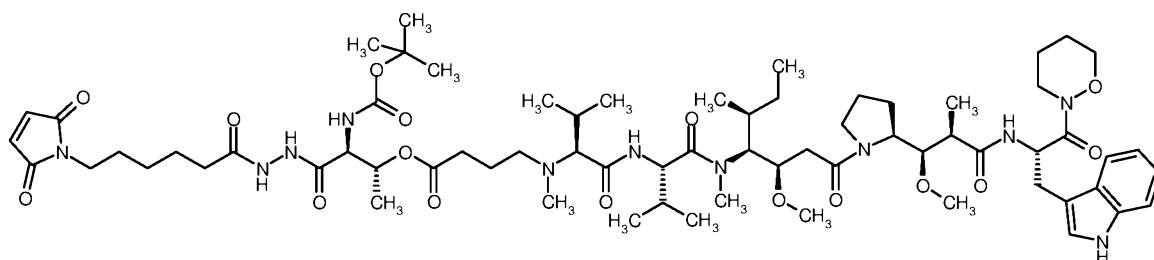
Yield: 1.4 mg (40% of theory)

HPLC (Method 12): R_t = 1.9 min;

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



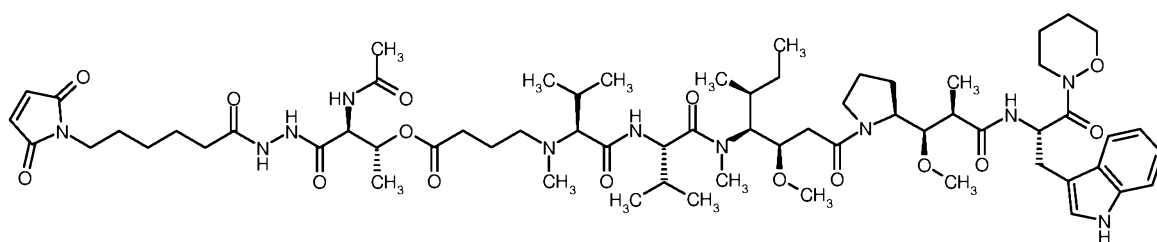
This compound was prepared in analogy to Intermediate 228, proceeding from Intermediate 193. 16 mg (30% of theory over 3 stages) of the title compound were obtained.

HPLC (Method 12): $R_t = 2.0$ min;

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



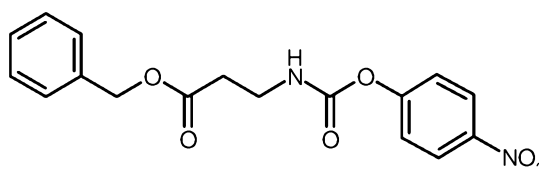
This compound was prepared from 8 mg (6 μ mol) of Intermediate 230, first by deprotection with trifluoroacetic acid and subsequent acetylation with acetic anhydride in DMF in the presence of *N,N*-diisopropylethylamine. 2 mg (37% of theory over 2 stages) of the title compound were obtained.

HPLC (Method 12): $R_t = 1.9$ min;

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



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

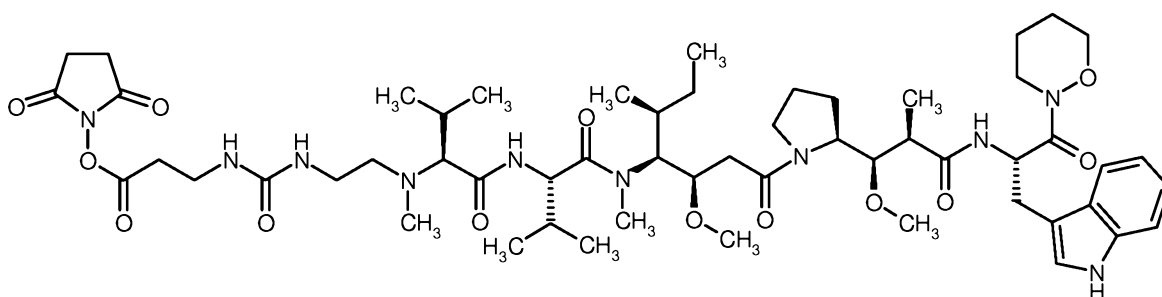
of preparative HPLC. After concentration of the corresponding fractions and drying of the residue under high vacuum, 86 mg (44% of theory) of the title compound were obtained.

HPLC (Method 12): $R_t = 1.8$ min;

LC-MS (Method 1): $R_t = 1.07$ min; MS (ESIpos): $m/z = 345$ (M+H)⁺.

5 **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



10 13 mg (10 μ mol) of Intermediate 225 and 6.7 mg (20 μ mol) of Intermediate 232 were dissolved in 3 ml of DMF, and then 7 μ l 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.

HPLC (Method 5): $R_t = 2.1$ min;

LC-MS (Method 1): $R_t = 0.6$ min; MS (ESIpos): $m/z = 1089$ (M+H)⁺.

5.4 mg (5 μ mol) 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.

HPLC (Method 12): $R_t = 1.8$ min;

LC-MS (Method 1): $R_t = 0.84$ min; MS (ESIpos): $m/z = 999$ (M+H)⁺.

25 5 mg (10 μ mol) 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 μ l of *N,N*-diisopropylethylamine and

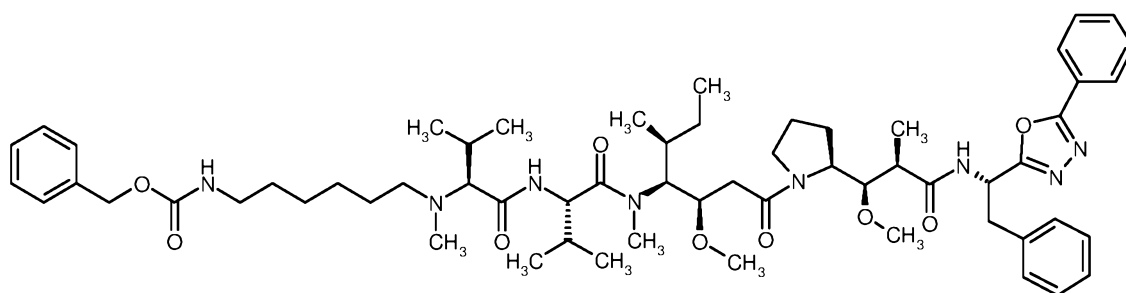
3.8 mg (10 μ mol) of HATU. After stirring at RT for 20 h, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from 1:1 dioxane/water, 1.1 mg (20% of theory) of the title compound were obtained.

5 HPLC (Method 12): R_t = 1.9 min;

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-
 10 [(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

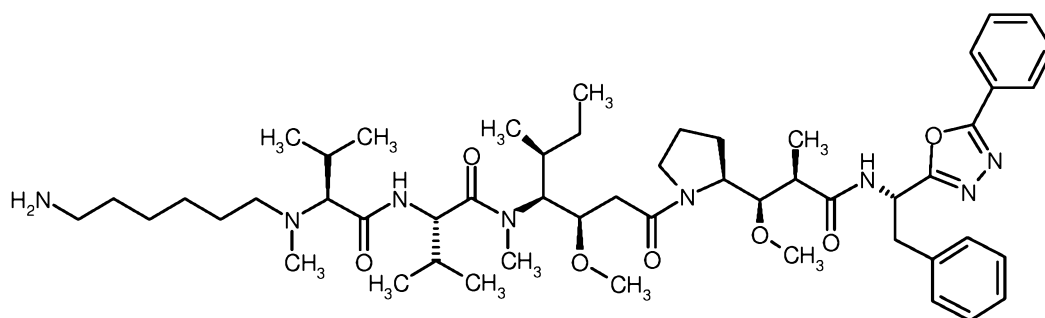


25 mg (30 μ mol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-[(2S)-2-[(1R,2R)-1-methoxy-2-
 methyl-3-oxo-3-[[[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino]propyl]pyrrolidin-
 1-yl]-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 55) and 45 mg (180 μ mol)
 15 of benzyl 6-oxohexyl carbamate were taken up in 3 ml of methanol and acidified with acetic acid. At room temperature, 15 μ l (144 μ mol; 9.4M) of borane-pyridine complex were subsequently added. The mixture was subsequently stirred at RT for 24 h, and acetic acid and 15 μ l (144 μ mol; 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
 20 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.

LC-MS (Method 1): R_t = 1.03 min; m/z = 1066 ($M+H$)⁺.

Intermediate 235

N-(6-aminoethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-[(2S)-2-[(1R,2R)-1-methoxy-2-
 25 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

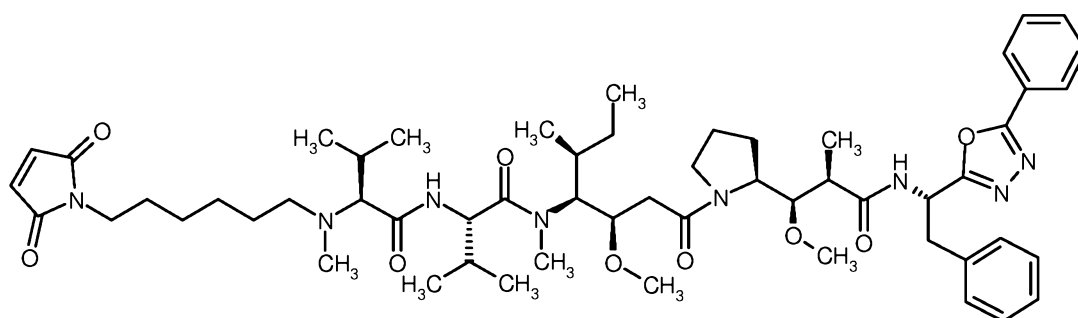


15 mg (14 μ mol) of N-(6-((benzyloxy)carbonylamino)hexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-((2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino)propyl]pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 234) were 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.

10 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



15

11 mg (12 μ mol) 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 μ l of 1:1 dioxane/water and admixed with 253 μ l of 1M aqueous sodium hydrogencarbonate solution and then with 2.8 mg (18 μ mol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 30 min and then

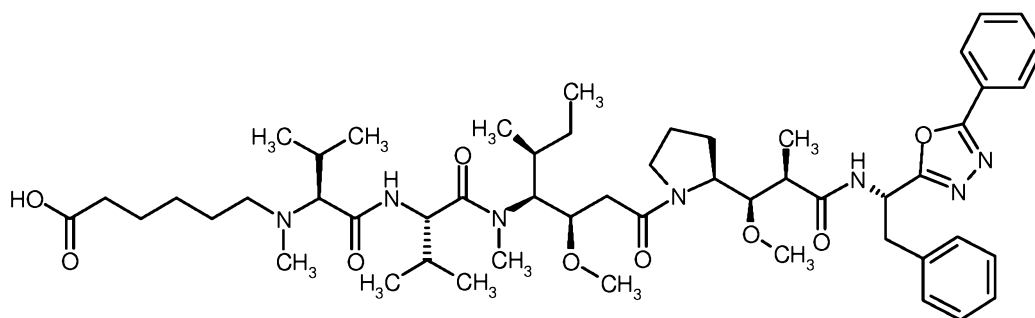
20

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.

LC-MS (Method 1): $R_t = 1.01$ min; $m/z = 1012$ ($M+H$)⁺.

Intermediate 237

- 5 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



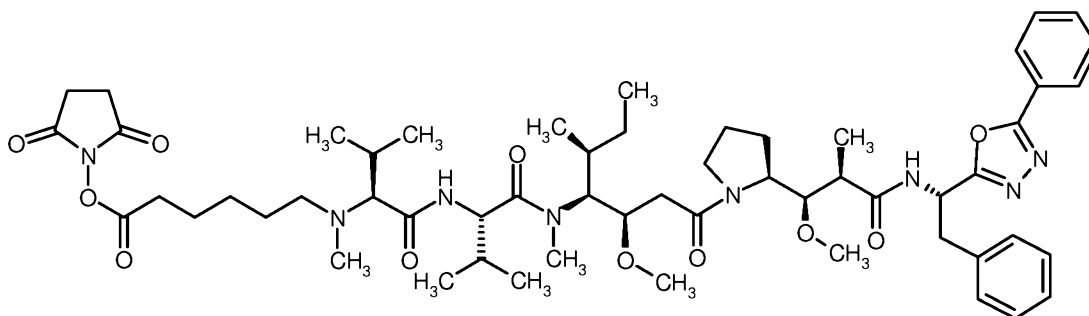
- 25 mg (30 μ mol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[[[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino]propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 55) and 23 mg (180 μ mol) of 6-oxohexanoic acid were taken up in 3 ml of methanol and acidified with acetic acid. At room temperature, 15 μ l (144 μ mol; 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 μ l (144 μ mol; 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.

LC-MS (Method 1): $R_t = 0.91$ min; $m/z = 947$ ($M+H$)⁺.

- 20 **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

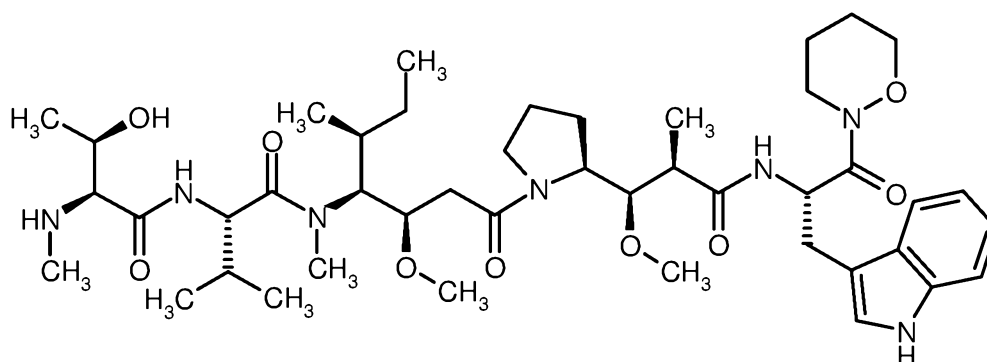


21 mg (22 μ mol) of Intermediate 237 were dissolved in 1 ml of DMF and admixed with 38 mg (333 μ mol) of 1-hydroxypyrrolidine-2,5-dione and then with 2.4 mg (10 μ mol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 19 μ l of N,N-diisopropylethylamine. After 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.

LC-MS (Method 1): R_t = 0.95 min; m/z = 1044 ($M+H$)⁺.

10 **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



15 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-1*H*-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.

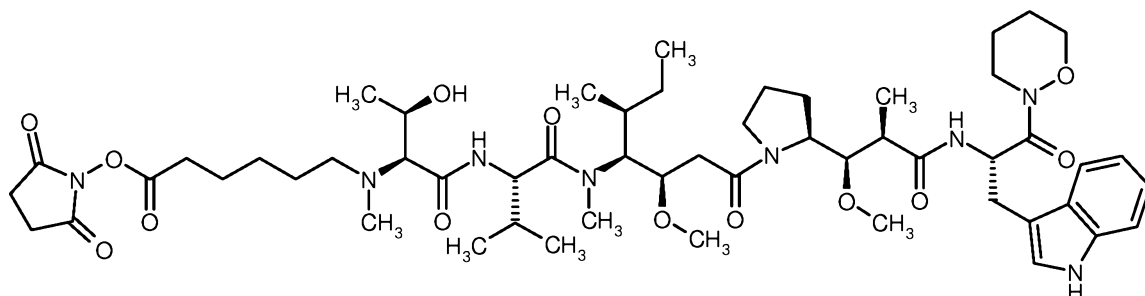
LC-MS (Method 1): $R_t = 1.15$ min; MS (ESIpos): $m/z = 976$ (M+H)⁺.

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.

LC-MS (Method 1): $R_t = 0.77$ min; MS (ESIpos): $m/z = 842$ (M+H)⁺.

Intermediate 240

10 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



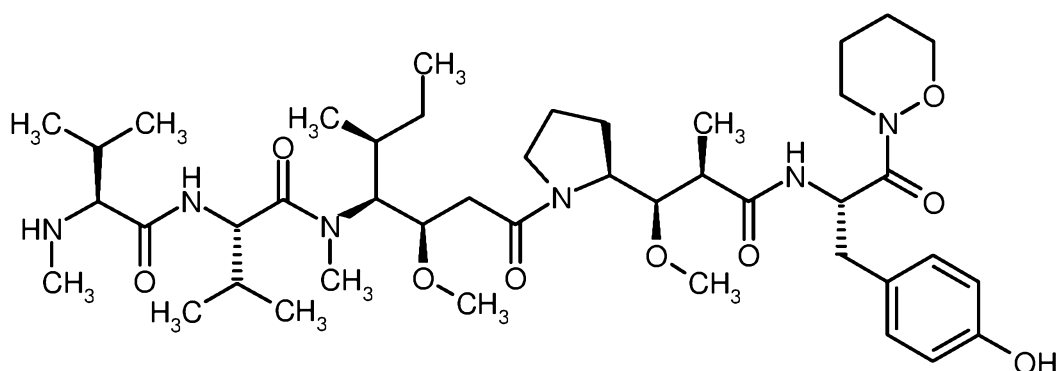
This compound was prepared in analogy to Intermediate 210 from 15.6 mg (0.016 mmol) of Intermediate 239. 10.8 mg (67% of theory over 2 stages) of the title compound were obtained.

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.85$ min; MS (ESIpos): $m/z = 1053$ (M+H)⁺.

Intermediate 241

20 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



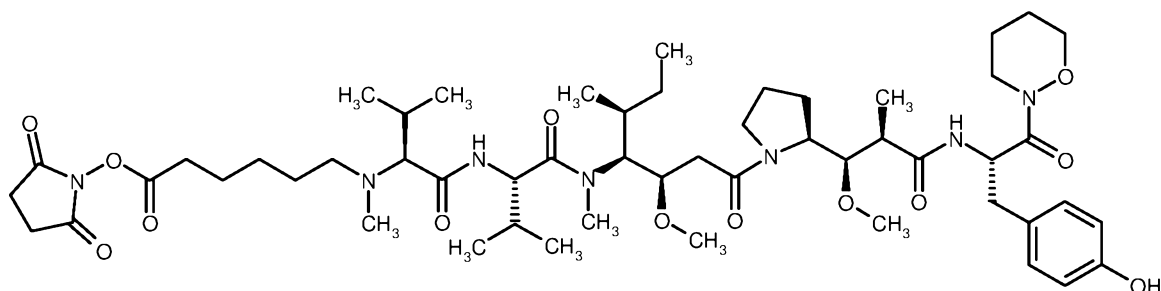
First, in analogy to Intermediate 5, trifluoroacetic acid-(2S)-2-amino-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)propan-1-one (1:1) was prepared. This reagent was then used, in analogy to the synthesis described in Intermediate 75, by coupling with *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-carboxy-1-methoxypropyl]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.

10 HPLC (Method 12): $R_t = 1.7$ min;

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*-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-3-[[[(2*S*)-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



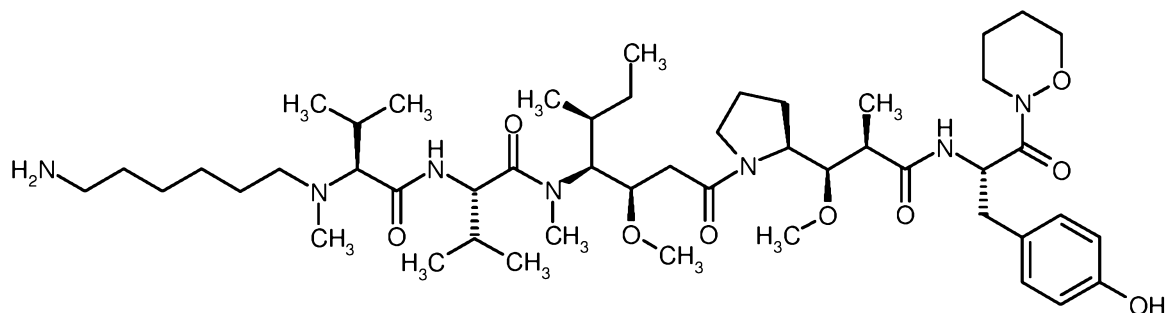
50 mg (0.05 mmol) of Intermediate 241 were reacted, in analogy to Intermediate 210, with 6-oxohexanoic acid in the presence of borane-pyridine complex. Subsequently, 22.5 mg (0.02 mmol) of the resulting acid were converted to the activated ester. 13.5 mg (36% of theory over 2 stages) of the title compound were obtained.

HPLC (Method 12): $R_t = 1.8$ min;

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



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.

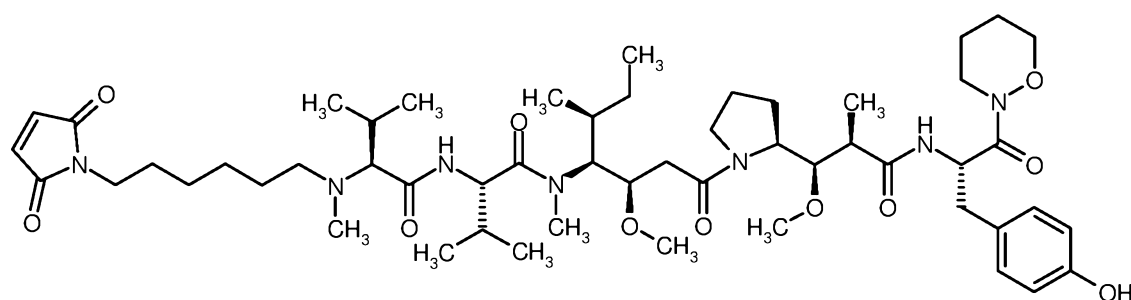
Yield: 17.5 mg (34% of theory over 2 stages)

HPLC (Method 12): $R_t = 1.7$ min;

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



The preparation was effected in analogy to Intermediate 166, proceeding from Intermediate 243.

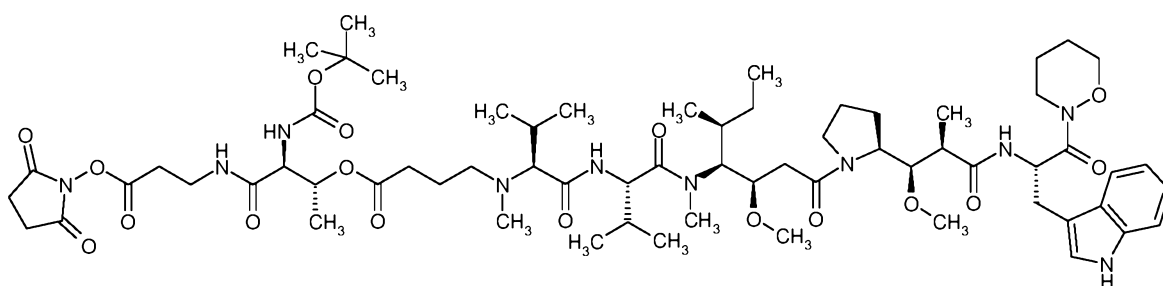
Yield: 1.3 mg (12% of theory)

HPLC (Method 12): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 0.89$ min; MS (ESIpos): $m/z = 996$ ($M+H$)⁺.

5 **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



10

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.

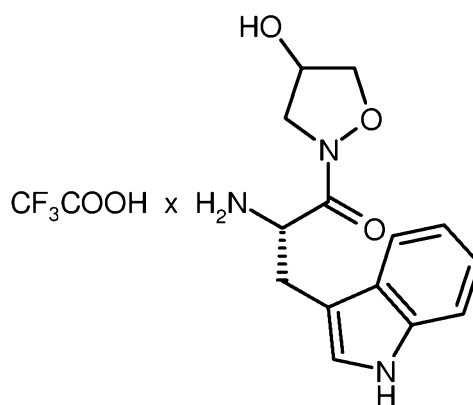
20

HPLC (Method 5): $R_t = 1.9$ min;

LC-MS (Method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 1295$ ($M+H$)⁺

Intermediate 246a

25 (2S)-2-amino-1-(4-hydroxy-1,2-oxazolidin-2-yl)-3-(1H-indol-3-yl)propan-1-one trifluoroacetate (Diastereomer 1)



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 μ l of *N,N*-diisopropylethylamine. The reaction mixture was stirred at RT overnight. Then another
 5 100 μ l 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
 10 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%
 15 of theory) of a mixed fraction of the Boc-protected intermediates were obtained.

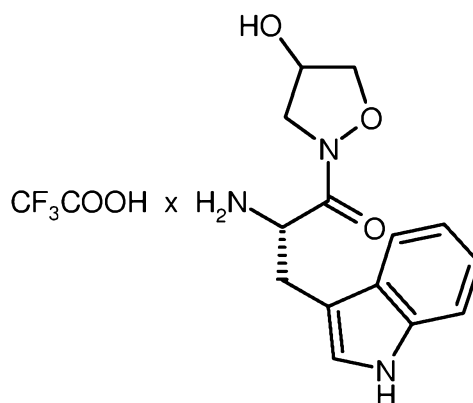
Under standard conditions, 5 ml of trifluoroacetic acid in 20 ml of dichloromethane were used to detach the Boc protecting group from 272 mg (725 μ mol) of Diastereomer 1 of this intermediate and, after lyophilization from dioxane/water, 290 mg (quant) of the title compound were obtained in 75% purity and used in the next stage without further purification.

20 HPLC (Method 12): R_t = 1.1 min;

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)

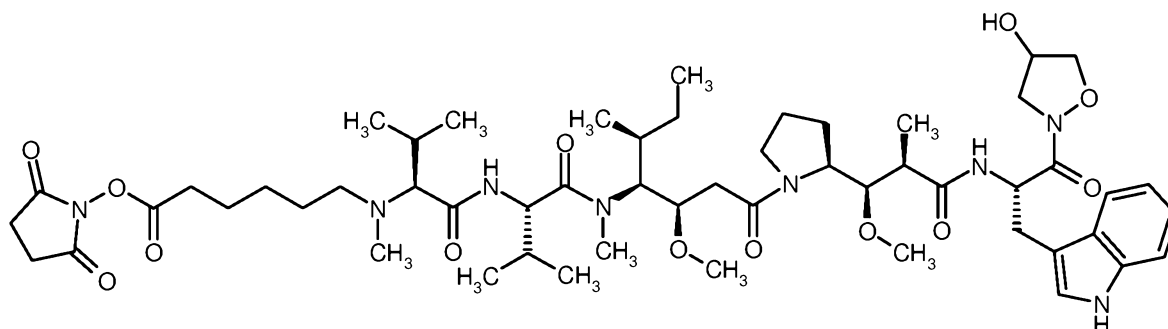


Under standard conditions, 5 ml of trifluoroacetic acid in 20 ml of dichloromethane were used to detach the Boc protecting group from 236 mg (630 μ mol) of Diastereomer 2 of the intermediate described in 246a and, after concentration, stirring with diethyl ether and drying of the residue
 5 under high vacuum, 214 mg (76%) of the title compound were obtained.

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-
 10 methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-
 valinamide (Diastereomer 1)



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.
 15 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.

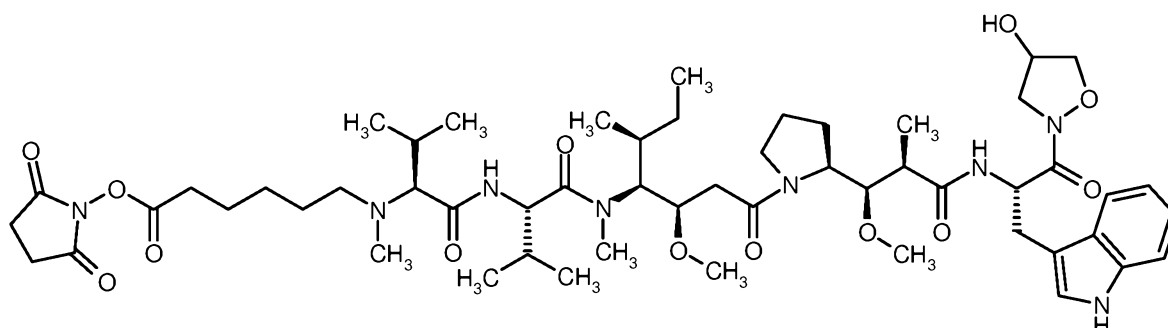
HPLC (Method 12): R_t = 1.8 min;

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-

5 valinamide (Diastereomer 2)



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

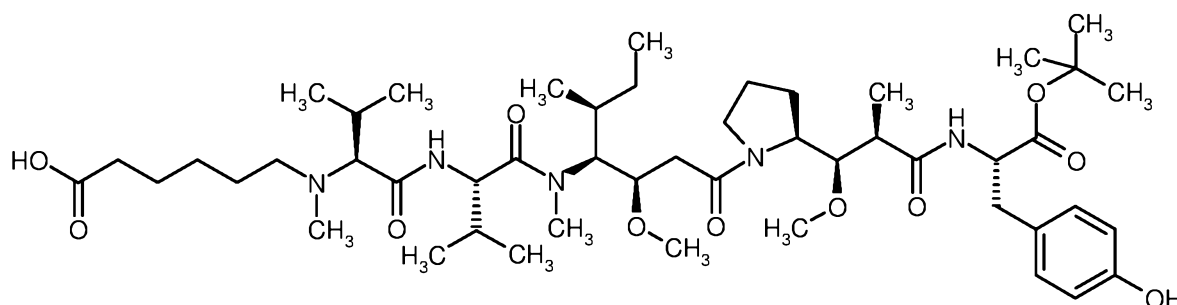
10 Intermediate 210. The title compound was purified by preparative HPLC.

HPLC (Method 12): $R_t = 1.8$ min;

LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 1053$ ($M+H$)⁺

Intermediate 248

15 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



20 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-
5 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]-L-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.

10 HPLC (Method 12): $R_t = 1.8$ min;

LC-MS (Method 1): $R_t = 0.88$ min; MS (ESIpos): $m/z = 918$ (M+H)⁺.

B: Preparation of antibody-drug conjugates (ADCs)**B-1. General process for generating anti-C4.4a antibodies**

The anti-C4.4a antibodies described by the sequences of Table 1 and Table 2 were generated by screening a phage display library for recombinant human C4.4a SEQ ID NO: 1 and murine C4.4a
5 SEQ ID NO: 2 and for cells expressing C4.4a. The antibodies obtained in this way were reformatted to the human IgG1 format and used for the working examples described here.

B-2. General process for expressing anti-C4.4a antibodies in mammalian cells

The antibodies, for example M31-B01 (light chain SEQ ID NO: 346 and heavy chain SEQ ID NO: 347) or further antibodies of Table 2 were produced in a mammalian cell culture. For this
10 purpose, HEK293 6E cells were transiently transfected with a suitable CMV promotor based expression plasmid. The heavy and light chains of the antibodies were cloned either together into a one-vector system, or separately into a two-vector system. The cell culture scale was either up to 1.5 L in a shake flask or 10 L in a "wave-bag". Expression took place at 37°C for 5-6 days in F17 Medium (Invitrogen) supplemented with Tryptone TN1 (Organotechnie) with 1% "FCS ultra low
15 IgG" (Invitrogen) and 0.5 mM valproic acid. The expression yields were between 100 and 600 mg/l.

B-3. General process for purifying antibodies from cell supernatants

The antibodies, for example M31-B01 (light chain SEQ ID NO: 346 and heavy chain SEQ ID NO: 347) or further antibodies of Table 2 were obtained from the cell culture supernatants. The
20 cell supernatants were clarified by centrifugation to remove cells. Subsequently the cell supernatant was purified by affinity chromatography on a MabSelect Sure (GE Healthcare) chromatography column. For this purpose the column was equilibrated in DPBS pH 7.4 (Sigma/Aldrich), the cell supernatant was applied, and the column was washed with about 10 column volumes of DPBS pH 7.4 + 500 mM sodium chloride. The antibodies were eluted in
25 50 mM sodium acetate pH 3.5 + 500 mM sodium chloride and subsequently purified further by gel filtration chromatography on a Superdex 200 column (GE Healthcare) in DPBS pH 7.4.

B-4. General process for coupling to cysteine side chains

The antibodies used in the coupling reactions were as follows:

anti-C4.4a M31-B01

30 anti-C4.4a B01-3

anti-C4.4a B01-10

anti-C4.4a B01-7

anti-C4.4a D02-4

anti-C4.4a D02-6

anti-C4.4a D02-7

- 5 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, 10 111-114, 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 15 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.

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 20 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 below.

This process was used to prepare the immunoconjugates represented in Examples 1-3, 5-30, 32-36, 38-59, 61-66, 68-70, 80, 82-85, 87, 88, 92-95, 97, 98, 107, 109-114, 119 and 122.

- 25 In the structural formulae illustrated, the definition of AK_{IA}-AK_{IG} is as follows

AK_{IA} = anti-C4.4a antibody M31-B01 (partially reduced)- S§¹

AK_{IB} = anti-C4.4a antibody B01-3 (partially reduced)- S§¹

AK_{IC} = anti-C4.4a antibody B01-10 (partially reduced)- S§¹

AK_{ID} = anti-C4.4a antibody B01-7 (partially reduced)-S§¹

- 30 AK_{IE} = anti-C4.4a antibody D02-4 (partially reduced)- S§¹

AK_{IF} = anti-C4.4a antibody D02-6 (partially reduced)- S§¹

AK_{IG} = anti-C4.4a antibody D02-7 (partially reduced)- S§¹

where

§¹ denotes the link with the succinimide group,

5 and

S stands for the sulphur atom of a cysteine residue of the partially reduced antibody.

B-5. General process for coupling to lysine side chains

The antibodies used in the coupling reactions were as follows:

anti-C4.4a antibody M31-B01

10 anti-C4.4a antibody B01-3

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, 15 245, 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 20 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.

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 25 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 below.

This process was used to prepare the immunoconjugates represented in Examples 4, 31, 37, 60, 67, 81, 86, 89-91, 96, 99-106, 108, 118, 120, 121 and 123-125.

In the structural formulae illustrated, the definition of AK_{2A} and A_{2B} is as follows

AK_{2A} = anti-C4.4a antibody M31-B01-NH§²

AK_{2B} = anti-C4.4a antibody B01-3-NH§²

where

5 §² denotes the link with the carbonyl group,

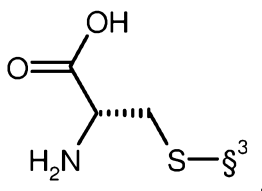
and

NH stands for the side chain amino group of a lysine residue of the antibody.

B-6. General process for preparing cysteine adducts:

10 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.

In the structural formulae illustrated, the definition of Cys is as follows



where

15 §³ denotes the link with the linker-toxophore unit.

Further purification and characterization of the conjugates of the invention

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
20 option is to lyophilize the conjugate.

B-7. Determination of the toxophore loading

The toxophore loading of the resultant solutions of the conjugates described in the working examples, in PBS buffer, was determined as follows:

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
5 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.

For protein identification, in addition to the molecular weight determination, a tryptic digestion
10 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.

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 μ L) was
15 admixed with guanidinium hydrochloride (GuHCl) (28.6 mg) and with a solution of DL-dithiothreitol (DTT) (500 mM, 3 μ L). The mixture was incubated at 55°C for an hour and analysed by HPLC.

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
20 (catalogue number PL1912-3802) (2.1 $\times$ 150 mm, 8 μ m 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.

The peaks detected were assigned by retention time comparison with the light chain (L0) and the
25 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).

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
30 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

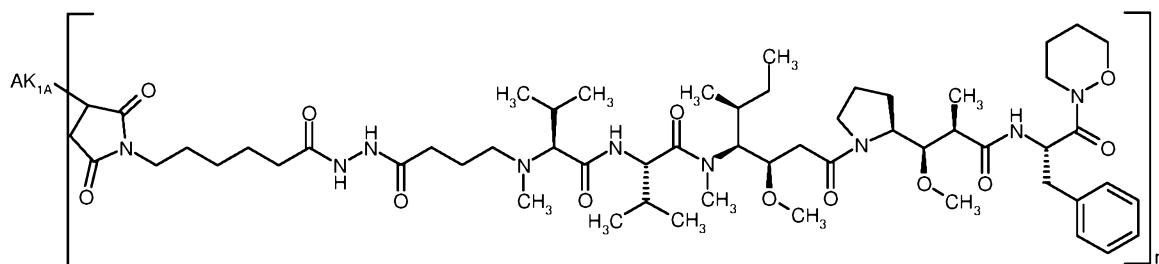
singularly weighted integration results of H0, H1, H2 and H3. The DAR is given by the light-chain loading and the heavy-chain loading, as the twofold sum of light-chain loading and heavy-chain loading. The factor 2 takes account of the fact that an antibody consists of two light chains and two heavy chains. In certain individual cases it may be impossible exactly to determine the toxophore loading, owing to co-elutions of certain peaks.

B-8. Testing of the antigen binding of the ADC

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; 110:616-623).

Working examples - immunoconjugates

Example 1

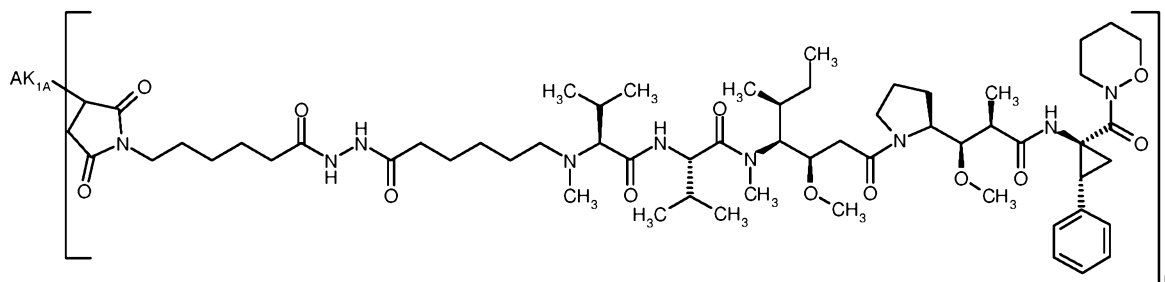


In this case coupling was carried out using 70 mg of anti-C4.4a M31-B01 in DPBS pH 7.4 and
5 following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 12.2 mg/ml

Drug/mAb Ratio: 1.5

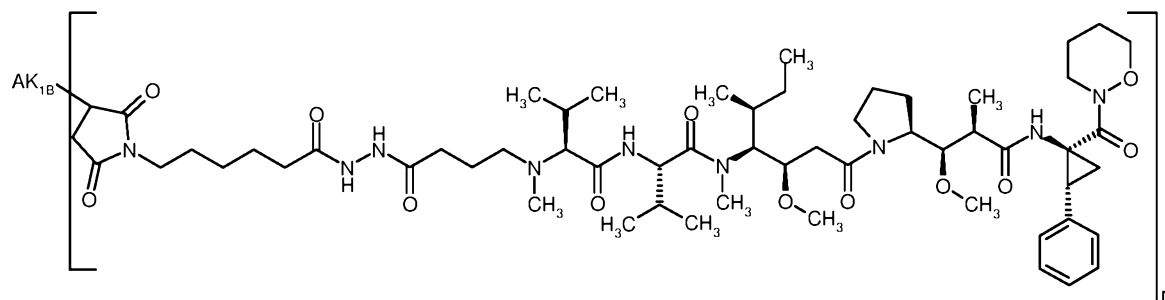
Example 2



10 Protein concentration: 0.87 mg/ml

Drug/mAb Ratio: 5.8

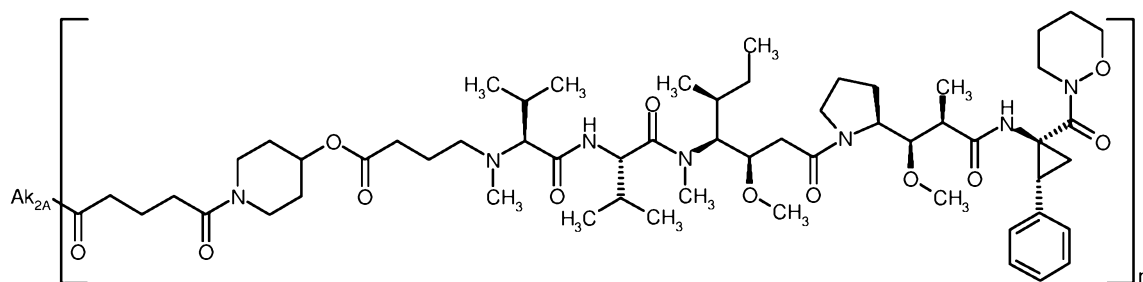
Example 3



Protein concentration: 1.16 mg/ml

Drug/mAb Ratio: 3.1

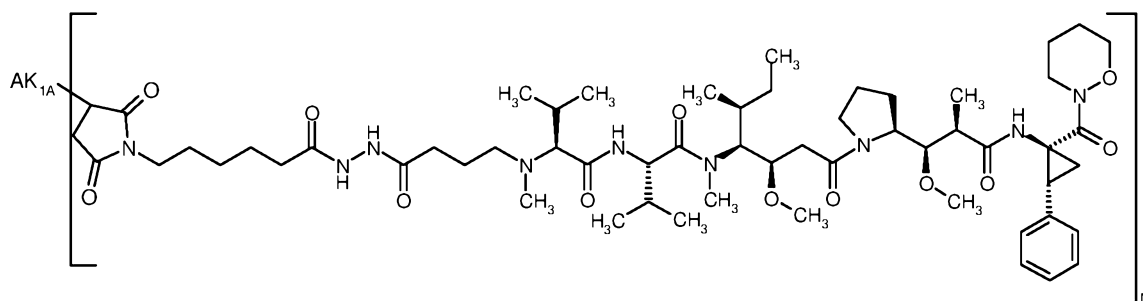
Example 4



5 Protein concentration: 1.24 mg/ml

Drug/mAb Ratio: 1.6

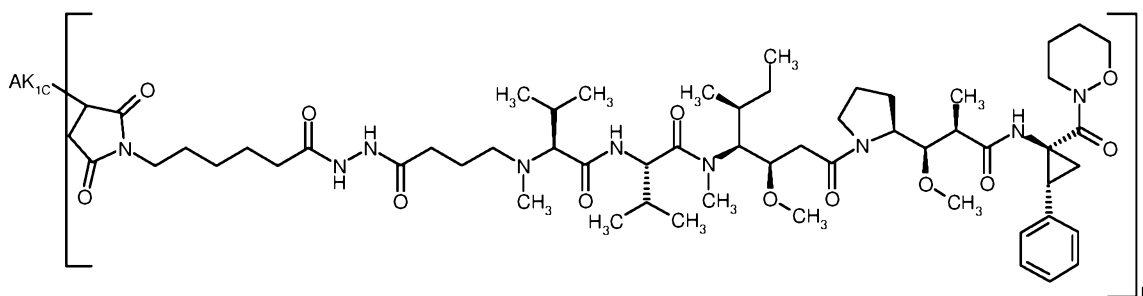
Example 5



Protein concentration: 0.88 mg/ml

10 Drug/mAb Ratio: 6.9

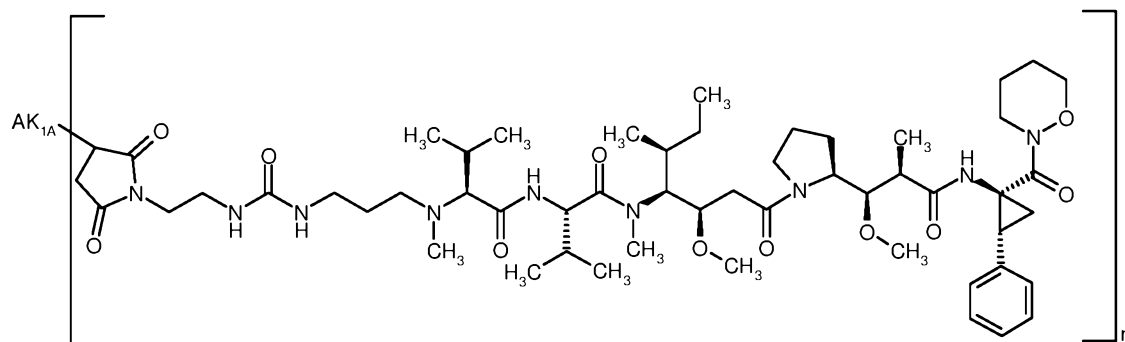
Example 6



Protein concentration: 1.2 mg/ml

Drug/mAb Ratio: 2.8

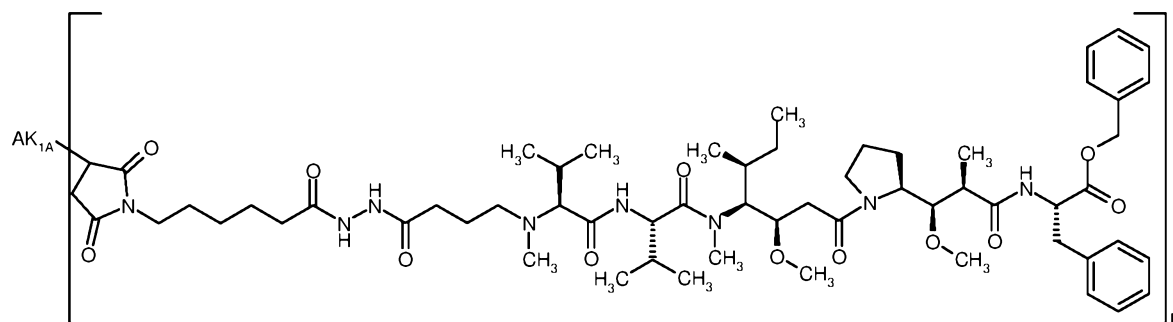
Example 7



5 Protein concentration: 0.9 mg/ml

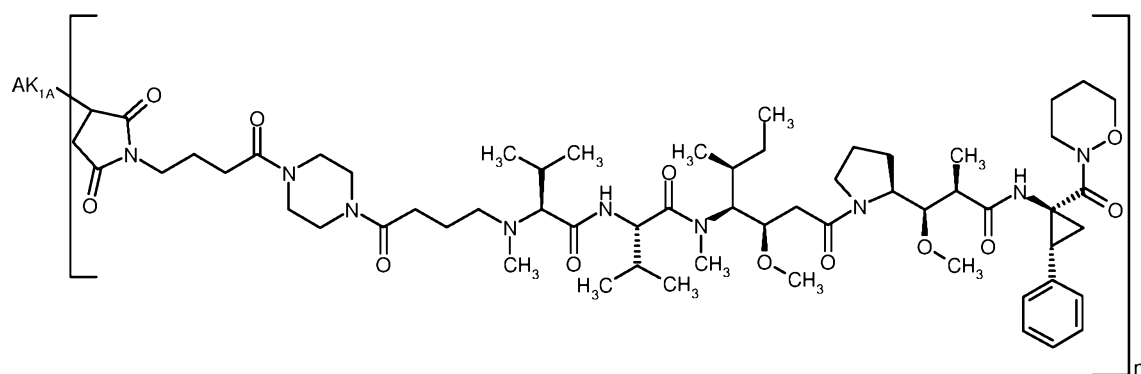
Drug/mAb Ratio: 3.9

Example 8



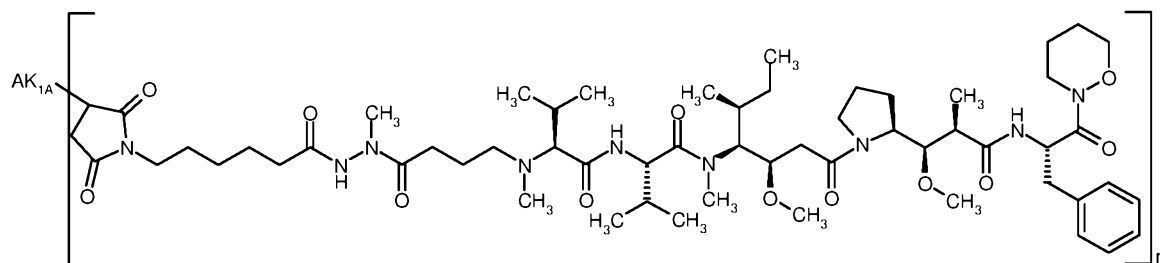
10 Protein concentration: 0.52 mg/ml

Drug/mAb Ratio: 1.6

Example 9

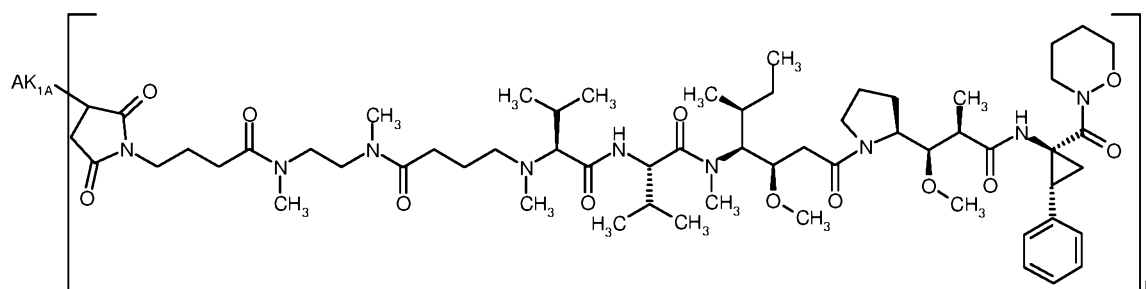
Protein concentration: 0.47 mg/ml

Drug/mAb Ratio: 6.6

5 Example 10

Protein concentration: 0.77 mg/ml

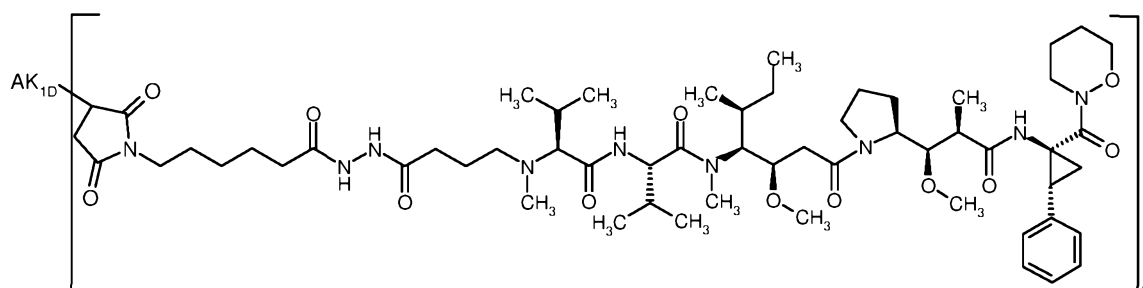
Drug/mAb Ratio: 6.9

Example 11

10

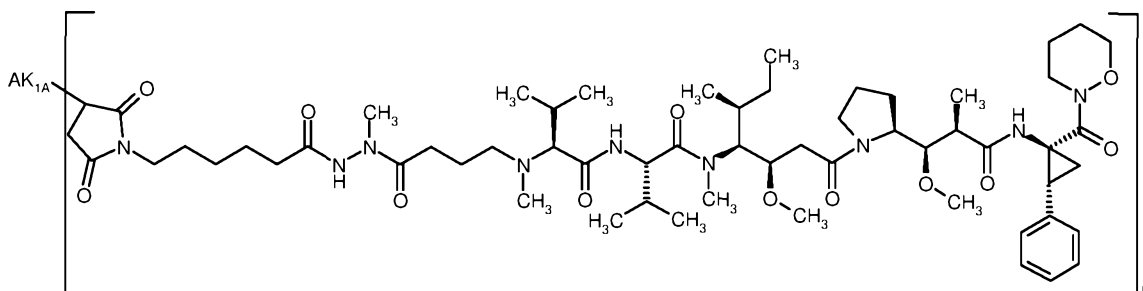
Protein concentration: 0.47 mg/ml

Drug/mAb Ratio: 4.0

Example 12

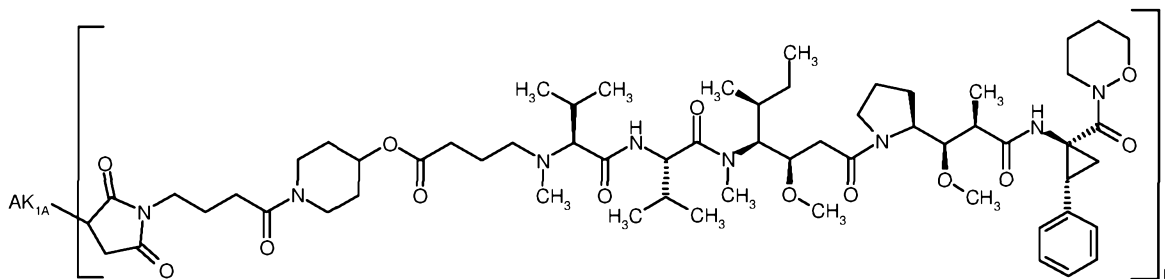
Protein concentration: 1.46 mg/ml

Drug/mAb Ratio: 2.5

5 **Example 13**

Protein concentration: 0.45 mg/ml

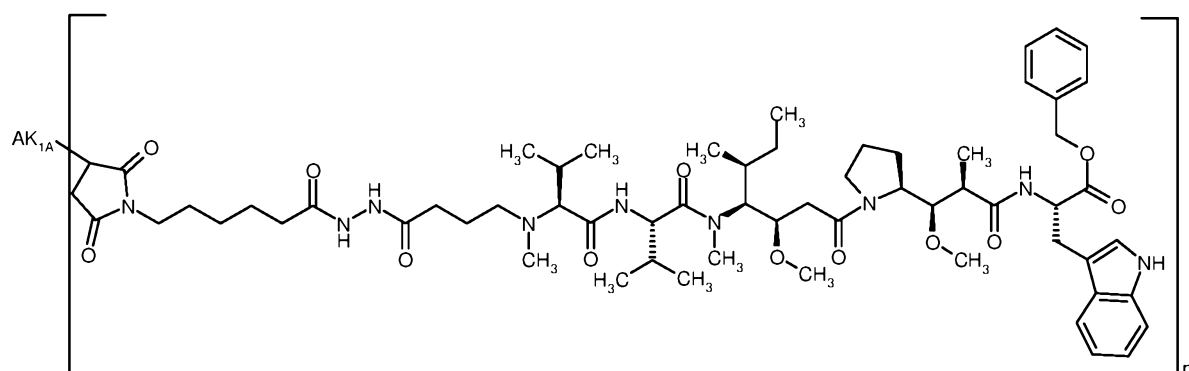
Drug/mAb Ratio: 3.3

Example 14

10

Protein concentration: 0.98 mg/ml

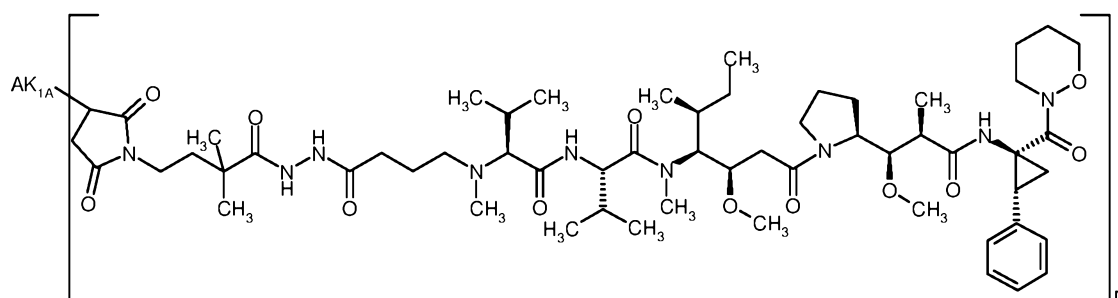
Drug/mAb Ratio: 3.6

Example 15

Coupling here was carried out using 70 mg of anti-C4.4a M31-B01 in DPBS pH 7.4, and following
 5 the Sephadex purification the batch was concentrated by ultracentrifugation.

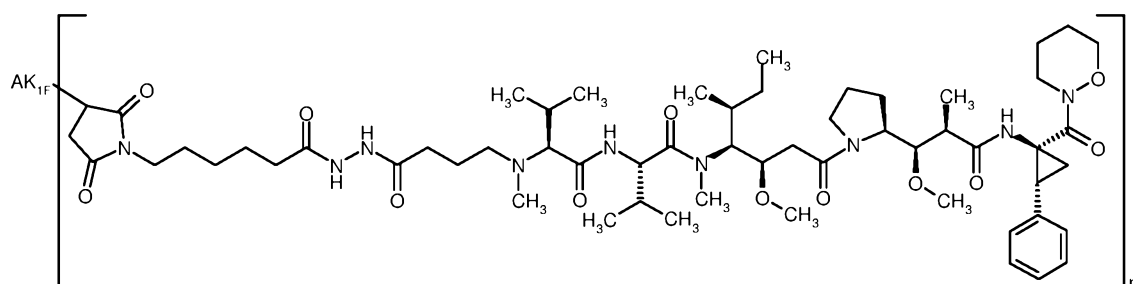
Protein concentration: 9.42 mg/ml

Drug/mAb Ratio: 4.1

Example 16

10 Protein concentration: 0.65 mg/ml

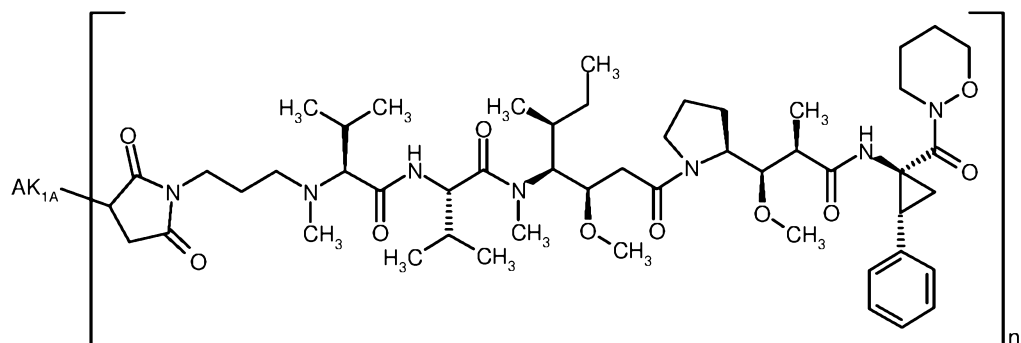
Drug/mAb Ratio: 1.8

Example 17

Protein concentration: 1.07 mg/ml

Drug/mAb Ratio: not determinable

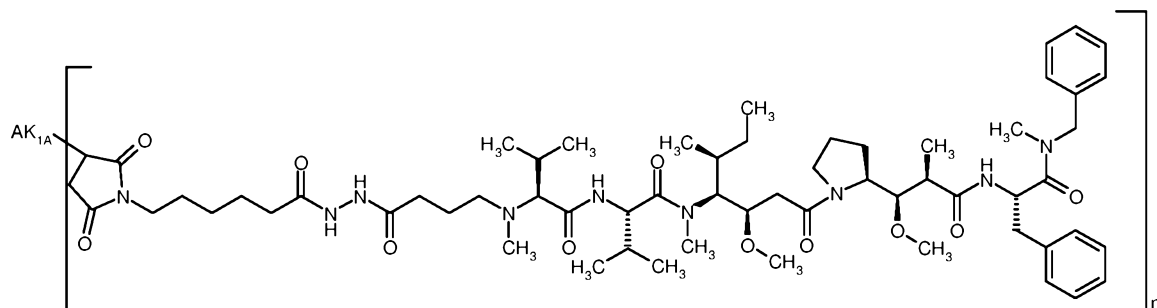
Example 18



5 Protein concentration: 0.47 mg/ml

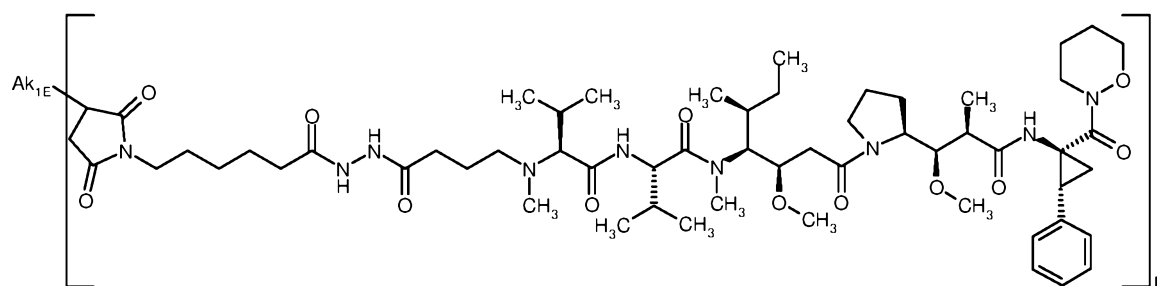
Drug/mAb Ratio: 4.4

Example 19



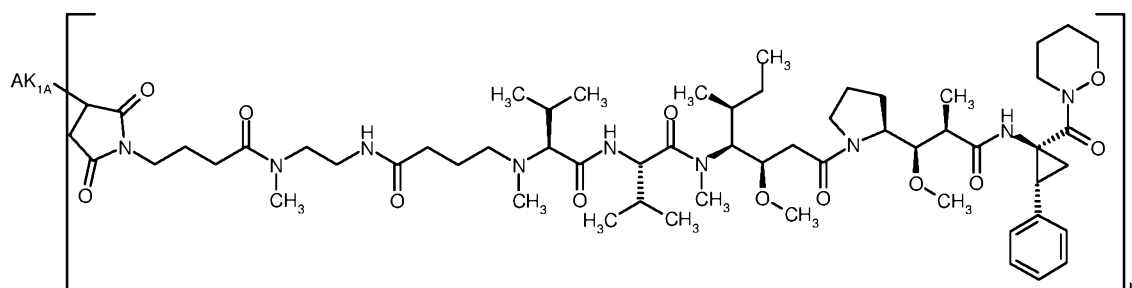
Protein concentration: 0.43 mg/ml

10 Drug/mAb Ratio: 4.8

Example 20

Protein concentration: 1.01 mg/ml

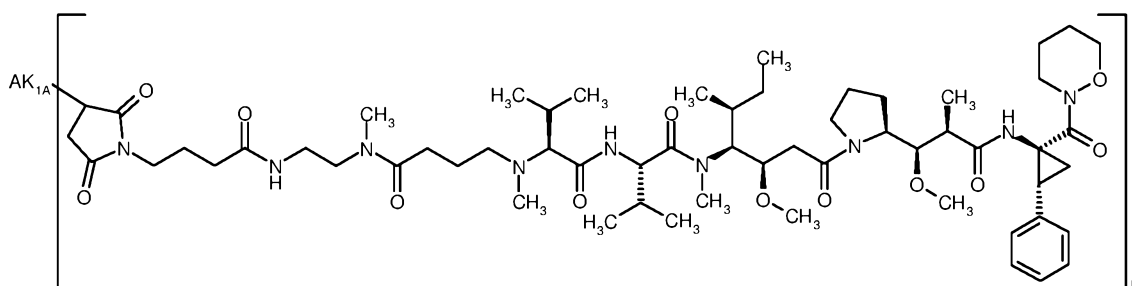
5 Drug/mAb Ratio: 2.6

Example 21

Protein concentration: 0.53 mg/ml

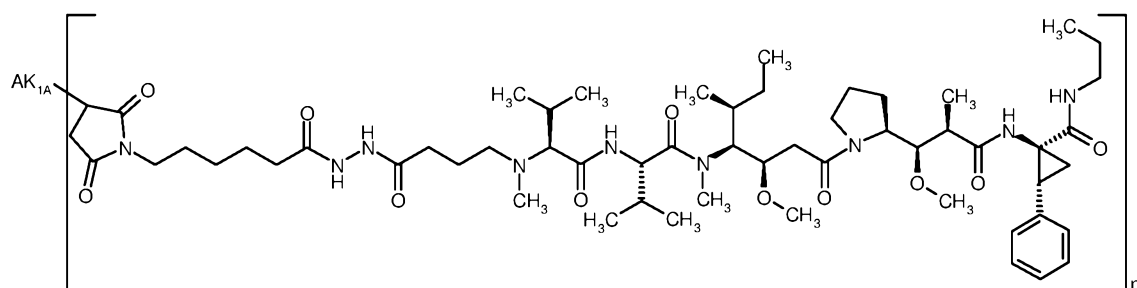
Drug/mAb Ratio: 0.6

10 **Example 22**



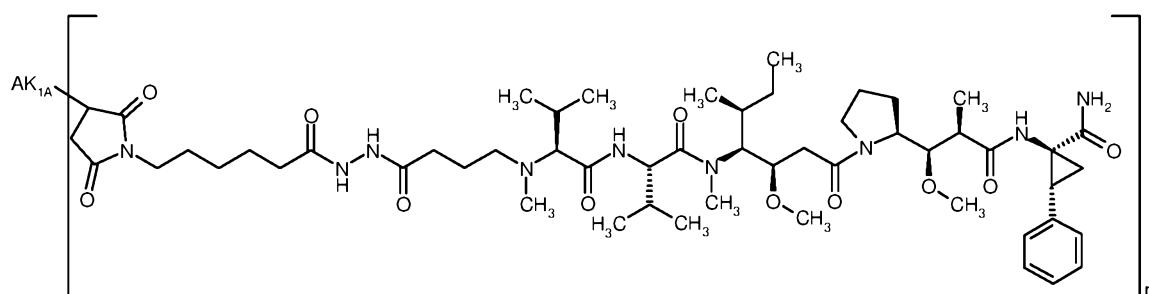
Protein concentration: 0.55 mg/ml

Drug/mAb Ratio: 1.3

Example 23

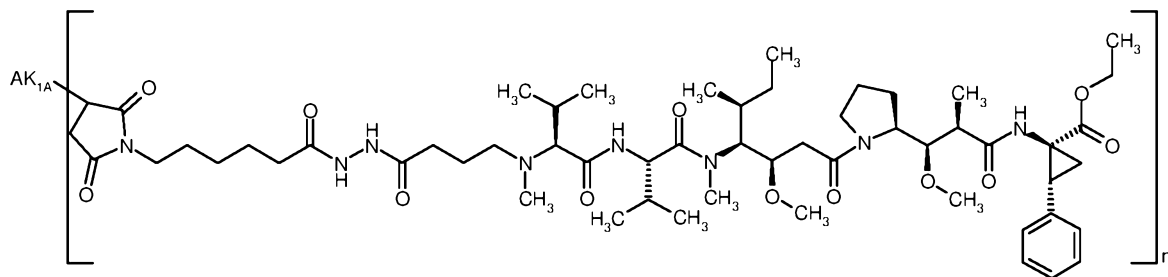
Protein concentration: 0.65 mg/ml

Drug/mAb Ratio: 1.1

5 **Example 24**

Protein concentration: 1.04

Drug/mAb Ratio: 3.5

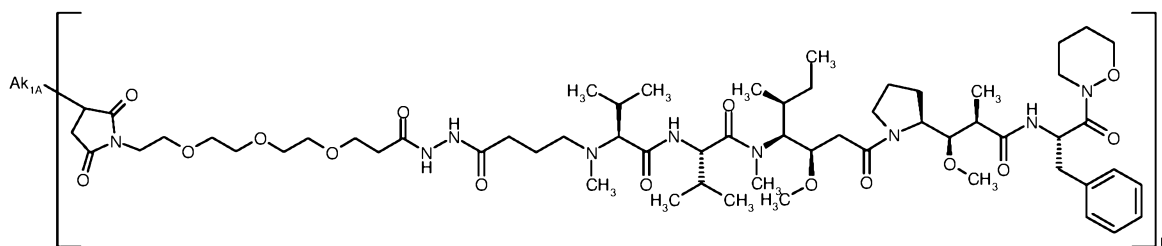
Example 25

10

Protein concentration: 0.62 mg/ml

Drug/mAb Ratio: 2.4

Example 26

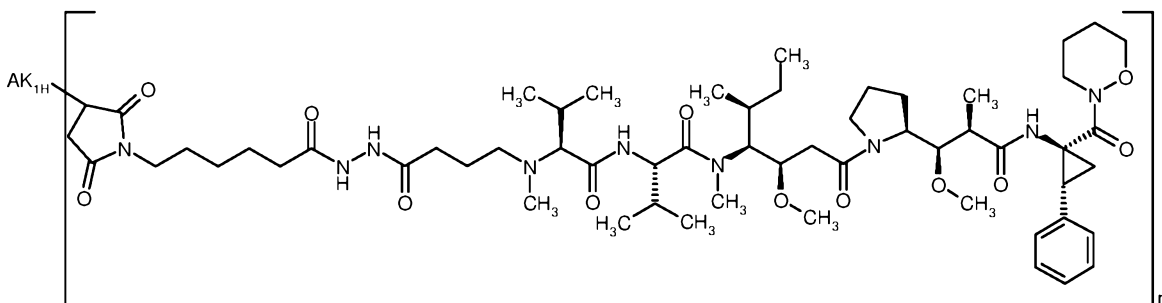


Coupling here was carried out using 90 mg of anti-C4.4a M31-B01 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

- 5 Protein concentration: 11.2 mg/ml

Drug/mAb-Ratio: 2.3

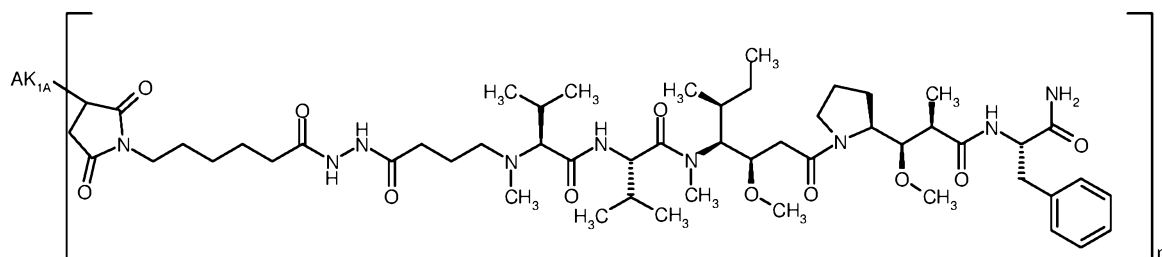
Example 27



Protein concentration: 1.11 mg/ml

- 10 Drug/mAb-Ratio: 2.4

Example 28

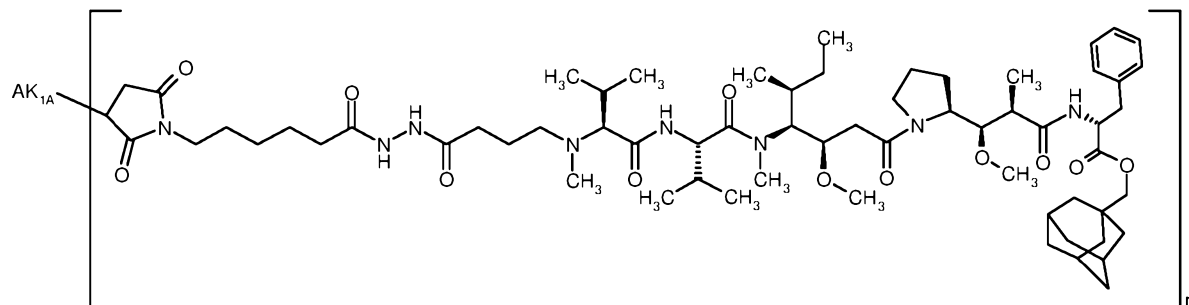


Coupling here was carried out using 70 mg of anti-C4.4a M31-B01 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 10.7 mg/ml

Drug/mAb Ratio: 2.2

Example 29

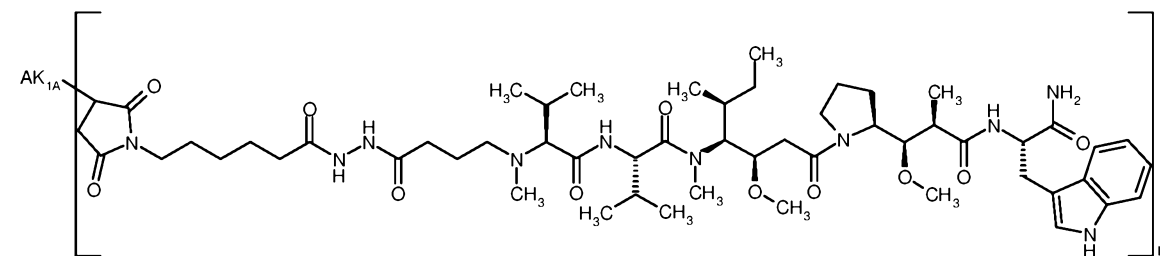


5

Protein concentration: 0.87 mg/ml

Drug/mAb Ratio: 1.8

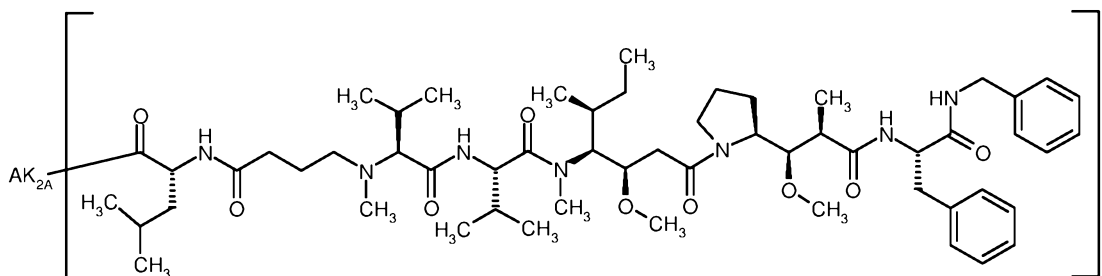
Example 30



10 Protein concentration: 1.3 mg/ml

Drug/mAb Ratio: 2.1

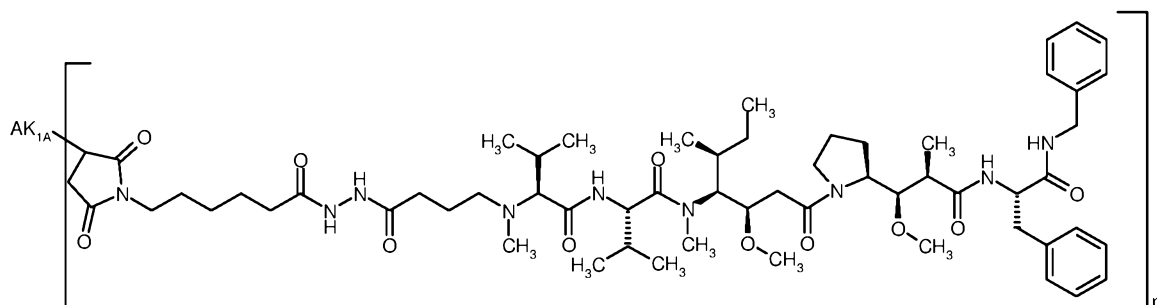
Example 31



Protein concentration: 1.3 mg/ml

Drug/mAb Ratio: 0.3

Example 32

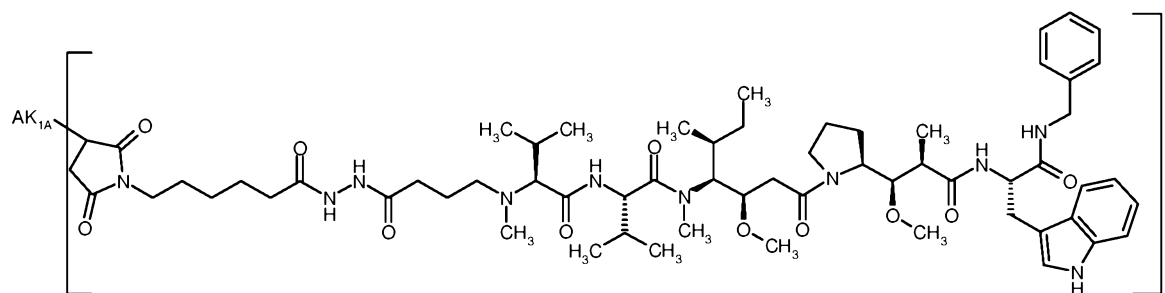


- 5 Coupling here was carried out using 70 mg of anti-C4.4a M31-B01 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 12.0 mg/ml

Drug/mAb Ratio: 3.2

Example 33

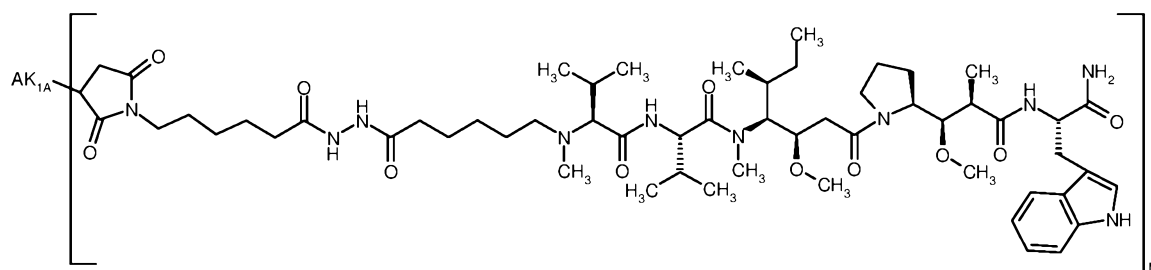


10

Coupling here was carried out using 90 mg of anti-C4.4a M31-B01 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

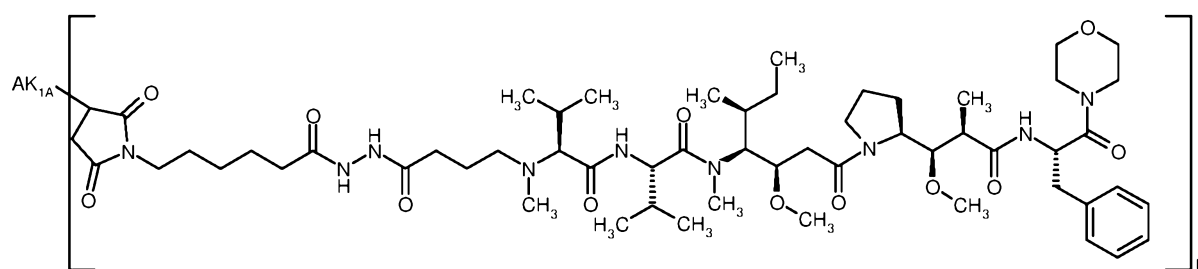
Protein concentration: 10.2 mg/ml

Drug/mAb Ratio: 4.3

Example 34

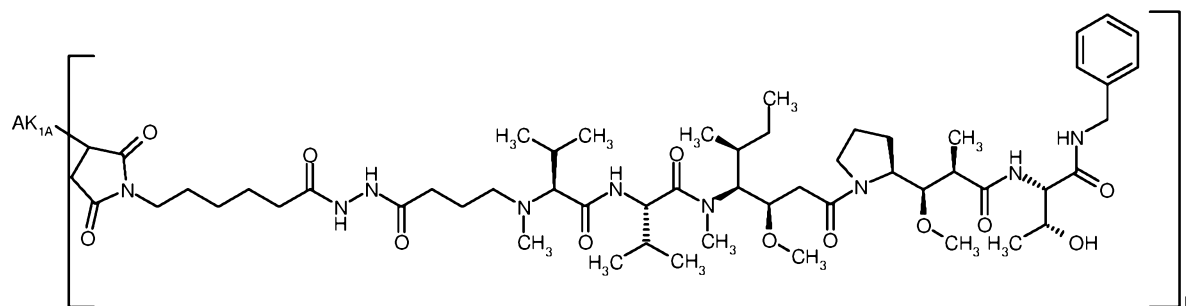
Protein concentration: 1.37 mg/ml

Drug/mAb Ratio: 2.6

5 **Example 35**

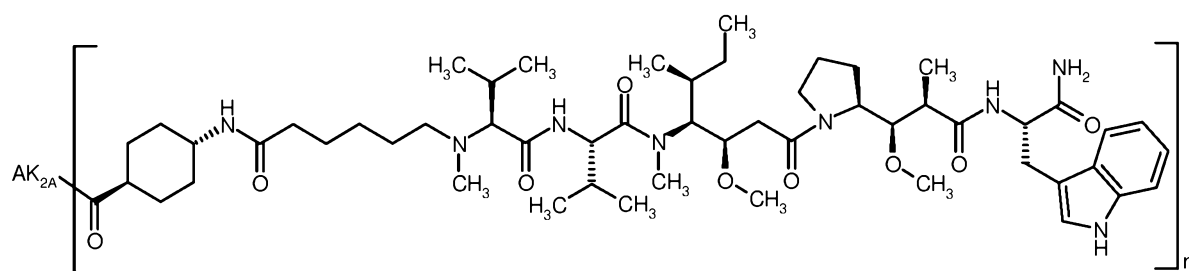
Protein concentration: 1.14 mg/ml

Drug/mAb Ratio: 2.0

10 **Example 36**

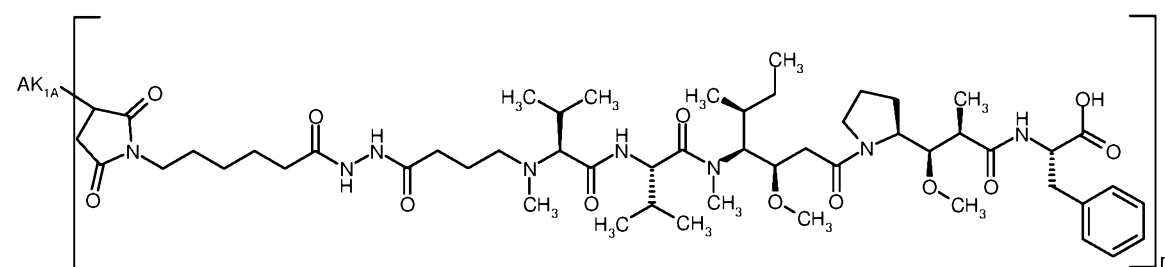
Protein concentration: 1.07 mg/ml

Drug/mAb Ratio: 3.5

Example 37

Protein concentration: 1.14 mg/ml

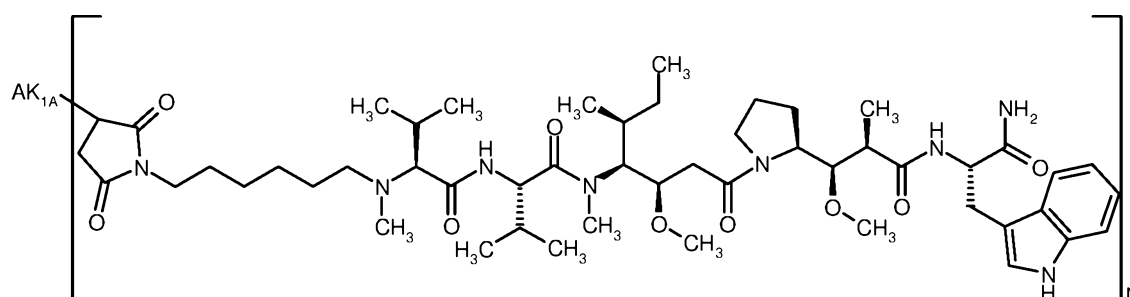
5 Drug/mAb Ratio: 1.9

Example 38

Protein concentration: 1.22 mg/ml

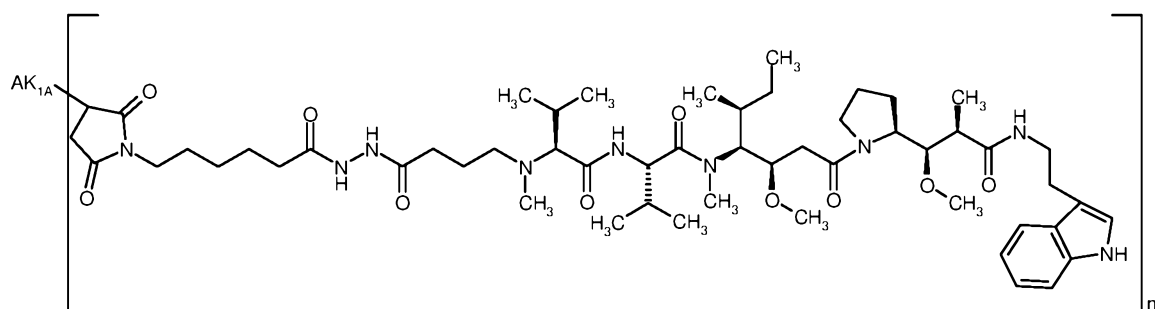
Drug/mAb Ratio: 3.3

10 **Example 39**



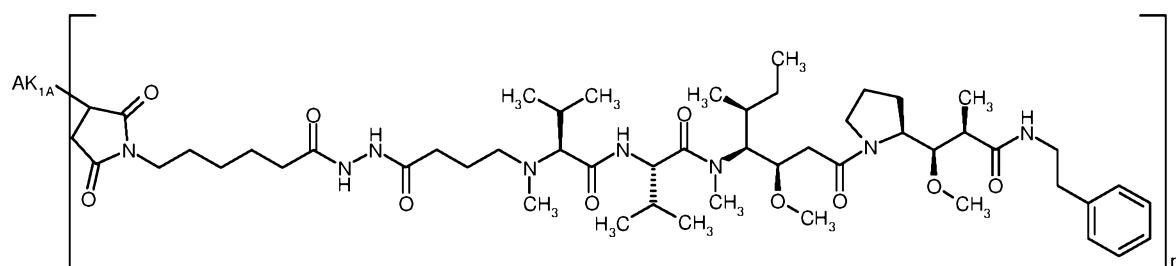
Protein concentration: 1.3 mg/ml

Drug/mAb Ratio: 3.2

Example 40

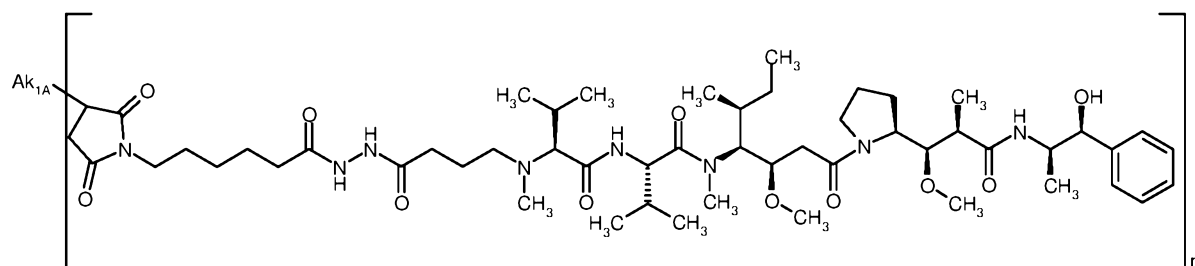
Protein concentration: 1.23 mg/ml

Drug/mAb Ratio: 3.3

5 **Example 41**

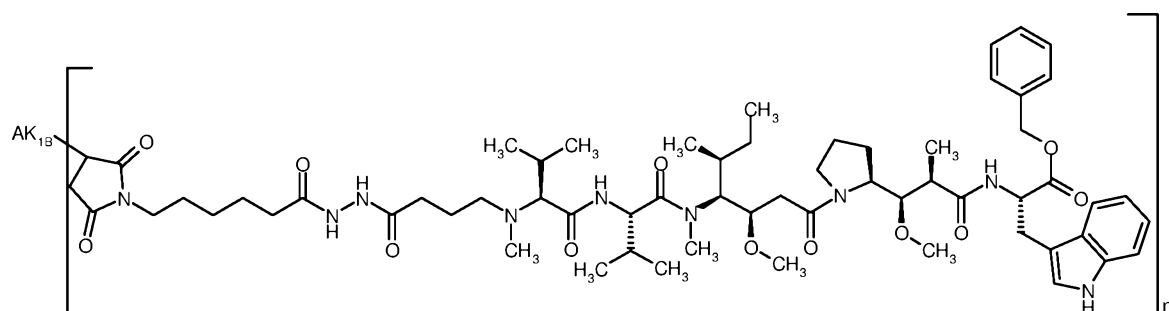
Protein concentration: 1.64 mg/ml

Drug/mAb Ratio: 1.8

10 **Example 42**

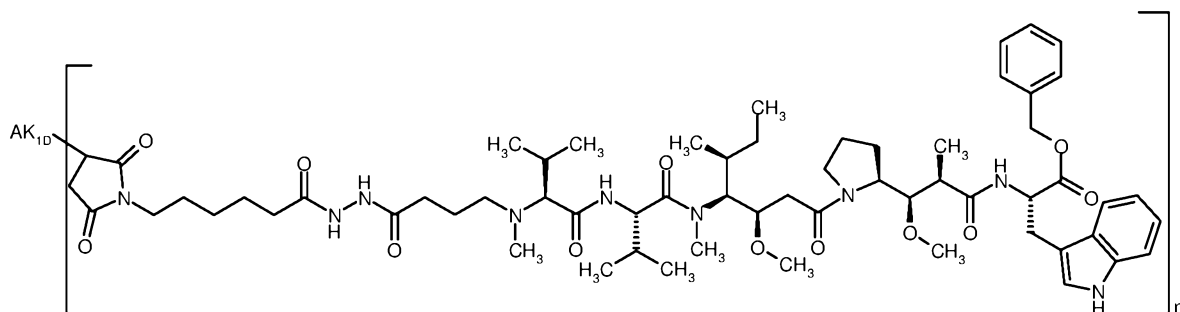
Protein concentration: 1.07 mg/ml

Drug/mAb Ratio: 3.1

Example 43

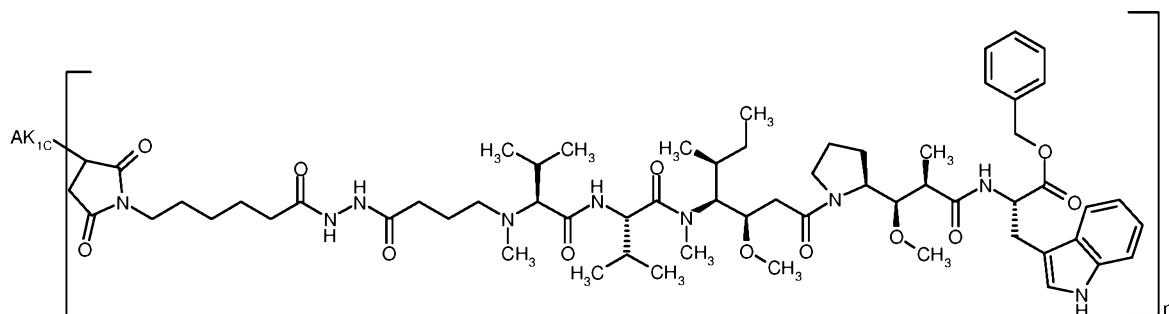
Protein concentration: 1.14 mg/ml

Drug/mAb Ratio: 2.3

5 **Example 44**

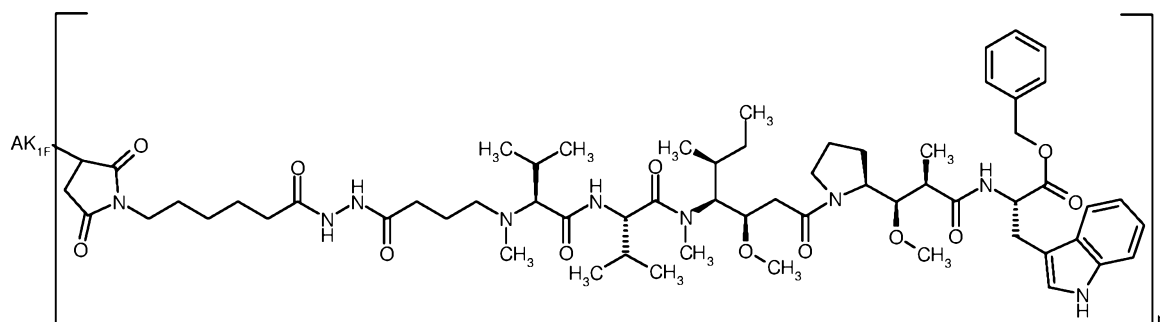
Protein concentration: 1.23 mg/ml

Drug/mAb Ratio: 3.4

10 **Example 45**

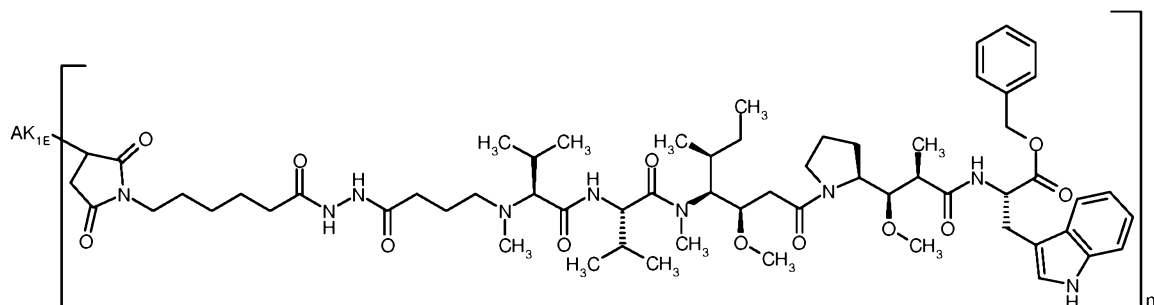
Protein concentration: 1.22 mg/ml

Drug/mAb Ratio: 2.5

Example 46

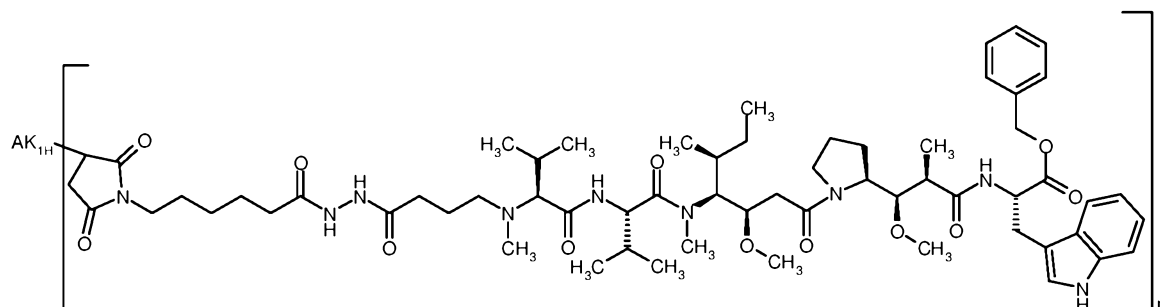
Protein concentration: 1.22 mg/ml

5 Drug/mAb Ratio: 2.4

Example 47

Protein concentration: 1.32 mg/ml

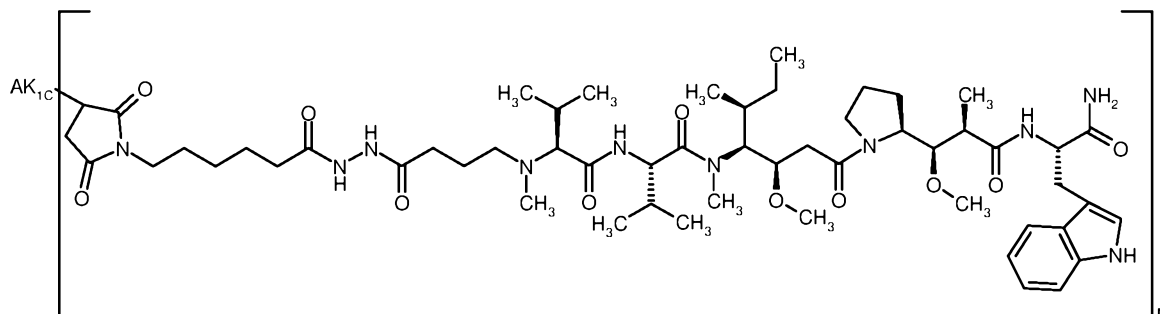
Drug/mAb Ratio: not determinable

10 **Example 48**

Protein concentration: 1.44 mg/ml

Drug/mAb Ratio: 2.3

Example 49

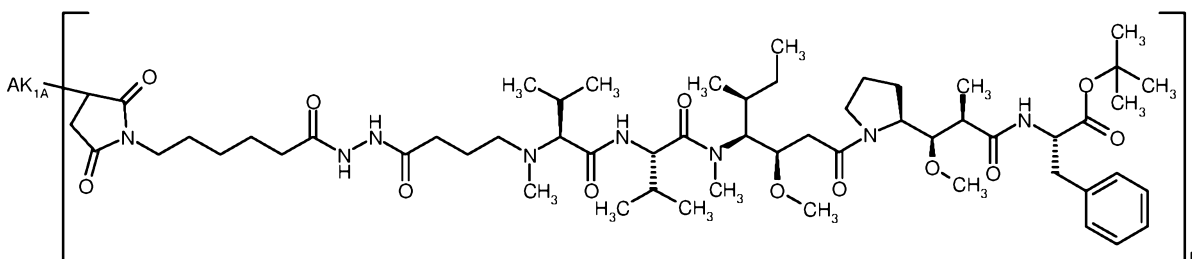


- 5 Coupling here was carried out using 250 mg of anti-C4.4a B01-10 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 12.8 mg/ml

Drug/mAb Ratio: 5.2

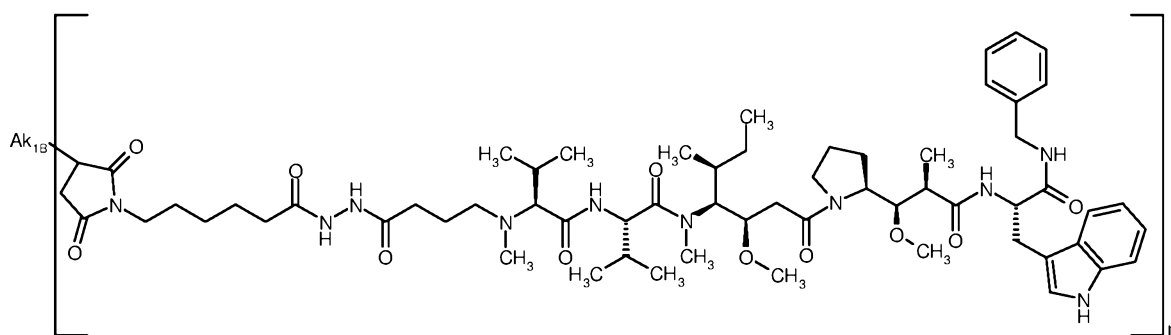
Example 50



10

Protein concentration: 0.9 mg/ml

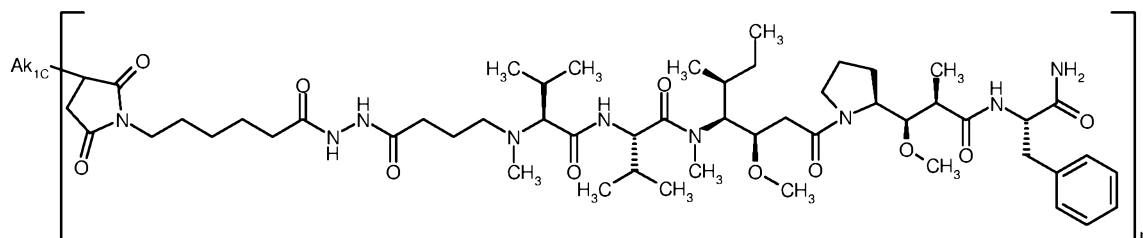
Drug/mAb Ratio: 2

Example 51

Coupling here was carried out using 250 mg of anti-C4.4a B01-3 in DPBS PH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 8.0 mg/ml

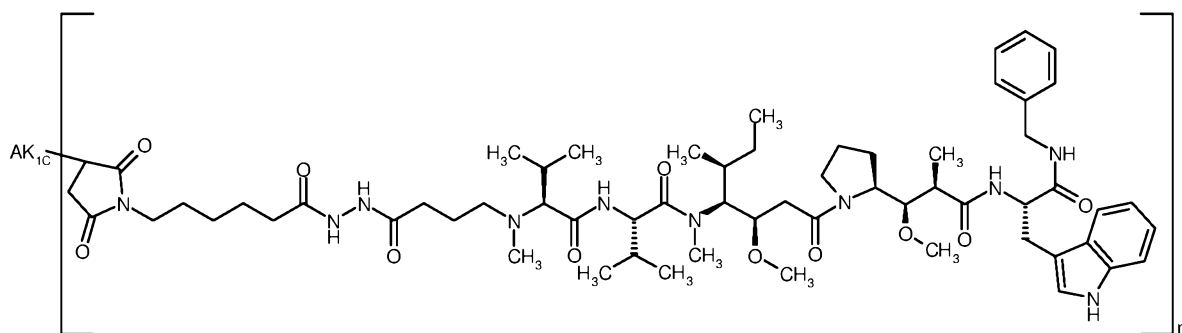
Drug/mAb Ratio: 4.5

Example 52

Coupling here was carried out using 250 mg of anti-C4.4a B01-10 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 12.3 mg/ml

Drug/mAb Ratio: 5.2

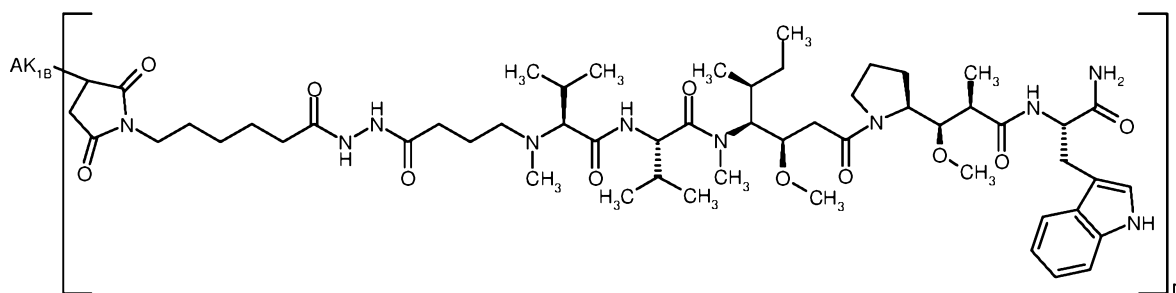
Example 53

Coupling here was carried out using 250 mg of anti-C4.4a B01-10 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 10.2 mg/ml

Drug/mAb Ratio: 4.4

5 **Example 54**

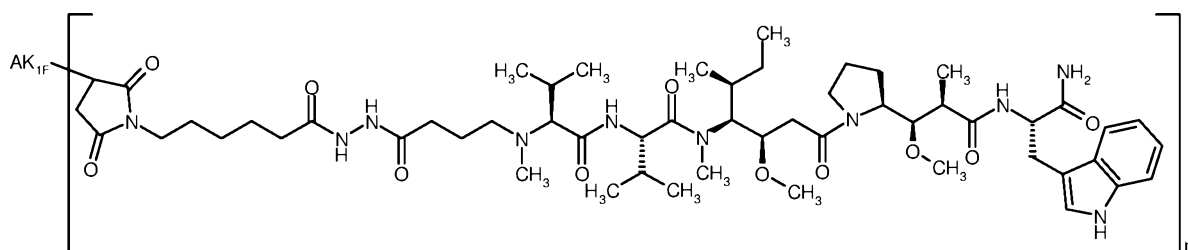


Coupling here was carried out using 50 mg of anti-C4.4a B01-3 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

10 Protein concentration: 11.5 mg/ml

Drug/mAb Ratio: 5.2

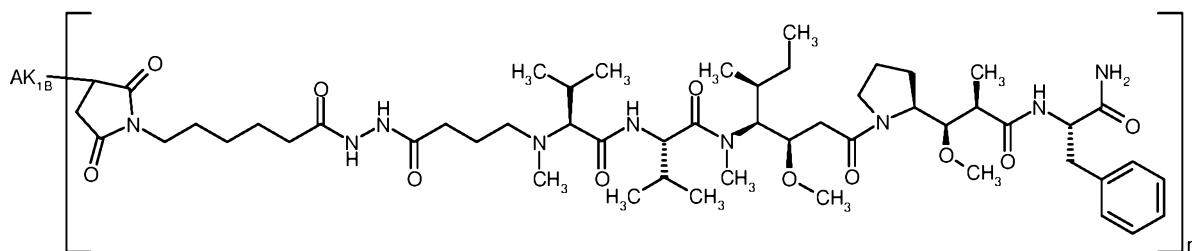
Example 55



15 Coupling here was carried out using 250 mg of anti-C4.4a D02-6 in DPBS pH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 13 mg/ml

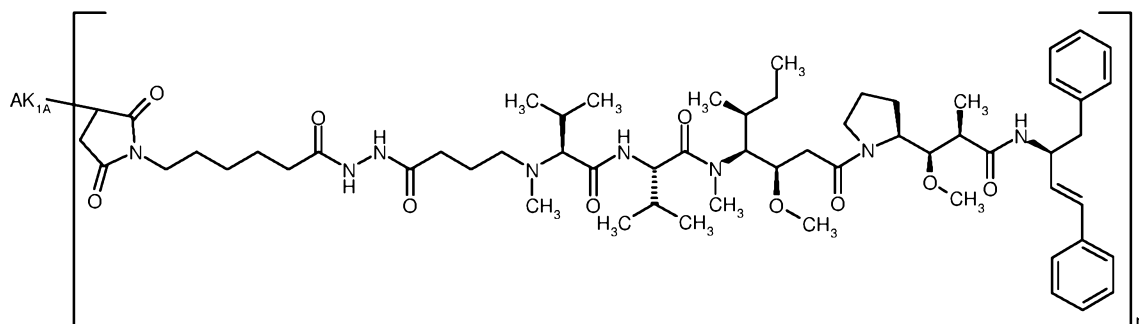
Drug/mAb Ratio: 5.2

Example 56

Coupling here was carried out using 250 mg of anti-C4.4a B01-3 in DPBS pH 7.4 and following
 5 the Sephadex purification the batch was concentrated by ultracentrifugation.

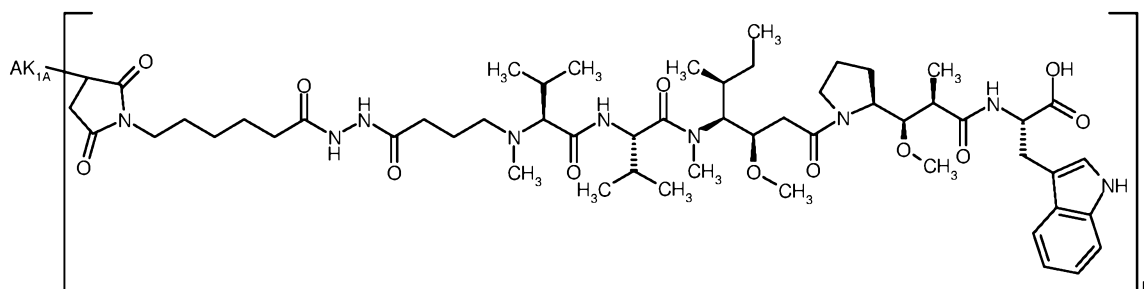
Protein concentration: 10.3 mg/ml

Drug/mAb Ratio: 4.9

Example 57

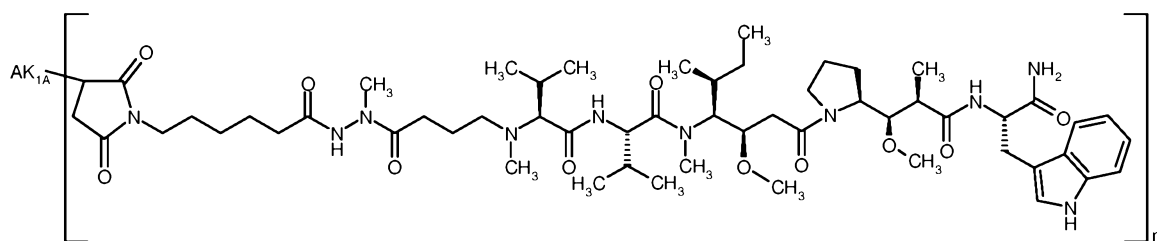
10 Protein concentration: 0.88 mg/ml

Drug/mAb Ratio: 3.2

Example 58

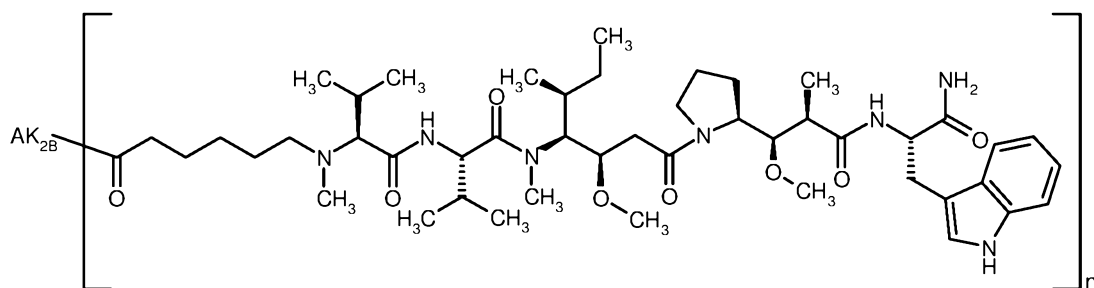
Protein concentration: 1.18 mg/ml

15 Drug/mAb Ratio: 3.4

Example 59

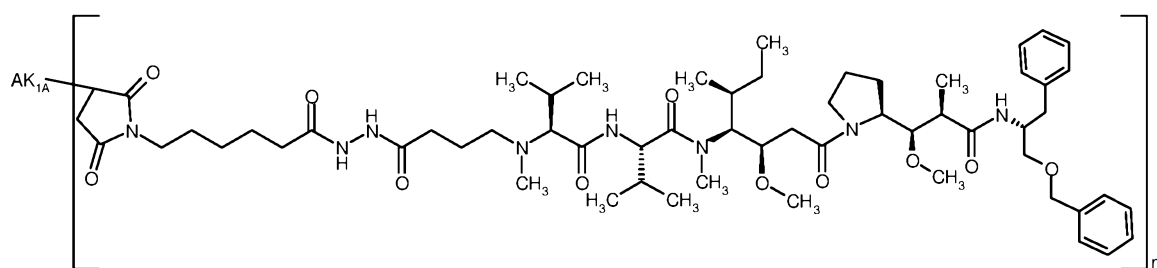
Protein concentration: 1.23 mg/ml

Drug/mAb Ratio: 3.0

5 **Example 60**

Protein concentration: 1.3 mg/ml

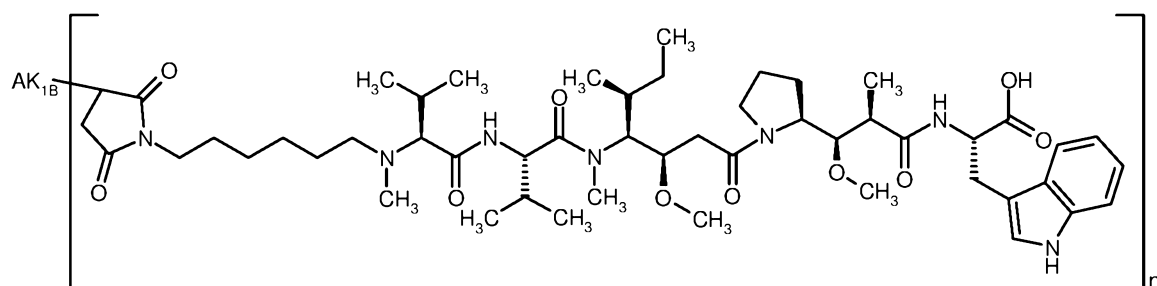
Drug/mAb Ratio: 3.3

Example 61

10

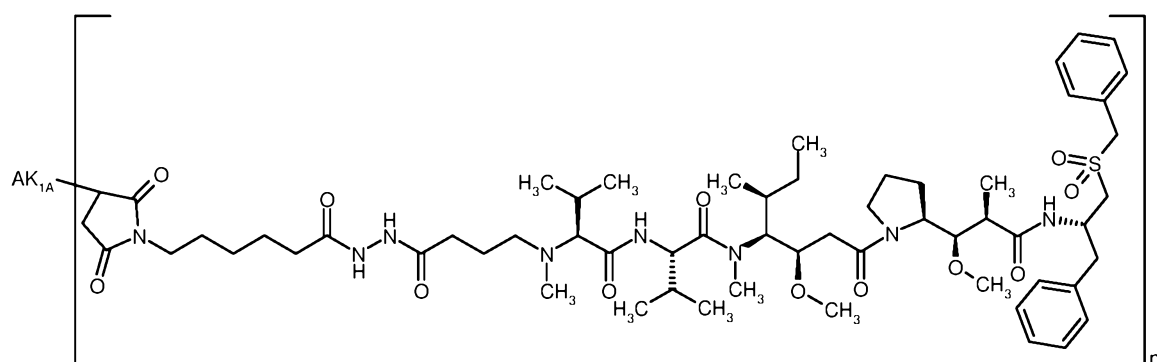
Protein concentration: 1.11 mg/ml

Drug/mAb Ratio: not determinable

Example 62

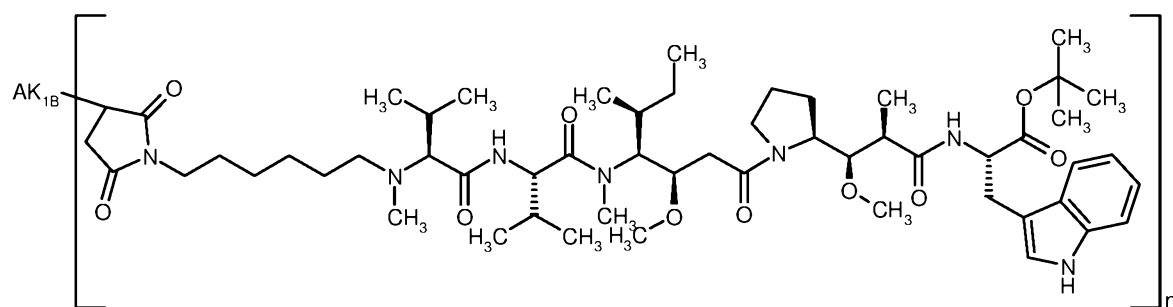
Protein concentration: 1.25 mg/ml

5 Drug/mAb Ratio: 2.4

Example 63

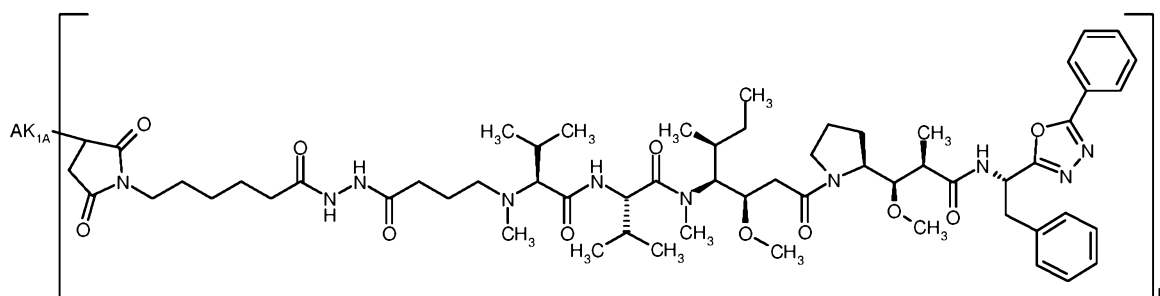
Protein concentration: 0.88 mg/ml

10 Drug/mAb Ratio: 5.0

Example 64

Protein concentration: 1.23 mg/ml

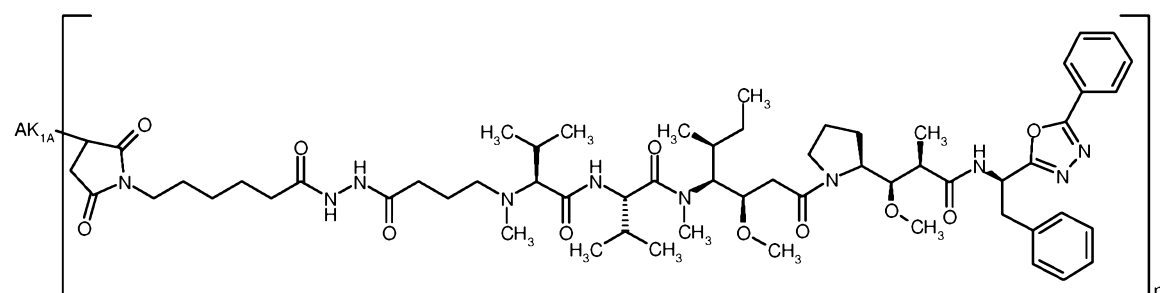
Drug/mAb Ratio: 3.3

Example 65

5

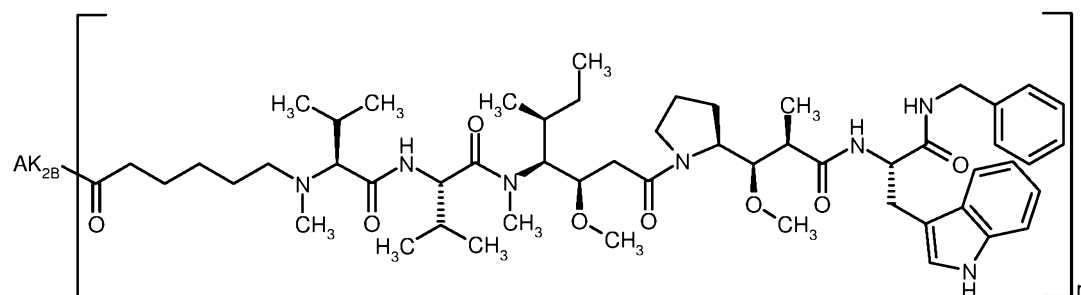
Protein concentration: 0.93 mg/ml

Drug/mAb Ratio: 1.8

Example 66

10 Protein concentration: 0.85 mg/ml

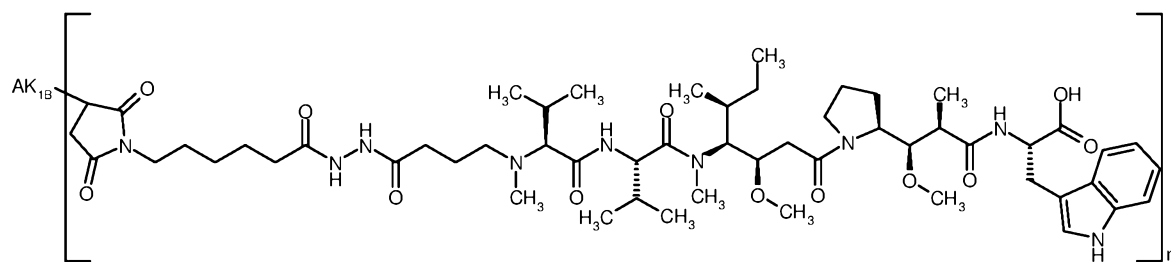
Drug/mAb Ratio: 5.3

Example 67

Protein concentration: 1.51 mg/ml

Drug/mAb Ratio: 1.4

Example 68

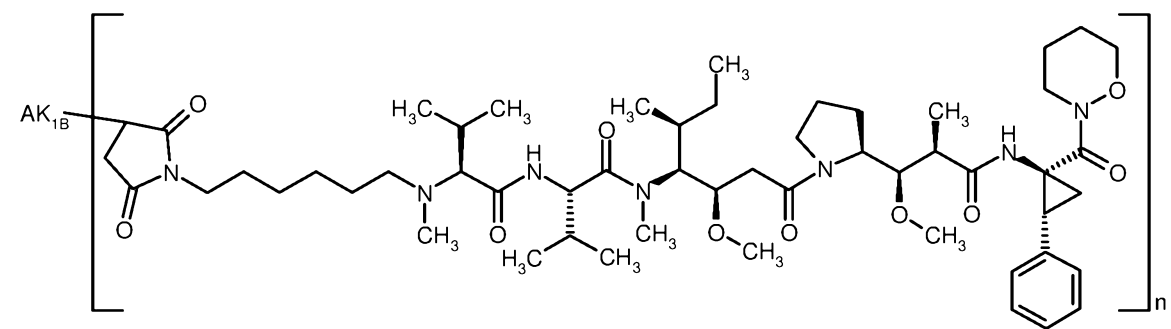


- 5 Coupling here was carried out using 150 mg of anti-C4.4a B01-3 in DPBS PH 7.4 and following the Sephadex purification the batch was concentrated by ultracentrifugation.

Protein concentration: 11.0 mg/ml

Drug/mAb Ratio: 4.5

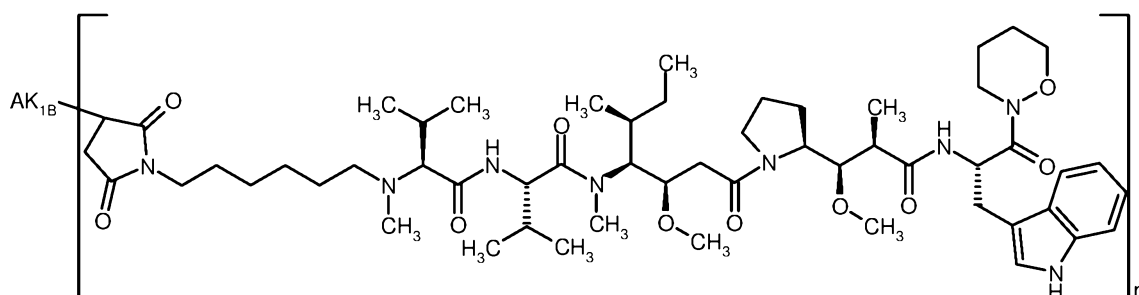
Example 69



10

Protein concentration: 1.2 mg/ml

Drug/mAb Ratio: 3.3

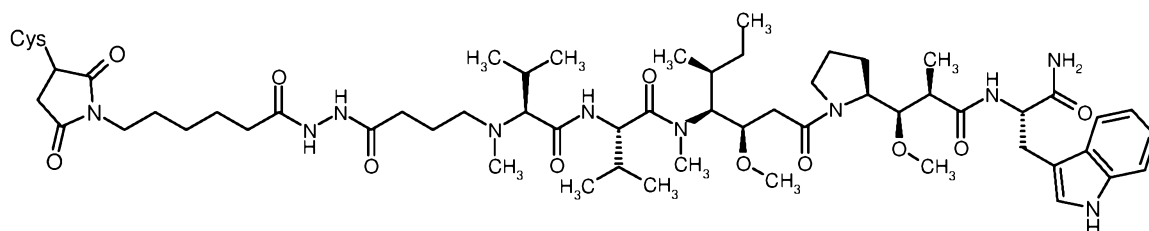
Example 70

Protein concentration: 1.25 mg/ml

Drug/mAb Ratio: 3.1

5 **Example 71**

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphonyl}-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



10

10 mg (10 μ mol) of Intermediate 157 were taken up in 5.2 ml of DMF and admixed with 2.28 mg (20 μ mol) 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.

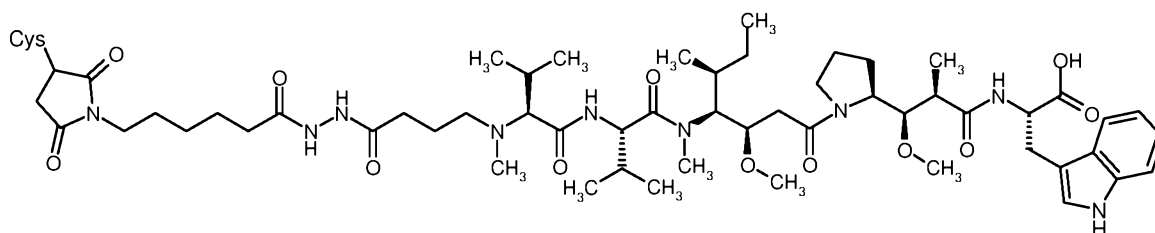
15 HPLC (Method 5): R_t = 1.45 min;

LC-MS (Method 1): R_t = 0.74 min; MS (ESIpos): m/z = 1184 ($M+H$)⁺.

Example 72

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphonyl}-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



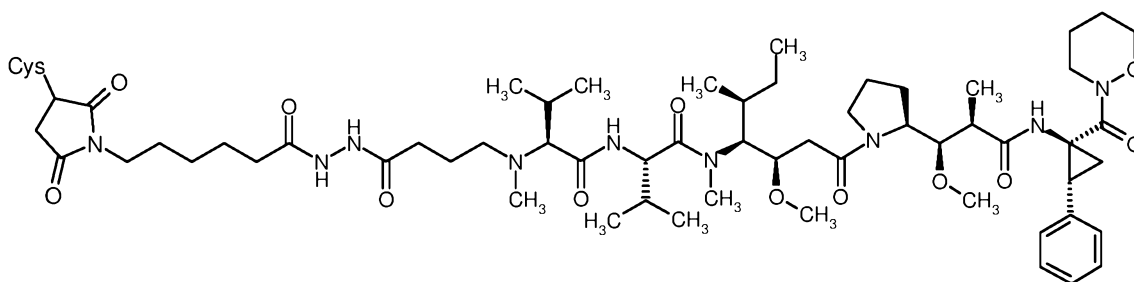
10 mg (10 μ mol) of Intermediate 113 were taken up in 5.2 ml of DMF and admixed with 2.28 mg
 5 (20 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 6 mg (54% of theory) of the title compound.

HPLC (Method 5): R_t = 1.5 min;

LC-MS (Method 1): R_t = 0.77 min; MS (ESIpos): m/z = 1185 ($M+H$)⁺.

10 **Example 73**

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphonyl}-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



15

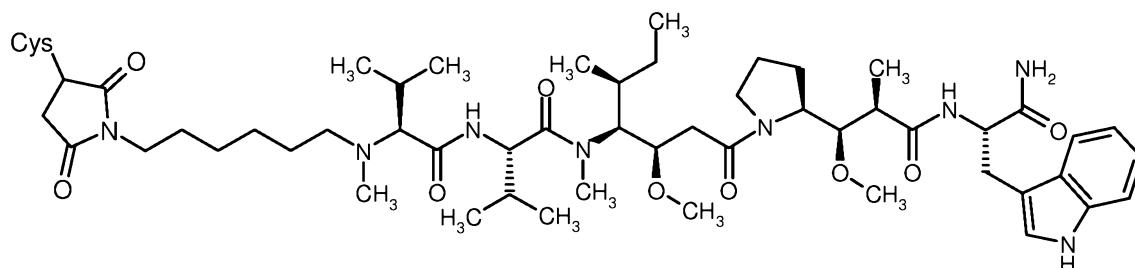
9 mg (8.3 μ mol) of Intermediate 132 were taken up in 4 ml of DMF and admixed with 3 mg
 (24.4 μ mol) of L-cysteine. The reaction mixture was stirred at RT overnight, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 6.8 mg (68% of theory) of the title compound.

20 HPLC (Method 12): R_t = 1.8 min;

LC-MS (Method 1): R_t = 0.78 min; MS (ESIpos): m/z = 1227 ($M+H$)⁺.

Example 74

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



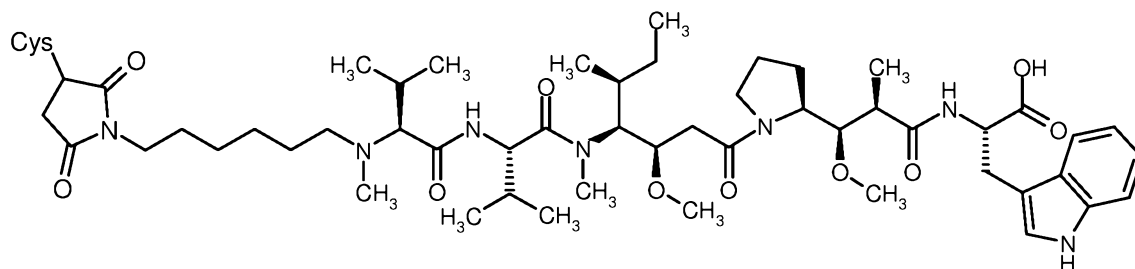
10 mg (10 μ mol) of Intermediate 106 were taken up in 5.8 ml of DMF and admixed with 2.5 mg (20 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 5.2 mg (46% of theory of the title compound).

HPLC (Method 5): $R_t = 1.5$ min;

LC-MS (Method 11): $R_t = 0.71$ min; MS (ESIpos): $m/z = 1070$ ($M+H$)⁺.

Example 75

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



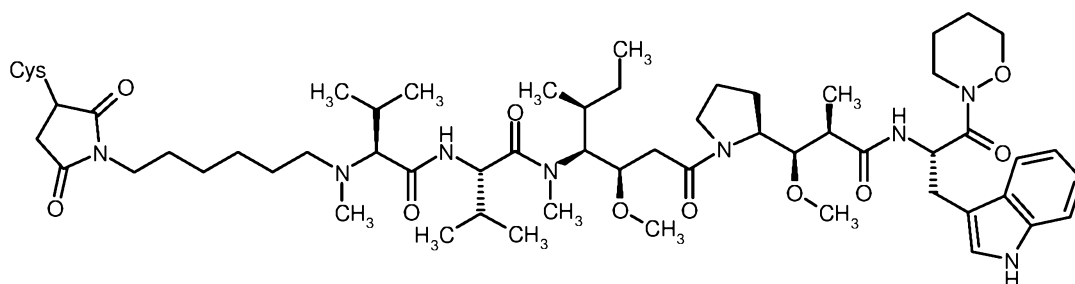
10 mg (10 μ mol) of Intermediate 124 were taken up in 4 ml of DMF and admixed with 2.5 mg (20 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 7.2 mg (64% of theory of the title compound).

HPLC (Method 5): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.8$ min; MS (ESIpos): $m/z = 1071$ ($M+H$)⁺.

Example 76

N-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphonyl}-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



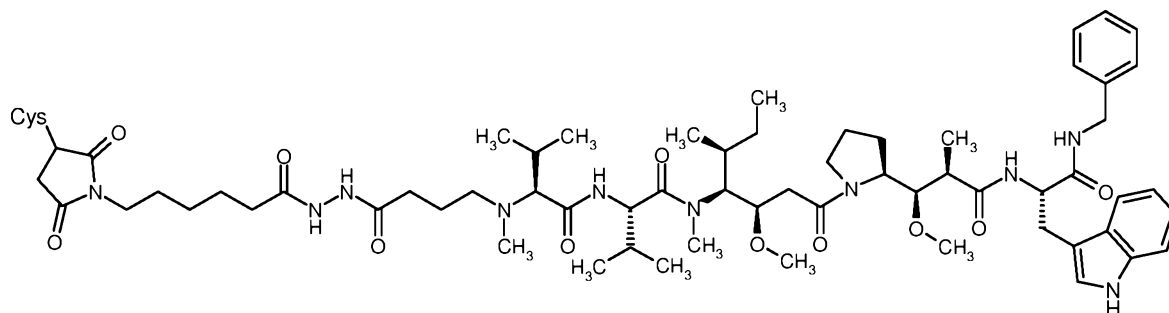
10 mg (10 μ mol) of Intermediate 125 were taken up in 4 ml of DMF and admixed with 2.4 mg (20 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 7.7 mg (69% of theory of the title compound).

HPLC (Method 5): $R_t = 1.7$ min;

LC-MS (Method 2): $R_t = 1.91$ min; MS (ESIpos): $m/z = 1140$ ($M+H$)⁺.

Example 77

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphonyl}-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



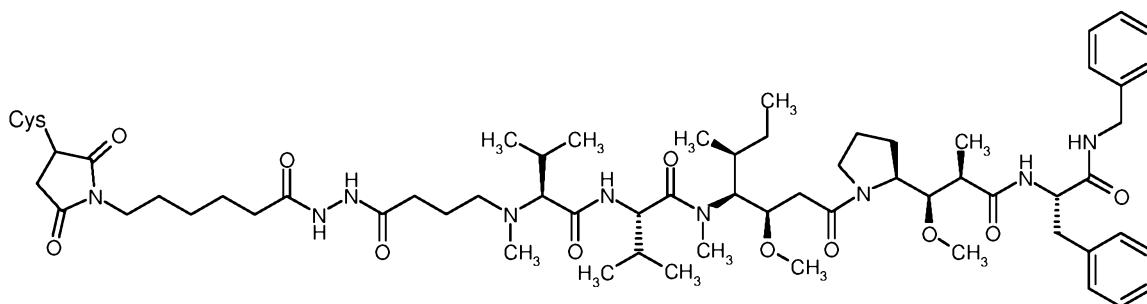
10 mg (10 μ mol) of Intermediate 160 were taken up in 3 ml of DMF and admixed with 2.1 mg (20 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 8.1 mg (73% of theory of the title compound).

5 HPLC (Method 5): R_t = 1.7 min;

LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos): m/z = 1274 ($M+H$)⁺.

Example 78

N-(4-{2-[6-(3-[[[(2R)-2-Amino-2-carboxyethyl]sulphonyl]-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



3.5 mg (3 μ mol) of Intermediate 159 were taken up in 1 ml of DMF and admixed with 0.76 mg (6 μ mol) 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).

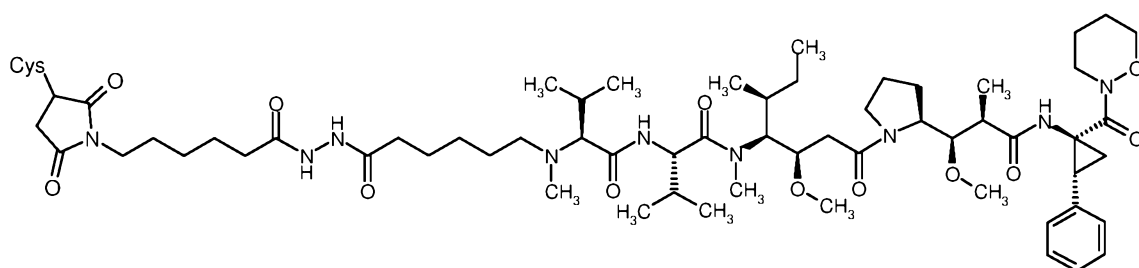
15

HPLC (Method 5): R_t = 1.75 min;

LC-MS (Method 1): R_t = 0.85 min; MS (ESIpos): m/z = 1235 ($M+H$)⁺.

Example 79

20 N-(6-{2-[6-(3-[[[(2R)-2-Amino-2-carboxyethyl]sulphonyl]-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

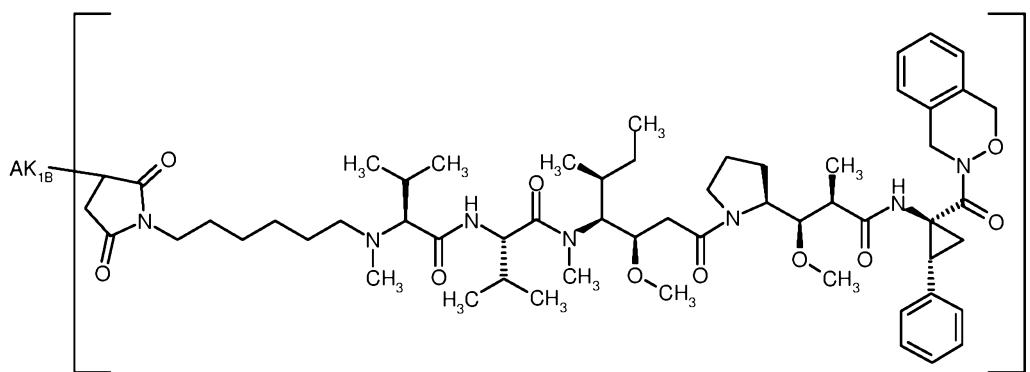


3.6 mg (3 μ mol) of Intermediate 129 were taken up in 1 ml of DMF and admixed with 0.77 mg (6 μ mol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 1.55 mg
5 (39% of theory of the title compound).

HPLC (Method 5): $R_t = 1.6$ min;

LC-MS (Method 1): $R_t = 0.87$ min; MS (ESIpos): $m/z = 1255$ ($M+H$) $^+$.

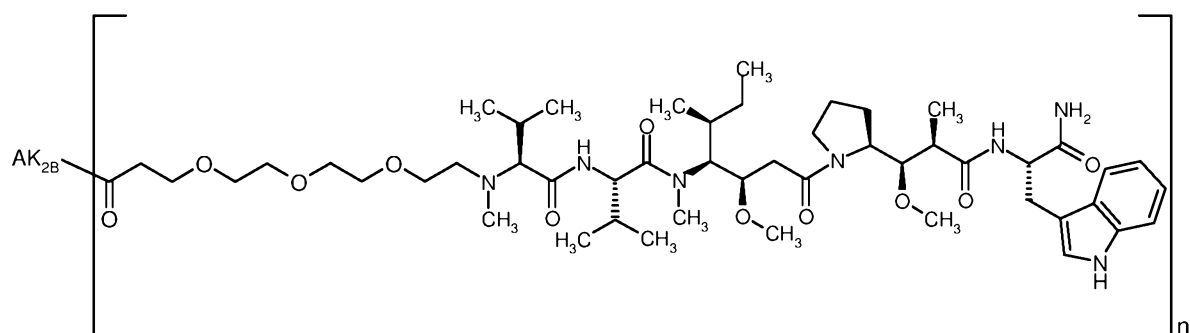
Example 80



10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 0.83 mg/ml

Drug/mAb Ratio: 1.6

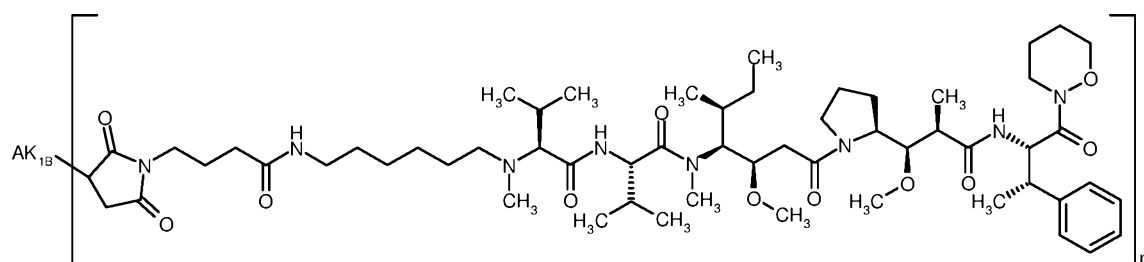
Example 81

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 5 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.59 mg/ml

Drug/mAb Ratio: 3.1

Drug/mAb Ratio: 2.9

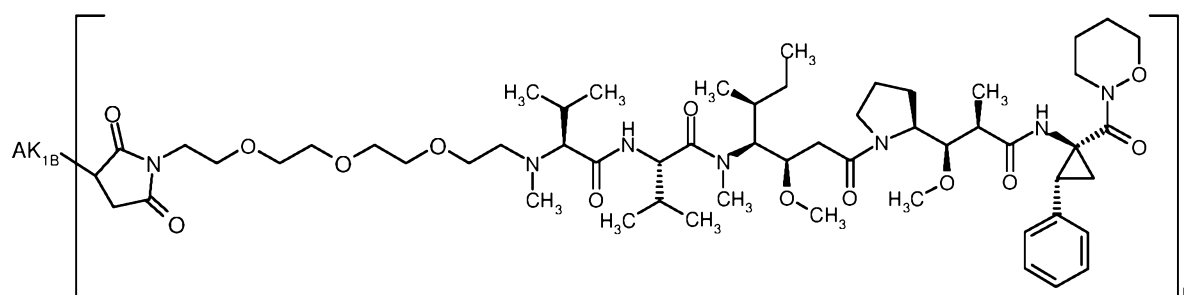
Example 82

10

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.25 mg/ml

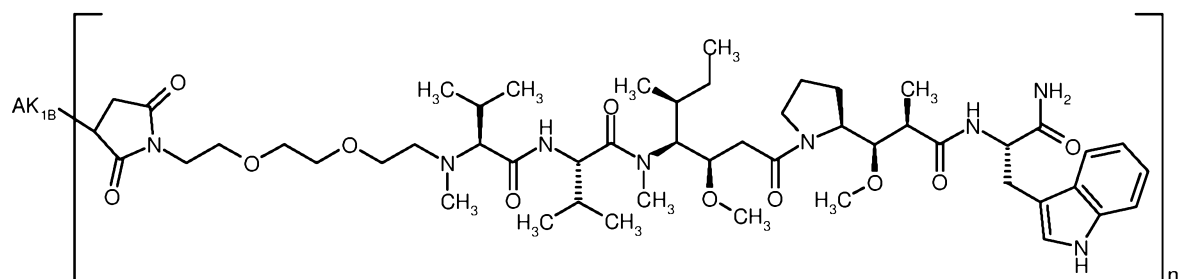
Drug/mAb Ratio: 4.0

Example 83

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 5 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.27 mg/ml

Drug/mAb Ratio: 3.6

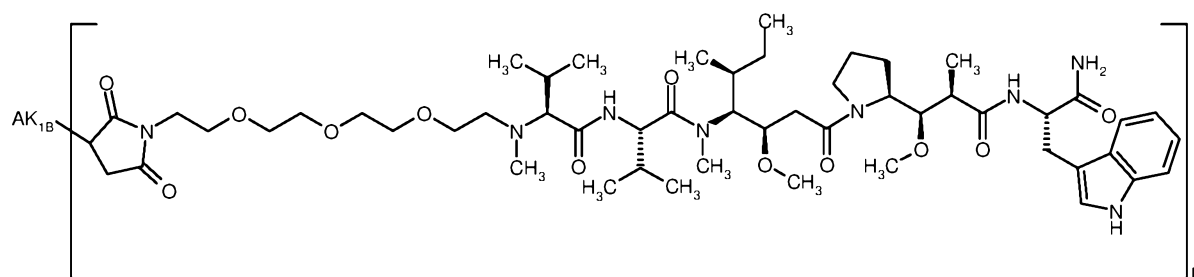
Example 84

10

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.54 mg/ml

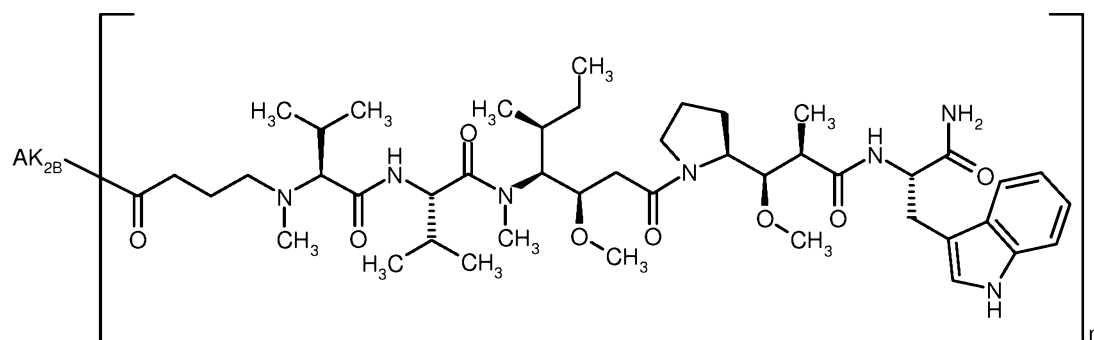
Drug/mAb Ratio: 4.7

Example 85

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 5 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.73 mg/ml

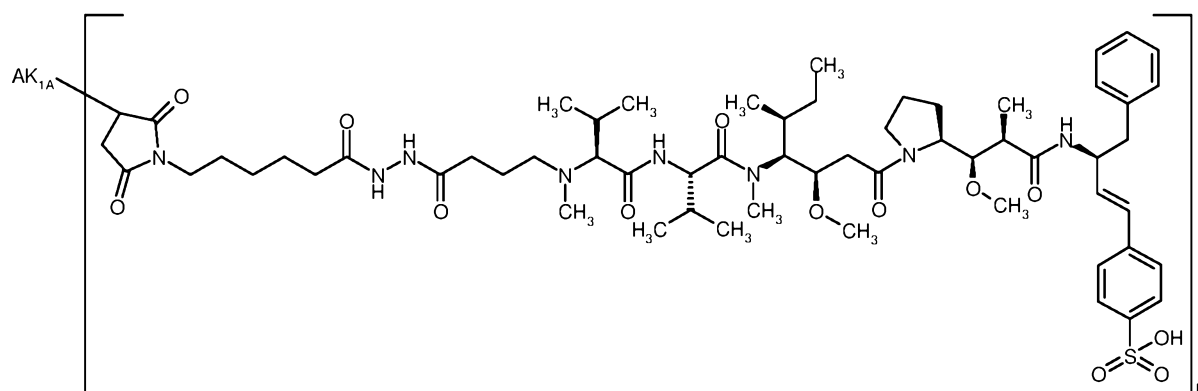
Drug/mAb Ratio: 4.7

Example 86

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.66 mg/ml

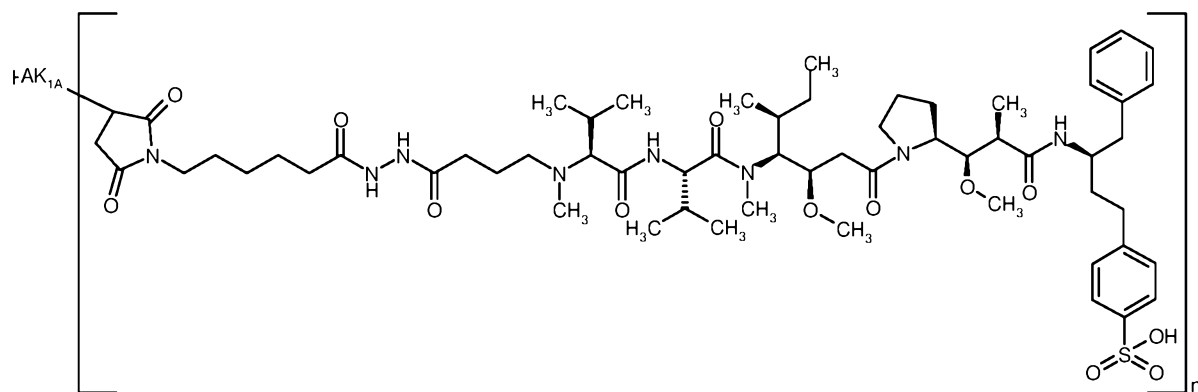
Drug/mAb Ratio: 1.3

Example 87

Protein concentration: 2.11 mg/ml

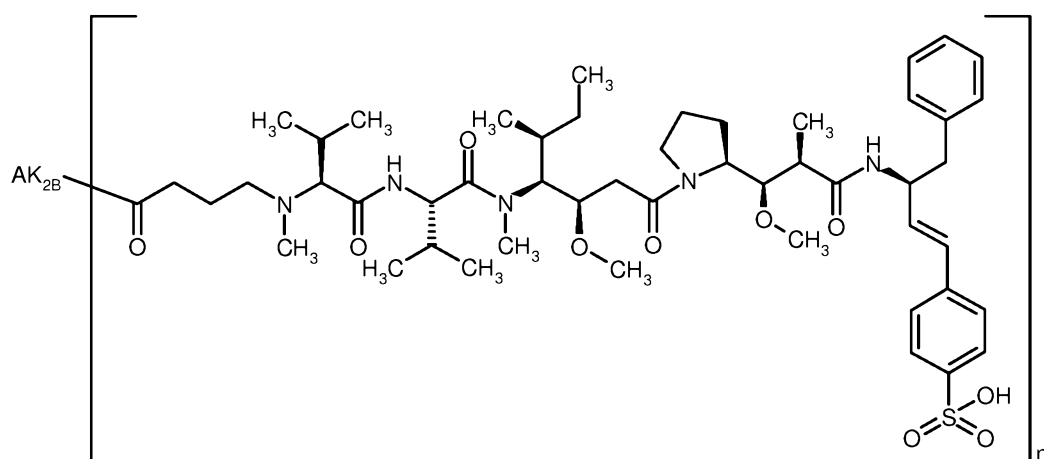
5 Drug/mAb Ratio: 5.5

10 **Example 88**



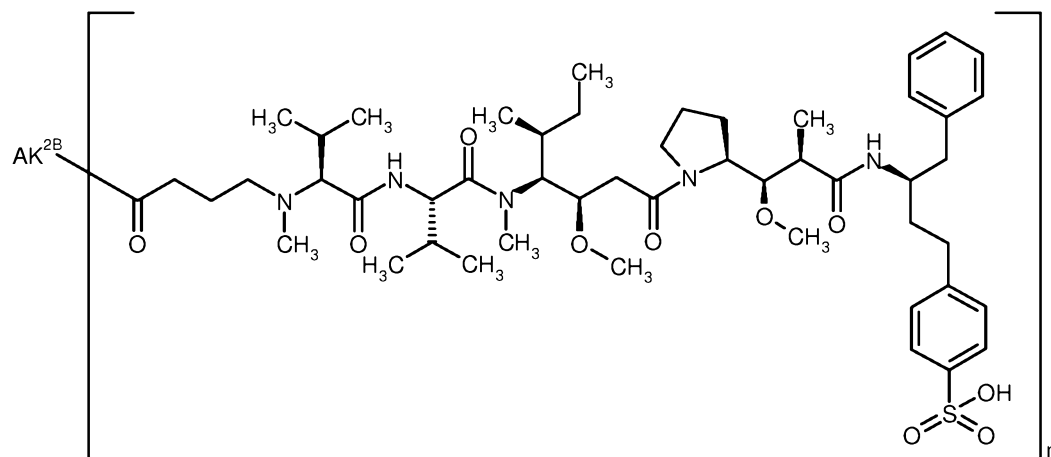
Protein concentration: 1.53 mg/ml

Drug/mAb Ratio: 3.4

Example 89

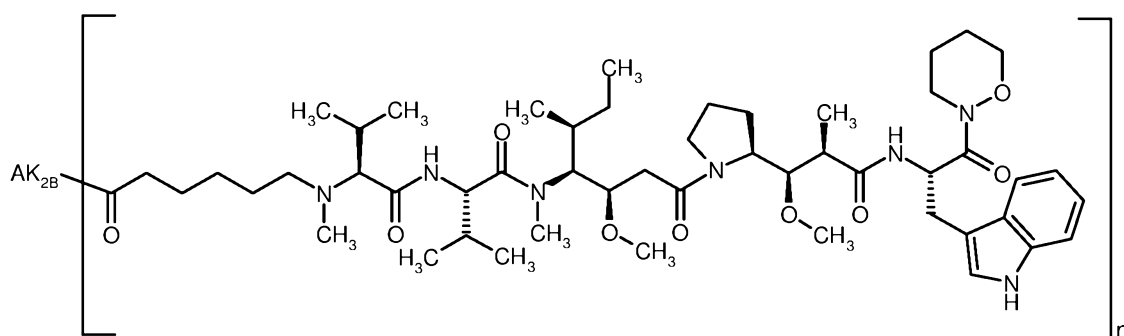
Protein concentration: 1.5 mg/ml

Drug/mAb Ratio: 0.2

5 Example 90

Protein concentration: 1.32 mg/ml

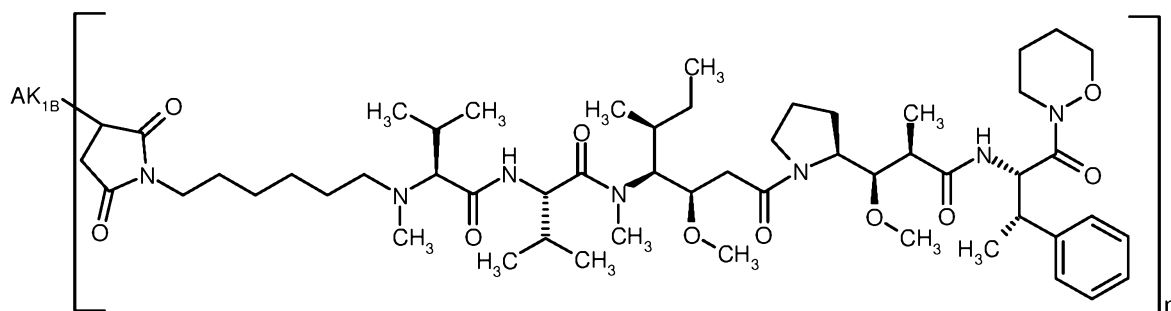
Drug/mAb Ratio: 0.1

Example 91

Coupling here was carried out using 80 mg of anti-C4.4a B01-3 in PBS and the batch, following
Sephadex purification, was concentrated by ultracentrifugation, re-diluted with PBS and
5 concentrated again.

Protein concentration: 10.3 mg/ml

Drug/mAb Ratio: 3.1

Example 92

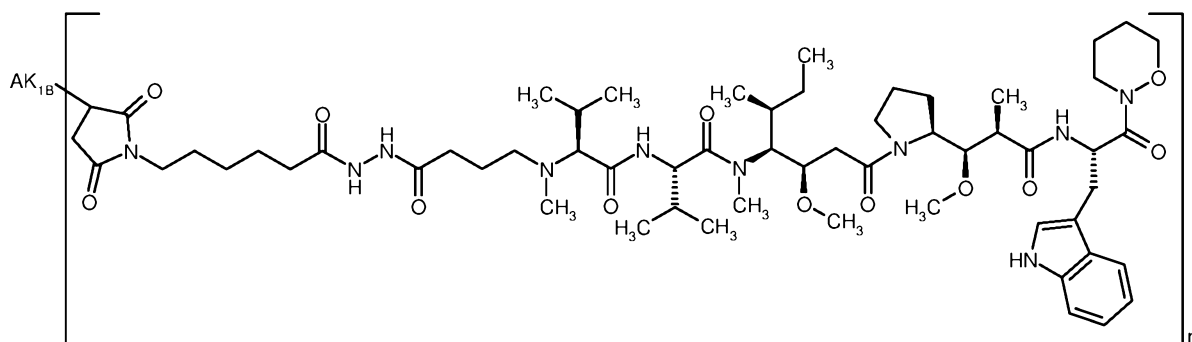
10

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.09 mg/ml

Drug/mAb Ratio: 1.8

Example 93

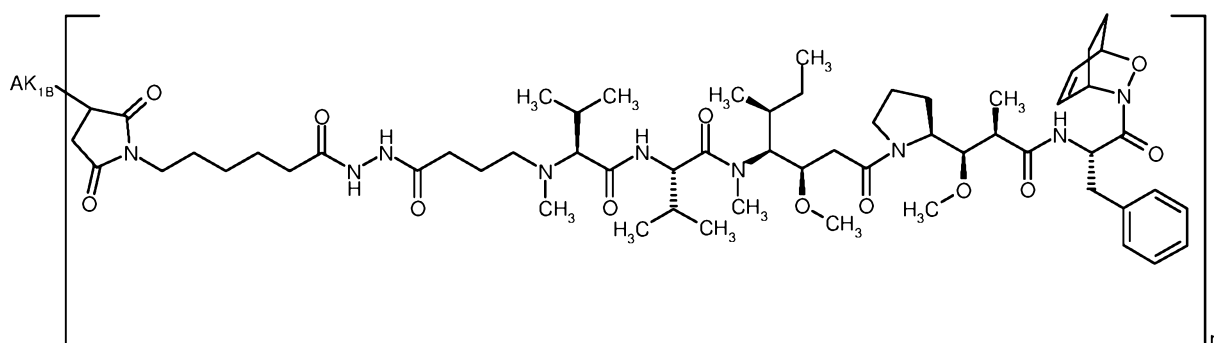


Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
5 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.52 mg/ml

Drug/mAb Ratio: 4.2

Example 94



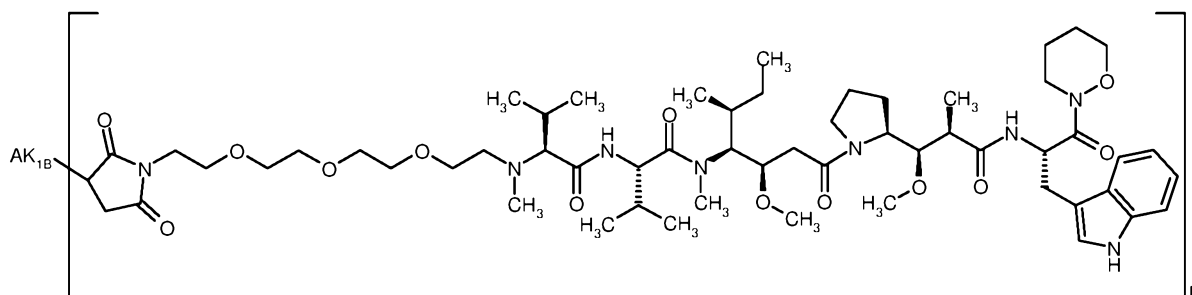
10

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.1 mg/ml

Drug/mAb Ratio: 3.3

Example 95

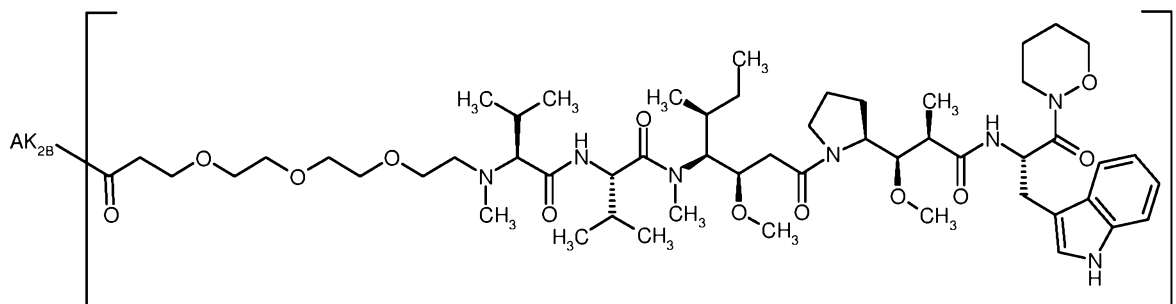


Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
5 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.43 mg/ml

Drug/mAb Ratio: 4.8

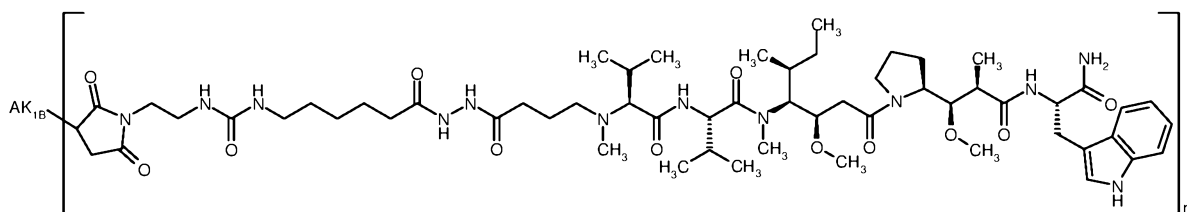
Example 96



10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following
Sephadex purification, was concentrated by ultracentrifugation, re-diluted with PBS and
concentrated again.

Protein concentration: 1.36 mg/ml

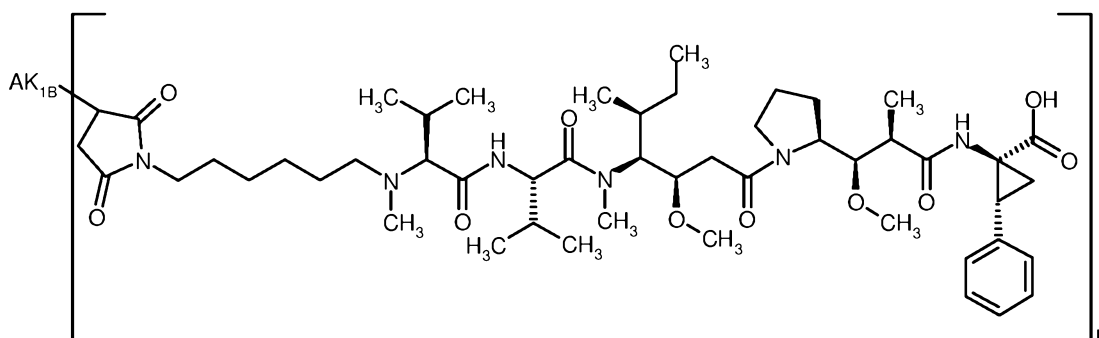
Drug/mAb Ratio: 4.6

Example 97

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.33 mg/ml

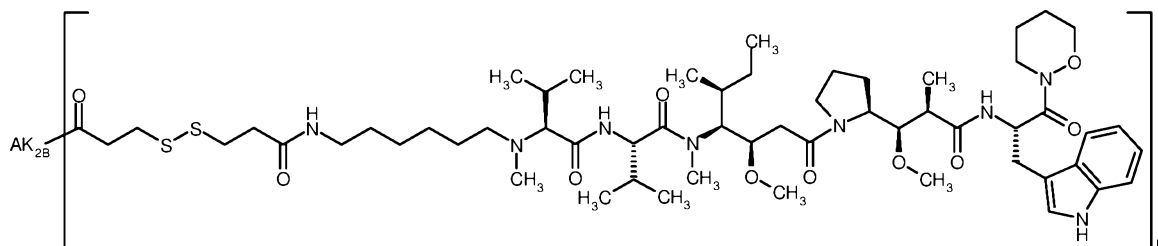
Drug/mAb Ratio: 4.0

Example 98

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.33 mg/ml

Drug/mAb Ratio: 4.6

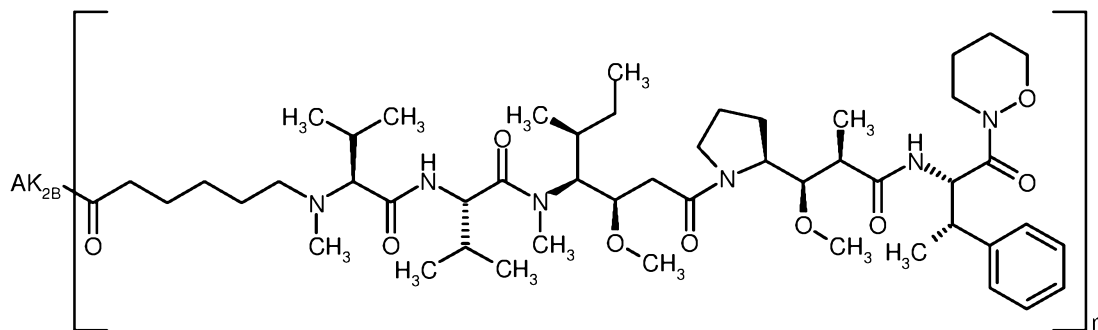
Example 99

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.47 mg/ml

Drug/mAb Ratio: 1.6

5 **Example 100**

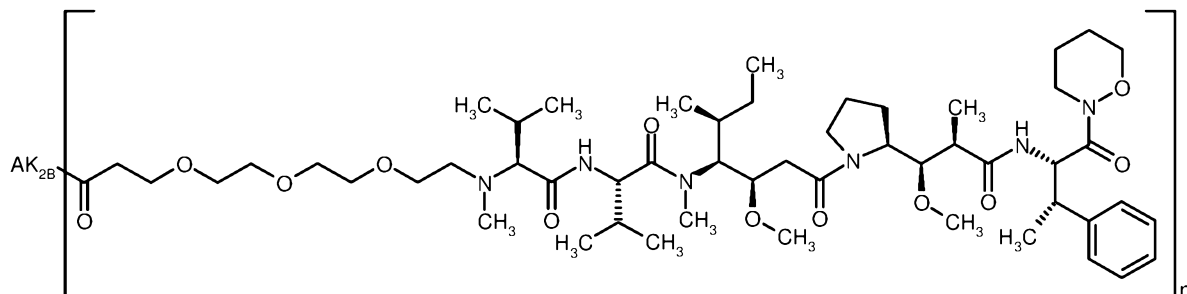


Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.49 mg/ml

10 Drug/mAb Ratio: 4.5

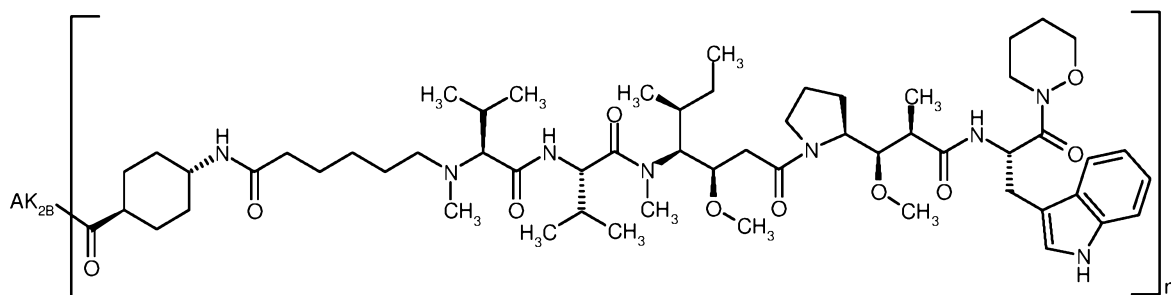
Example 101



Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

15 Protein concentration: 1.29 mg/ml

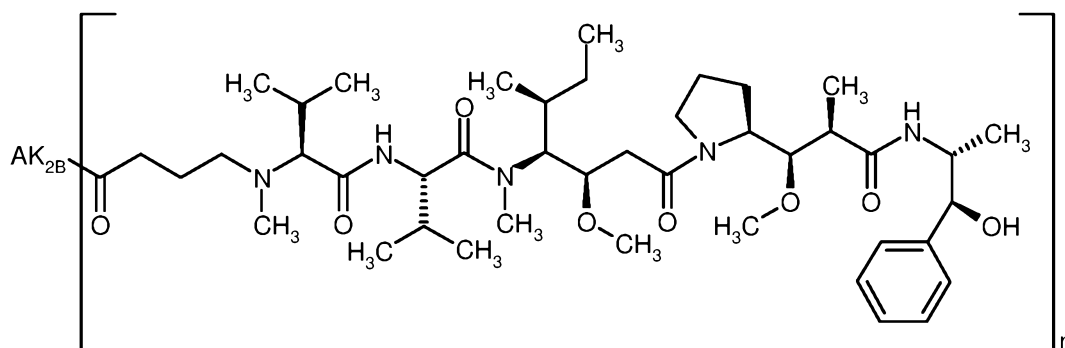
Drug/mAb Ratio: 3.3

Example 102

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.74 mg/ml

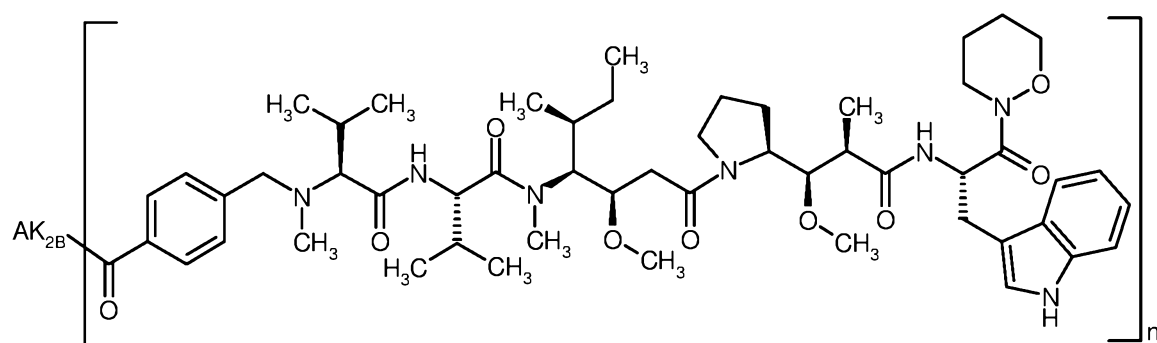
Drug/mAb Ratio: 3.5

Example 103

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.09 mg/ml

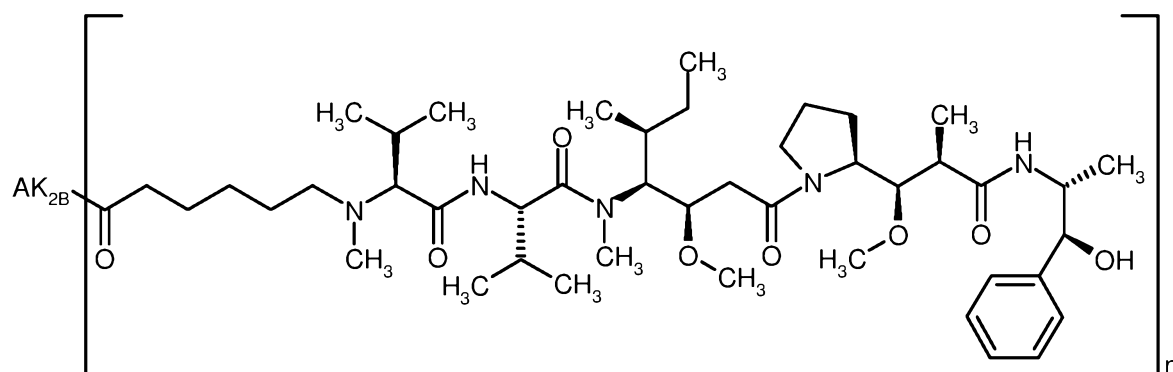
Drug/mAb Ratio: 3.2

Example 104

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.63 mg/ml

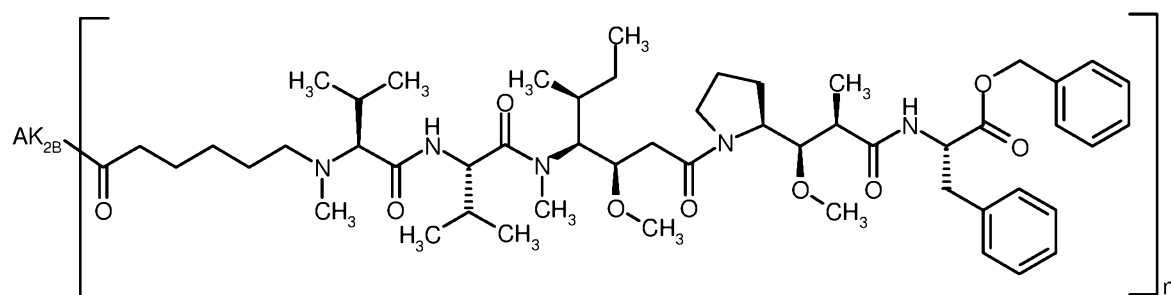
Drug/mAb Ratio: 0.2

Example 105

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.41 mg/ml

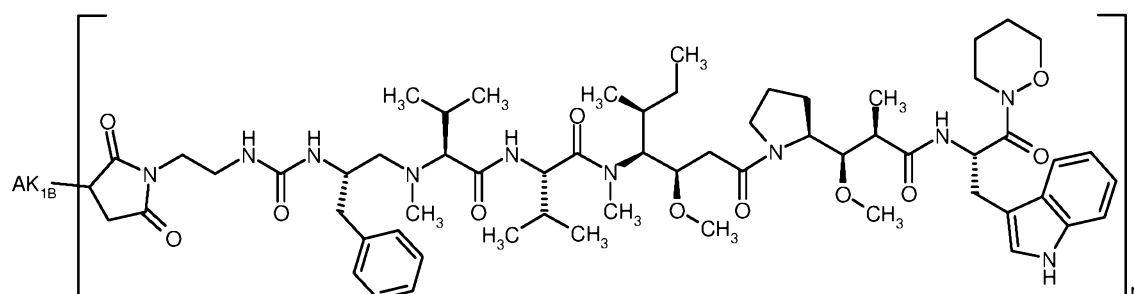
Drug/mAb Ratio: 7.6

Example 106

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 2.0 mg/ml

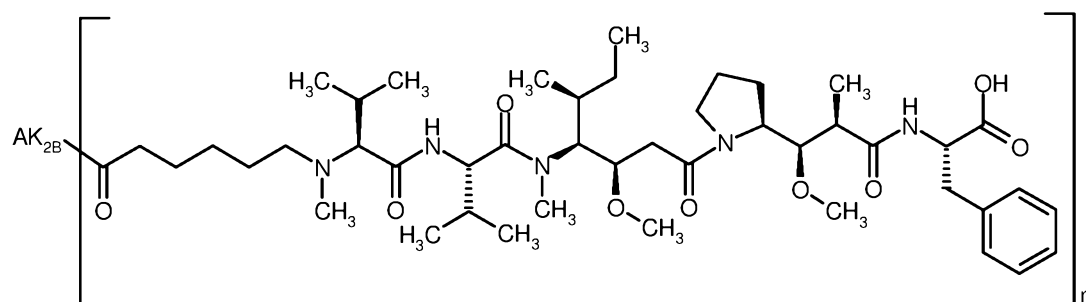
Drug/mAb Ratio: 1.6

Example 107

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.67 mg/ml

Drug/mAb Ratio: 2.8

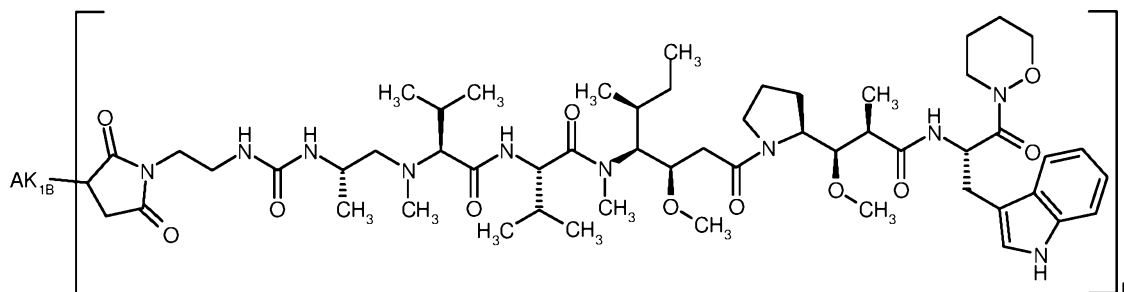
Example 108

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.91 mg/ml

Drug/mAb Ratio: 5.3

5 **Example 109**

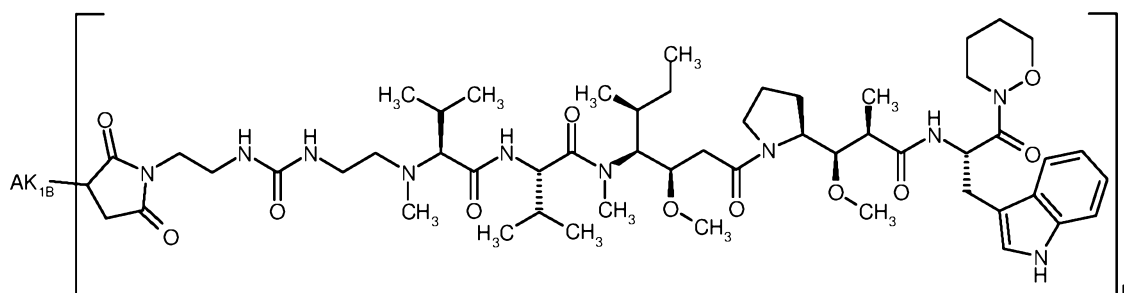


Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.82 mg/ml

10 Drug/mAb Ratio: 4.6

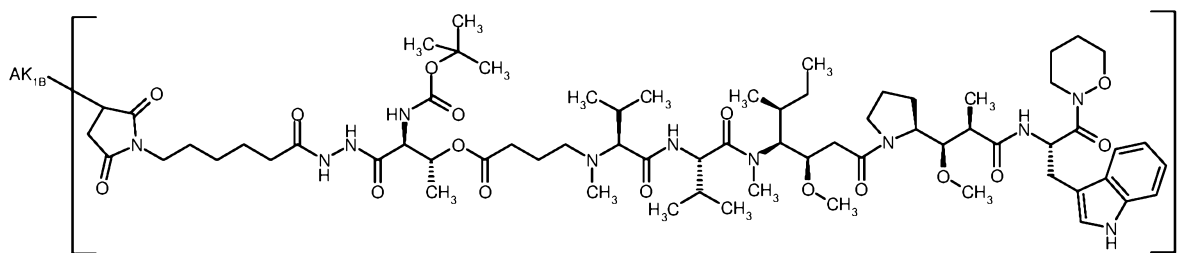
Example 110



Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

15 Protein concentration: 1.9 mg/ml

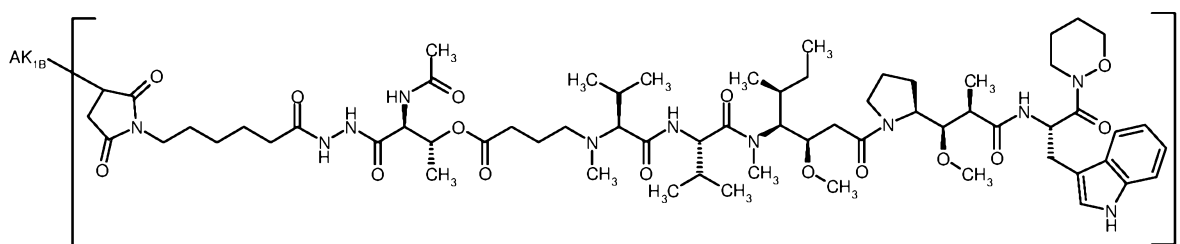
Drug/mAb Ratio: 4.2

Example 111

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.89 mg/ml

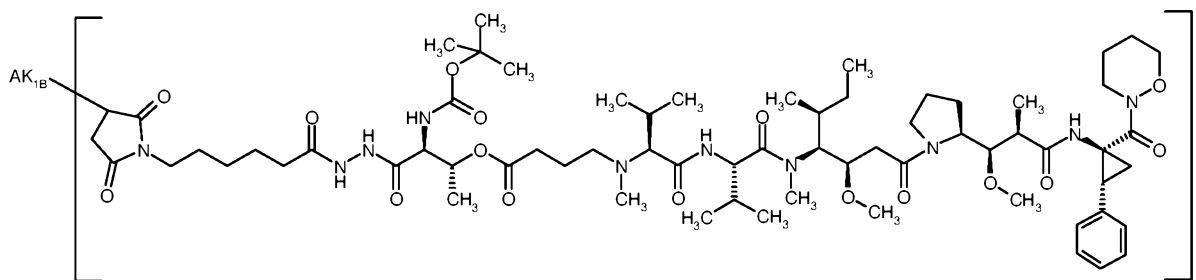
Drug/mAb-Ratio: 2.7

Example 112

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.73 mg/ml

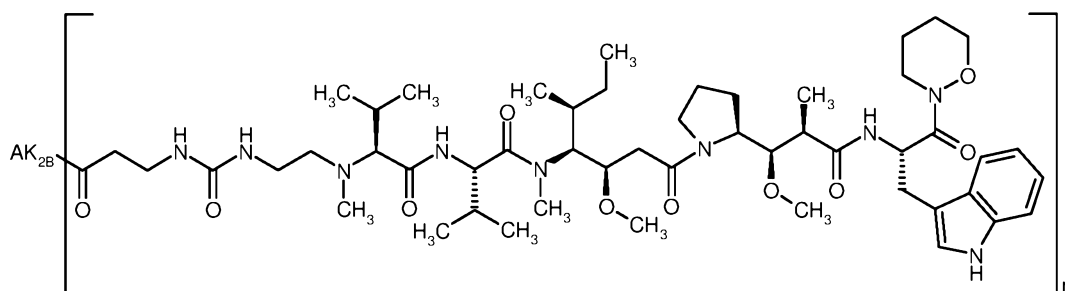
Drug/mAb-Ratio: 2.3

Example 113

15 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.71 mg/ml

Drug/mAb-Ratio: 3.3

Example 114

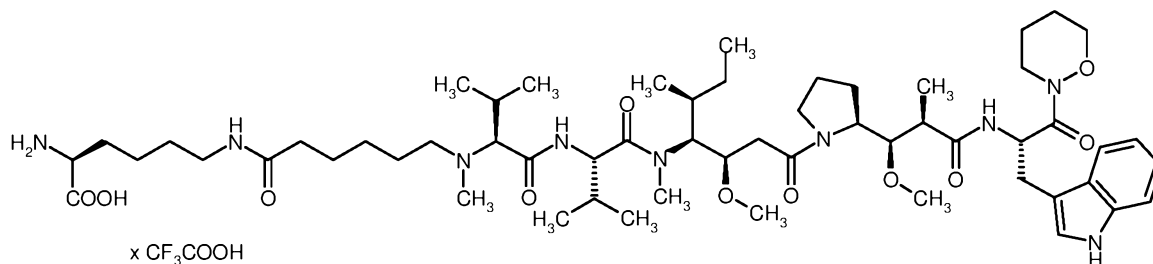
Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.47 mg/ml

Drug/mAb Ratio: 3.9

Example 115

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-
 10 methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-
 L-valinamide trifluoroacetate



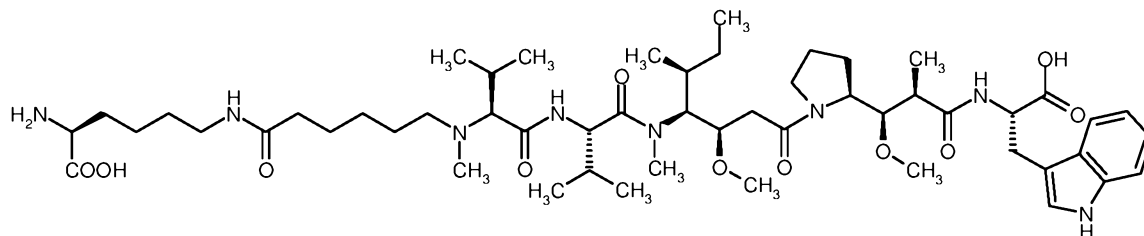
15.5 mg (15 μ mol) of Intermediate 210 were taken up in 5 ml of DMF and admixed with 4.4 mg (18 μ mol) of N²-(tert-butoxycarbonyl)-L-lysine and also 7.7 μ L (44 μ mol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The residue 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 batch was concentrated and, following lyophilization of the residue from acetonitrile/water (1:1), 15 mg (97% of theory) of the title compound were obtained.

HPLC (Method 12): R_t = 1.8 min;

LC-MS (Method 1): $R_t = 0.79$ min; MS (ESIpos): $m/z = 1083$ ($M+H$)⁺.

Example 116

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



40 mg (40 μ mol) of Intermediate 227 were taken up in 5 ml of DMF and admixed with 11.5 mg (40 μ mol) of N²-[(benzyloxy)carbonyl]-L-lysine and also 13 μ L (80 μ mol) 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.

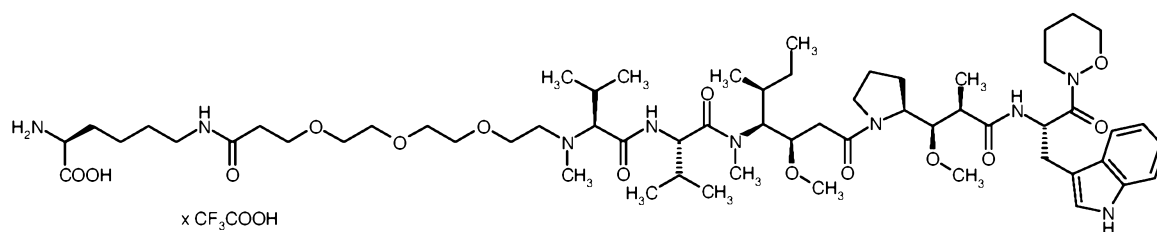
32.5 mg of this intermediate were dissolved in 10 ml of methanol and, following addition of 2 mg of 10% palladium on activated carbon, were hydrogenated under standard hydrogen pressure at RT for 30 minutes. The catalyst was then removed by filtration and the solvent was removed under reduced pressure. Lyophilization of the residue from dioxane/water 1:1 gave 26 mg (99% of theory) of the title compound.

HPLC (Method 12): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.76$ min; MS (ESIpos): $m/z = 1014$ ($M+H$)⁺.

Example 117

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

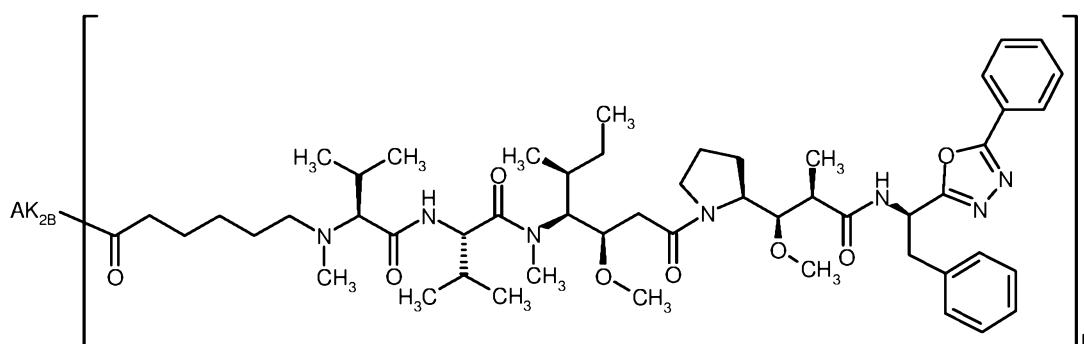


3.5 mg (3 μ mol) of Intermediate 202 were taken up in 2 ml of DMF and admixed with 0.8 mg (3 μ mol) of N²-(tert-butoxycarbonyl)-L-lysine and also 1.6 μ L (10 μ mol) of *N,N*-diisopropylethylamine. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The residue 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 μ l of dichloromethane and deprotected with 500 μ l of trifluoroacetic acid. The batch was concentrated and, following lyophilization of the residue from acetonitrile/water (1:1), 1 mg (89% of theory) of the title compound was obtained.

HPLC (Method 12): R_t = 1.9 min;

LC-MS (Method 1): R_t = 0.82 min; MS (ESIpos): m/z = 1173 (M+H)⁺.

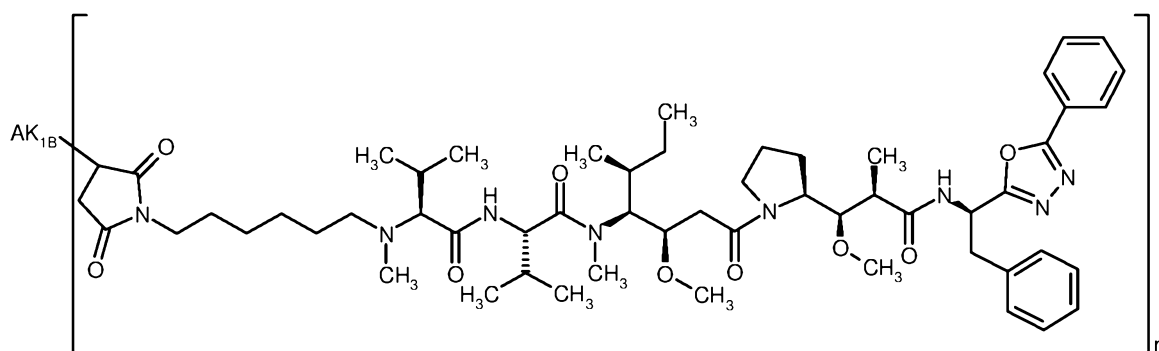
Example 118



15 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 0.89 mg/ml

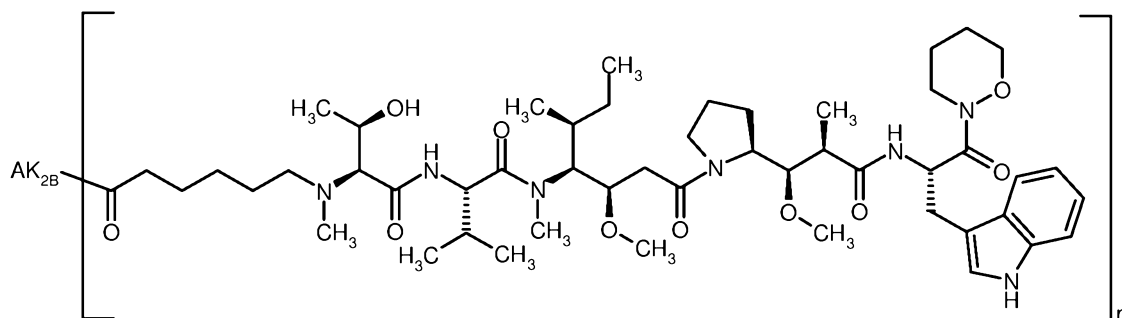
Drug/mAb Ratio: 1.8

Example 119

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 0.57 mg/ml

Drug/mAb Ratio: 1.5

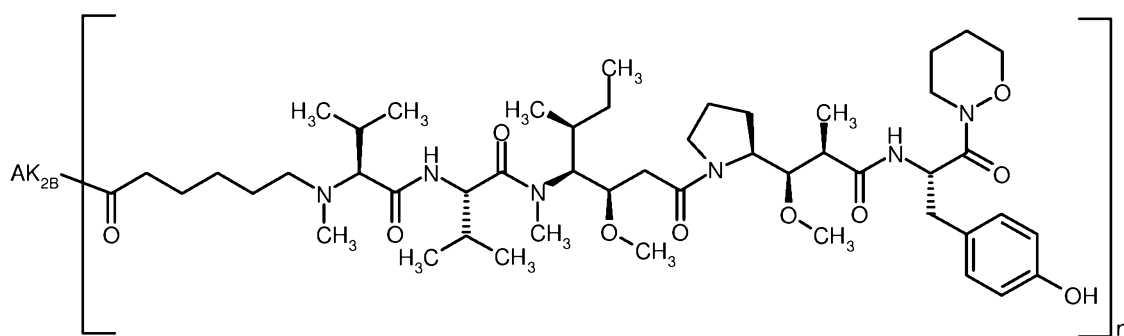
Example 120

10 Coupling here was carried out using 5 mg of anti-C4.4a B01-3 and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

Protein concentration: 1.39 mg/ml

Drug/mAb Ratio: 7.1

Example 121

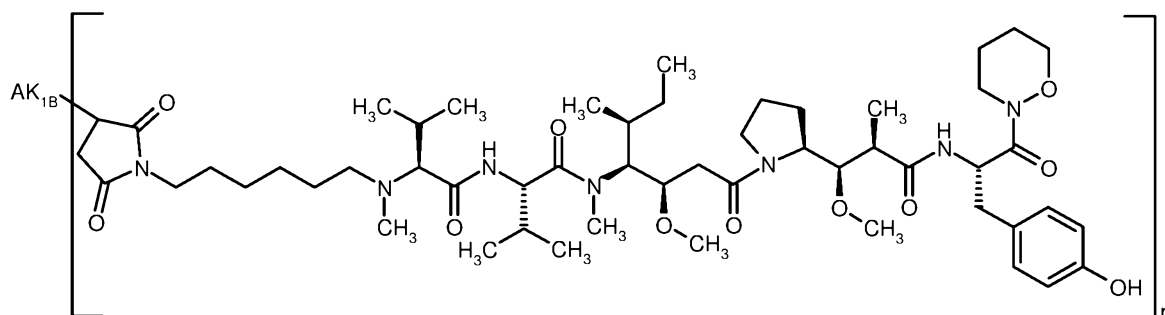


Coupling here was carried out using 5 mg of anti-C4.4a B01-3 and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

- 5 Protein concentration: 1.54 mg/ml

Drug/mAb Ratio: 2.4

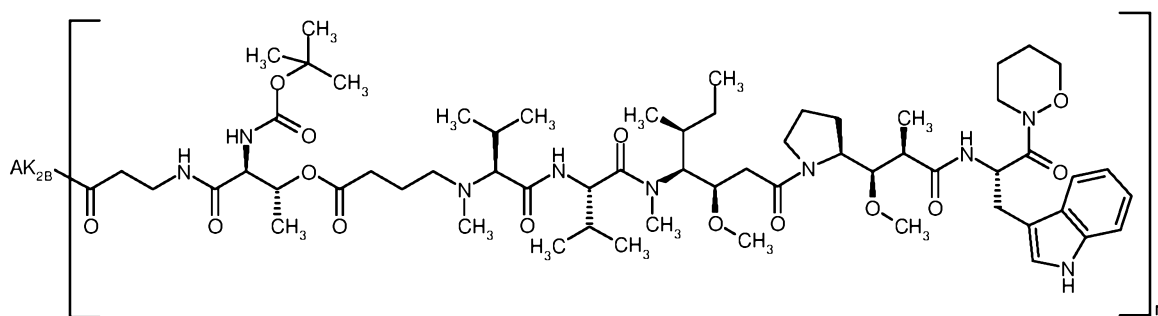
Example 122



Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS, and the batch, following
10 Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

Protein concentration: 1.48 mg/ml

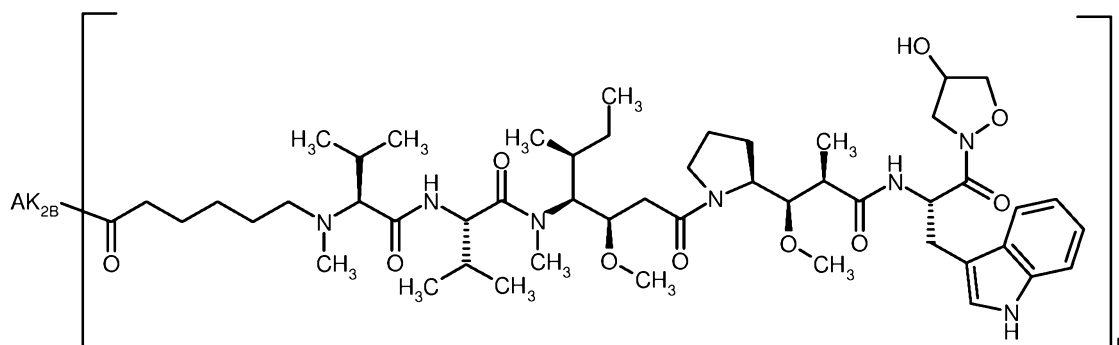
Drug/mAb Ratio: 2.4

Example 123

Coupling here was carried out using 5 mg of anti-C4.4a B01-3 in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

5 Protein concentration: 1.43 mg/ml

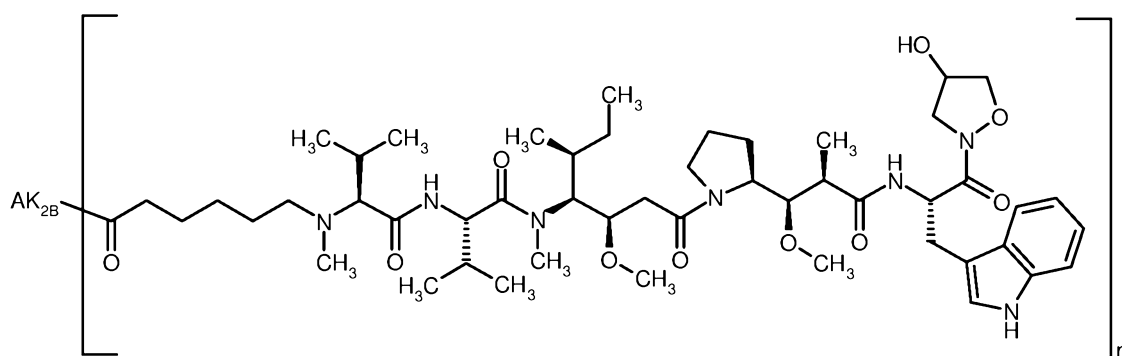
Drug/mAb-Ratio: 3.6

Example 124 Diastereomer 1

10 Coupling here was carried out using Intermediate 247a and 5 mg of anti-C4.4a B01-3 in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

Protein concentration: 1.45 mg/ml

Drug/mAb Ratio: 3.8

Example 125 Diastereomer 2

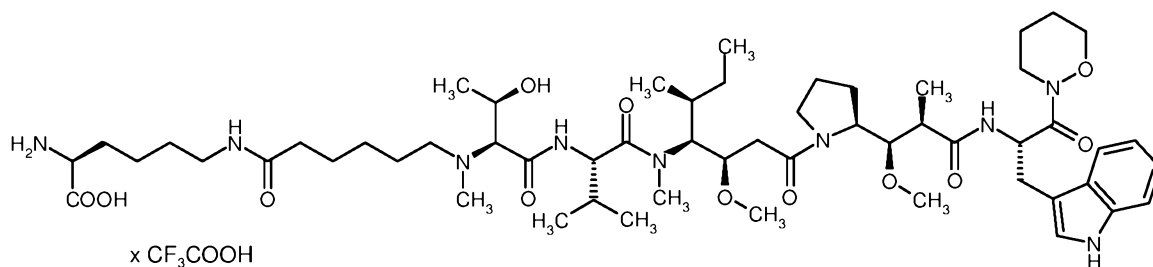
Coupling here was carried out using Intermediate 247a and 5 mg of anti-C4.4a B01-3 in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

Protein concentration: 1.42 mg/ml

Drug/mAb Ratio: 4.0

Example 126

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



8.6 mg (8 μ mol) of Intermediate 240 were taken up in 5 ml of DMF and admixed with 4.0 mg (16 μ mol) of N^2 -(tert-butoxycarbonyl)-L-lysine and also 2 μ L (16 μ mol) 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 reaction mixture 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 reaction mixture was

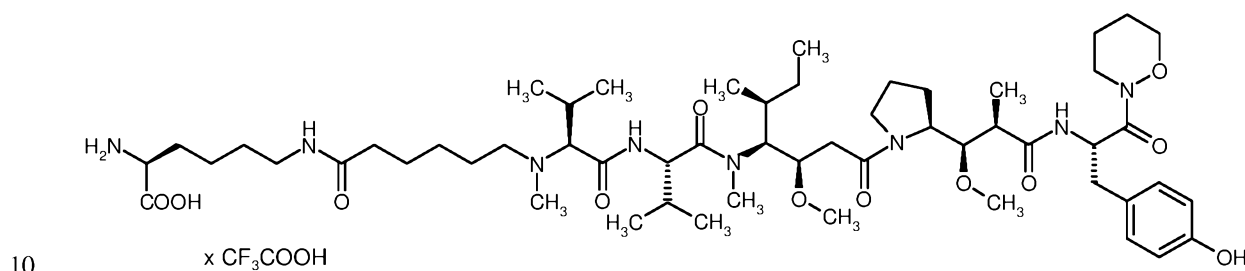
concentrated and the residue was purified by preparative HPLC. Drying under a high vacuum gave 3.3 mg (47% of theory) of the title compound.

HPLC (Method 5): $R_t = 1.5$ min;

LC-MS (Method 1): $R_t = 0.8$ min; MS (ESIpos): $m/z = 1084$ ($M+H$)⁺.

5 Example 127

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



8 mg (8 μ mol) of Intermediate 242 were taken up in 3 ml of DMF and admixed with 2.9 mg (12 μ mol) of N²-(tert-butoxycarbonyl)-L-lysine and also 2.7 μ L (16 μ mol) of *N,N*-diisopropylethylamine. The reaction mixture was stirred at RT overnight, then admixed again with the same amounts of N²-(tert-butoxycarbonyl)-L-lysine and *N,N*-diisopropylethylamine, and stirred at RT for a further 4 hours. The reaction mixture 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.

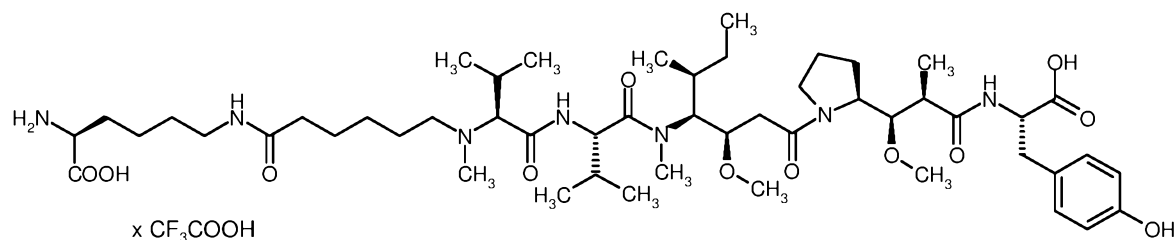
HPLC (Method 12): $R_t = 1.7$ min;

LC-MS (Method 1): $R_t = 0.69$ min; MS (ESIpos): $m/z = 1059$ ($M+H$)⁺.

Example 128

25 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



38 mg (41 μ mol) of Intermediate 248 were first converted into the N-hydroxysuccinimide ester.
 5 72 mg of the crude product obtained were taken up in 5 ml of DMF and admixed with 24 mg
 (100 μ mol) of N²-(tert-butoxycarbonyl)-L-lysine and 23 μ L of *N,N*-diisopropylethylamine. The
 reaction mixture was stirred at RT overnight, and then admixed again with 16 mg of N²-(tert-
 butoxycarbonyl)-L-lysine and 12 μ L 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
 10 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.

15 15 mg (12 μ mol) 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 reaction mixture was concentrated, and lyophilization of the residue from
 dioxane/water gave 13 mg (90% of theory) of the title compound.

HPLC (Method 12): R_t = 1.5 min;

LC-MS (Method 1): R_t = 0.68 min; MS (ESIpos): m/z = 990 (M+H)⁺.

C: Evaluation of biological activity:

The biological effect of the compounds of the invention was demonstrated in the assays described below

C-1. Analysis of the cytotoxic effect of the ADCs directed against C4.4a

5 The cytotoxic effect of the anti-C4.4a ADCs is analysed in different cell lines:

- A549 (CCL-185, ATCC), transfected with the sequence for the complete C4.4a receptor,
- A549, Mock transfected
- A549 Wildtype (DSMZ, lot 11)
- NCI-H292, endogenously C4.4a expressing lung cancer cell line (CRL-1848, ATCC)
- 10 – SCC-4 endogenously C4.4a expressing squamous epithelial carcinoma cell line (CRL-1624, ATCC)
- SCC-9 endogenously C4.4a expressing squamous epithelial carcinoma cell line (CRL-1629, ATCC)
- HCT-116 endogenously C4.4a expressing colonic carcinoma cell line (CCL-247, ATCC)
- 15 – HCT-116/VM46, HCT-116 transfected with VM46
- A431NS (CRL-2592, ATCC)

The cells are cultivated by a standard method, as indicated in the American Tissue Type Collection (ATCC) for the respective cell lines. For the procedure, the cells are detached using a solution of trypsin (0.05%) and EDTA (0.02%) in PBS (Biochrom AG #L2143), pelleted, resuspended in
20 culture medium, counted and seeded out into a 96-well culture plate with a white base (Costar #3610) (2500 cells in 100 µl/well) and incubated in an incubator at 37°C with 5% carbon dioxide. After 24 hours, the antibody-drug conjugates in 100 µl of culture medium are applied to the cells at concentrations of 10^{-7} M to 10^{-11} M (duplicate values), and were incubated in the incubator at 37°C with 5% carbon dioxide. After 72 hours, cell viability is determined using the Cell Titer Glow
25 Luminescent Cell Viability Assay (Promega #G7573 and #G7571). For this purpose, 100 µl of the substrate are added per cell batch, and the plates are subsequently covered with aluminium foil, shaken at 180 rpm in a plate shaker for 2 minutes, left to stand on the laboratory bench for 8 minutes, and then measured using a Victor X2 (Perkin Elmer). The substrate detects the ATP content of the living cells, producing a luminescence signal whose extent is directly proportional to

the vitality of the cells. The data measured is used for calculating the IC₅₀ using the Graph Pad Prism Laboratory software.

Table 3 lists the IC₅₀ values¹⁾ of representative working examples from this assay:

Table 3

Example	IC ₅₀	IC ₅₀	Example	IC ₅₀	IC ₅₀	Example	IC ₅₀	IC ₅₀
	[nM]	[nM]		[nM]	[nM]		[nM]	[nM]
	A549	A549		A549	A549		A549	A549
	:C4.4a	Mock		:C4.4a	Mock		:C4.4a	Mock
1	0.081	11.15	41	0.4	2	90	>100	>100
2	0.7	50	42	0.1	14	91	0.15	kH
3	0.47	4.75	43	0.062	6.33	92	0.29	>100
4	0.6	100	44	0.044	6.93	93	0.04	>100
5	0.4	20	45	0.058	4.01	94	0.035	100
	0.2	26						
	0.1	17						
6	0.53	4.50	46	0.062	7.74	95	0.036	>100
7	0.39	32	47	0.066	9.11	96	0.018	>100
8	0.01	0.15	48	0.061	6.78	97	0.062	>100
9	0.43	10	49	0.076	100	98	0.06	>100
10	0.01	25	50	0.02	0.02	99	0.1	80
11	4	>100	51	0.044	44	100	0.1	kH
12	0.58	6.36	52	0.04	45	101	0.3	kH
13	0.7	14.9	53	0.046	26	102	0.1	kH
14	0.1	65.5	54	0.074	>100	103	0.2	30
15	0.030	9.53	55	0.053	>100	104	3	kH
16	3.8	21	56	0.037	60	105	0.03	50
17	0.62	4.19	57	0.3	1	106	0.05	20
18	0.4	>100	58	0.04	>100	107	>100	kH
19	1.2	66.1	59	0.1	>100	108	0.03	>100
20	0.46	4.20	60	0.04	>100	109	1	>100
21	4.5	12.7	61	0.44	6.8	110	0.2	kH
22	5	16	62	0.09	50	112	0.27	>100
23	0.4	0.7	63	0.1	0.4	113	3	>100
24	0.3	23	64	0.04	0.52	114	0.05	>100
25	5.4	53	65	0.03	0.04	118	0.29	20

	IC ₅₀	IC ₅₀	Example	IC ₅₀	IC ₅₀	Example	IC ₅₀	IC ₅₀
Example	[nM]	[nM]		[nM]	[nM]		[nM]	[nM]
	A549	A549		A549	A549		A549	A549
	:C4.4a	Mock		:C4.4a	Mock		:C4.4a	Mock
26	0.052	11.27	66	0.03	0.04	119	0.32	15
27	0.65	6.70	67	0.08	26	120	0.07	>100
28	0.062	>100	68	0.02	>100	121	0.03	7
29	0.02	2.5	69	0.17	0.27	122	0.04	>100
30	0.1	71	70	0.06	7	123	0.02	>100
31	0.32	9	80	3.0	>100	124	0.04	>100
32	0.035	6.19	81	0.045	>100	125	0.04	>100
33	0.037	~30	82	0.06	>100			
34			83	0.27	>100			
35	0.3	20	84	0.13	>100			
36	0.08	>100	85	0.14	>100			
37	0.1	kH	86	0.17	>100			
38	0.03	50	87	0.28	>100			
39	0.04	1.5	88	1.1	>100			
40	0.6	50	89	1.3	>100			

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.

5 C-2. Determination of the effect on tubulin polymerization

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.

Tubulin polymerization was investigated using the "Fluorescence-based Microtubule Polymerisation Assay Kit" from Cytoskeleton (Denver, Colorado, 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.

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 μ M 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 ($\Delta F/\text{min}$), 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.

The value for the inhibition of MMAF at a concentration of 1 μ M is set as being 100%.

Table 4 gives data for the inhibition of tubulin polymerization by representative working examples.

Table 4.

Working example	Concentration of toxophore [μ M]	Tubulin polymerization in the presence of toxophore in [%]. Tubulin polymerization rate at 1 μ M MMAF set at 100%
MMAF	1	100
MMAF	10	34
MMAF	100	0
115	1	45

Working example	Concentration of toxophore [μM]	Tubulin polymerization in the presence of toxophore in [%]. Tubulin polymerization rate at 1 μM MMAF set at 100%
115	10	1
116	1	80
116	10	14
117	1	60
117	10	0
71	1	88
71	10	25
72	1	109
72	10	27
73	1	120
74	1	117
74	10	64
75	1	107
75	10	25
76	1	121
76	10	35
77	1	111
77	10	45
78	1	110

Working example	Concentration of toxophore [μ M]	Tubulin polymerization in the presence of toxophore in [%]. Tubulin polymerization rate at 1 μ M MMAF set at 100%
117	1	78
117	10	24
126	1	102
126	10	31
127	1	88
127	10	21
128	1	90
128	10	17

The MMAF toxophore and the working examples inhibit tubulin polymerization as a function of their concentration. At 100 μ M MMAF, the tubulin polymerization is inhibited completely. Working Example 115 inhibits the tubulin polymerization rate at 1 μ M to 45% of the value
5 measured for 1 μ M MMAF.

C-3. In vitro tests for determining cell permeability

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
10 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
15 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)].

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).

- 5 Table 5 below sets out permeability data for representative working examples from this assay:

Table 5

Working example	P_{app} (B-A) [nm/s]
71	2
72	1.6
73	2.5
74	5
75	1
77	7
115	2
116	1
126	1.8
127	1.5

- 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-4. In vitro tests for determining the substrate properties for P-glycoprotein (P-gp)

- 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.

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)].

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).

Table 6 below lists permeability data for representative working examples from this assay, which was carried out in L-MDR1 cells:

Table 6

Working example	P_{app} (B-A) [nm/s]
71	3
72	3.6
73	2.1
74	3.6
75	4
77	2
115	6
116	4

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-5. Activity test *in vivo*

5 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 a conjugate 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. These tumour-bearing rodents
10 were subsequently administered either a conjugate of the invention or a control antibody conjugate, or isotonic salt solution. Administration took place singularly or more often. Tumour growth was determined twice weekly with the aid of a sliding calliper. After tumour growth for several weeks, the tumour size of conjugate-treated animals was compared with that of the control group. The conjugate-treated animals showed a significantly smaller tumour size.

15 C-5a. Testing of ADCs in experimental tumours in the mouse

The predictive force of mice xenograft tumour models, relative to the clinical situation in the case of immunotoxin therapies, is often limited, on the one hand by the deficient cross-reactivity of the therapeutic antibodies with the murine species, and on the other hand by the incidence of anti-drug antibodies (ADAs) in the human body on administration of murine or chimeric antibodies. In order
20 to utilize the full potential of the specific C4.4a expression for cancer therapy, for an immunoconjugate approach, for example, there is a need for human antibodies which are of high affinity, are selective and exhibit species cross-reactivity, of the kind employed preferably in accordance with the invention. With such antibodies, mice xenograft tumour models yield meaningful findings relative to the clinical situation.

25 Human tumour cells which express C4.4a are inoculated 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 μ l of medium or 50% medium/50% Matrigel. The cell suspension is injected beneath the skin of the mouse.

Within a few days, a tumour grows. Treatment begins no earlier than after tumour establishment
30 with a tumour size of 25 mm².

Treatment with ADCs takes place by the intravenous route into the caudal vein of the mouse. The ADC is dissolved in PBS and is administered with a volume of 10 ml/kg.

The treatment scheme is governed by the pharmacokinetics of the antibody. As a standard, the 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.

- 5 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.

10 In the course of the experiment, the area of the tumour is measured regularly using a sliding calliper in two dimensions (length/width).

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. Where control groups and treatment groups are ended at different times, the T/C value is calculated on the basis of the tumour areas of the last joint measurement of all the treatment groups and control
15 groups.

1 million SCC-4 cells are inoculated subcutaneously into the flank of female NMRI nude mice.

Intravenous treatment with the ADCs is commenced at an average tumour size of 30 – 35 mm². When the control groups have reached the maximum allowed size, the experiment is ended and the
20 tumours are removed and weighed. All of the ADCs tested that target C4.4a have inhibited tumour growth in a dose-dependent manner. At a dose of 30 mg/kg, Example 54, Example 49, Example 51 and Example 53 each reached a T/C of < 0.1. Significant anti-tumour activity in comparison to the control was achieved for Examples 49, 52, 53, 54 and 56 at a dose of down to 15 mg/kg, achieving T/C values of ≤ 0.29.

25

1 million NCI-H292 cells were inoculated subcutaneously into the flank of female NMRI nude mice.

Intravenous treatment with the ADCs is commenced at an average tumour size of 30-35 mm².
30 Control groups and treatment groups are each ended when the maximum allowable tumour size is reached. In this way, differences in the further growth of tumours after the end of treatment may contribute to further characterization of the ADCs. Consequently, the tumour areas at the last joint point in time of measurement was employed for determining the anti-tumour activity in comparison to the control (T/C). In the NCI-H292 mouse model used, it is shown that all of the
35 ADCs tested reduce tumour growth dose-dependently in comparison to the control. A significant

anti-tumour effect was obtained for Example 54 at a dose of down to 1.9 mg/kg, and for Example 49 at a dose of down to 3.75 mg/kg. The minimum T/C values obtained in this model are a T/C of 0.16 at 30 mg/kg for Example 54, a T/C of 0.17 at 30 mg/kg for Example 49, a T/C of 0.16 at 30 mg/kg for Example 53, a T/C of 0.17 at 15 mg/kg for Example 51, and a T/C of 0.19 at 3.75 mg/kg for Example 70. On comparative administration of the ADCs with a constant dose of 7.5 mg/kg, it was possible to achieve a T/C of 0.20 with each of Examples 49 and 54, a T/C of 0.27 with Example 51, a T/C of 0.22 with Example 52, a T/C of 0.23 with Example 53, a T/C of 0.24 with Example 55, a T/C of 0.21 with Example 56 and a T/C of 0.17 with Example 70.

10 C-6. Pharmacokinetics in the A549 tumour model with C4.4a-transfected and non-transfected A549 cells

Following intravenous administration of 7-30 mg/kg of various ADCs, the plasma concentrations and tumour concentrations of ADC and also of potential metabolites were measured, and the pharmacokinetic parameters such as clearance (CL), area under the curve (AUC) and half-life ($t_{1/2}$) were calculated.

Analysis for quantifying the potential metabolites

The measurement of the compounds 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).

20 For the processing of 100 μ L of plasma, it was admixed with 400 μ L of methanol and 10 μ L of internal standard (ISTD, 50 ng/mL in methanol) and shaken for 10 seconds. After centrifuging for 5 minutes at 16 000 g, 250 μ L of supernatant were transferred to an autosampler vial, which was made up with 250 μ L of ammonium acetate buffer (AAC, 10 mM, pH 6.8) and shaken again.

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 μ L of the supernatant were transferred to an autosampler vial and made up with 50 μ L of ammonium acetate buffer (10 mM, pH 6.8) and with 5 μ L of ISTD. After again being shaken, the tumour sample was ready for measurement.

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.

HPLC/LC-MSMS (TISP) analysis ran on an HP1100 pump (Agilent) with a Gemini column (5 μ m C18 110 A, 50 $\times$ 3 mm, Phenomenex).

For calibration, plasma samples were admixed with concentrations of 0.5 – 2000 µg/L. The detection limit (LOQ) was about 2 µg/L. The linear range extended from 2 to 1000 µg/L

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 5 to 200 µg/L.

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).

D. Working examples for pharmaceutical compositions

The compounds of the invention can be converted as follows into pharmaceutical preparations:

i.v. Solution:

5 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:

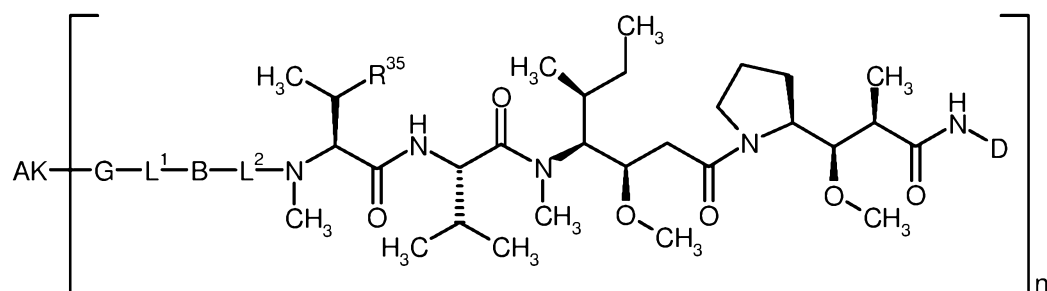
10 The compounds of the invention can be converted into the administration forms cited. This can be accomplished in a known way by "mixing with" or "dissolving in" inert, non-toxic, pharmaceutically suitable excipients (e.g. buffer substances, stabilizers, solubilizers, preservatives). The following, 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, 15 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 systems, 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), 20 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:

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 25 suitable solvent (e.g. injection-grade water, isotonic saline solution) and administered.

Claims

1. Binder-drug conjugates of the general formula (Ia)



(Ia),

5 in which

n is a number from 1 to 50,

AK is a binder,

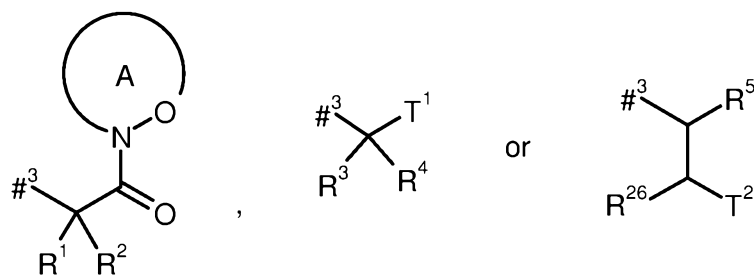
the group $\text{-G-L}^1\text{-B-L}^2\text{-}$ is a linker,

where

10 § 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

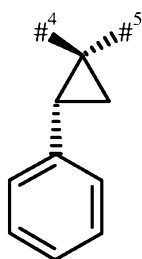
15 #³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

5 or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

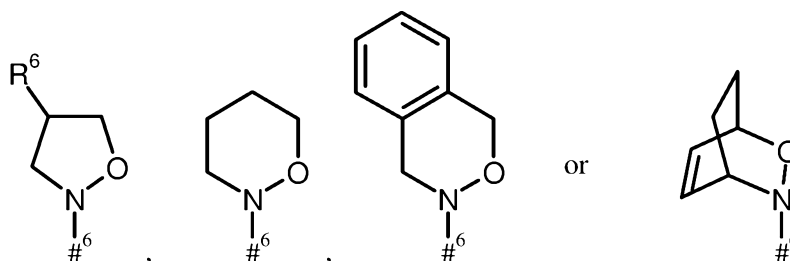


in which

10 #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



15

in which

#⁶ marks the linkage site with the carbonyl group,

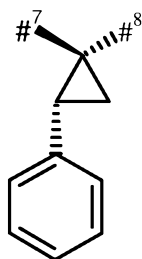
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

5 or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

10 #⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

15 R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

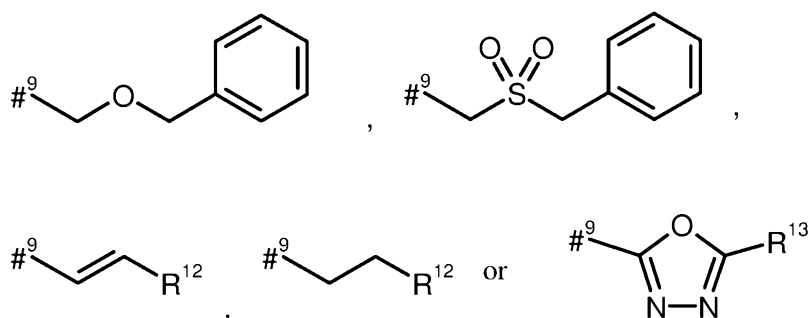
or

20 R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R¹⁰ 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



5 in which

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

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

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

15 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

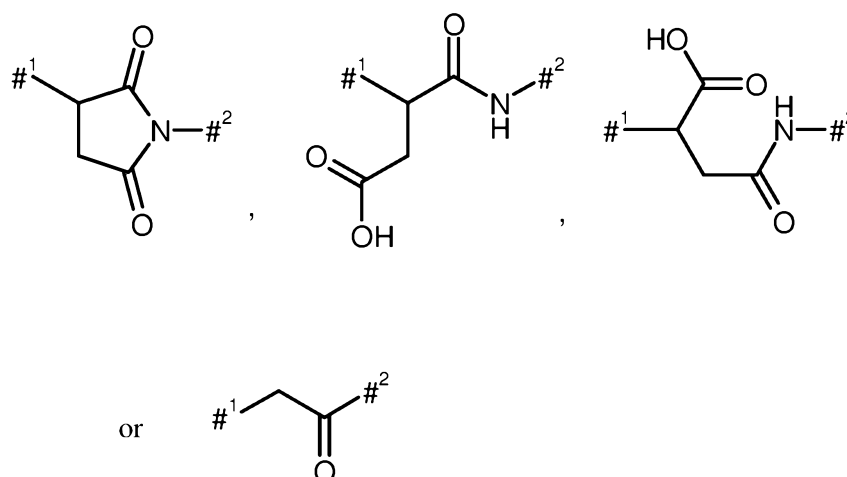
where

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

20

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

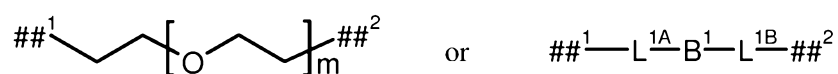
$\#^1$ marks the linkage site with the sulphur atom of the binder,

5 $\#^2$ marks the linkage site with the group L^1 ,

or

when $AK = AK_2$, is carbonyl,

L^1 is a bond, linear (C₁-C₁₀)-alkanediyl, a group of the formula



10 where

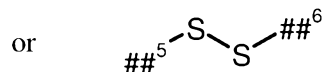
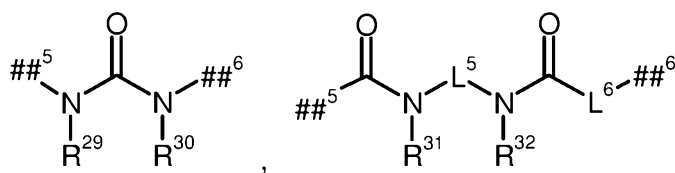
m is a number from 2 to 6,

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

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

L^{1A} is linear (C₂-C₁₀)-alkanediyl,

15 B^1 is a group of the formula



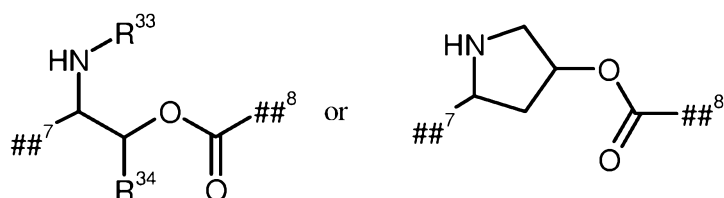
in which

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

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

5 L⁵ is a bond or (C₂-C₄)-alkanediyl,

L⁶ is a bond or a group of the formula



in which

##⁷ marks the linkage site with the carbonyl group,

10 ##⁸ marks the linkage site with L^{1B},

R³³ is hydrogen, (C₁-C₄)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

15 R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{31} is hydrogen or (C₁-C₄)-alkyl,

R^{32} is hydrogen or (C₁-C₄)-alkyl,

or

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

5

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

and

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

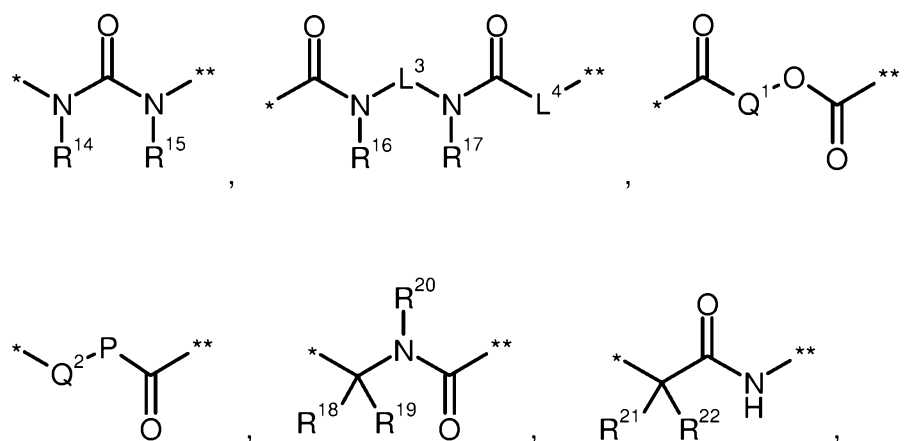
10

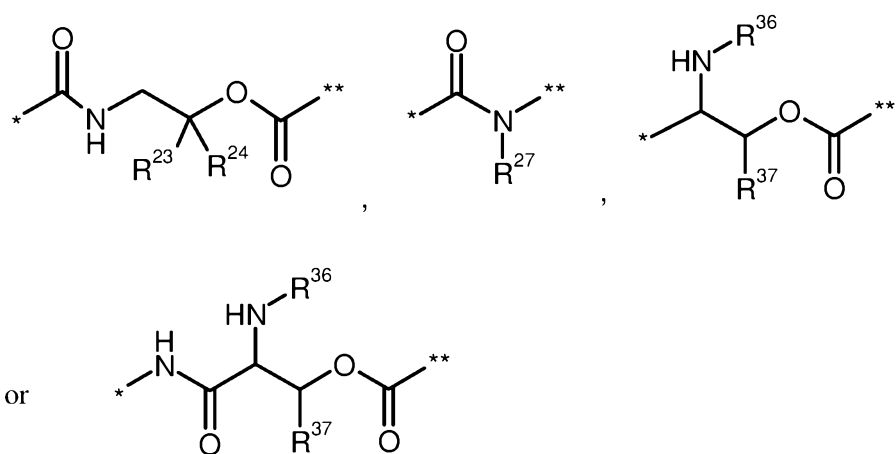
and

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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

15

B is a bond or a group of the formula





where

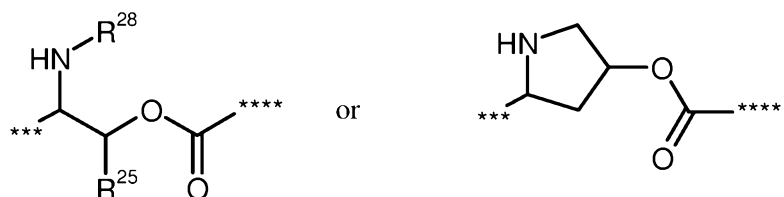
* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

5 P is O or NH,

L^3 is a bond or $(\text{C}_2\text{-C}_4)$ -alkanediyl,

L^4 is a bond or a group of the formula



in which

10 *** 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, $(\text{C}_1\text{-C}_4)$ -alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

15 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,

R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

5 R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

10 R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

15 or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

R²² is hydrogen or (C₁-C₄)-alkyl,

20 or

R²¹ and R²² together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R²³ is (C₁-C₄)-alkyl,

R²⁴ is hydrogen or (C₁-C₄)-alkyl,

25 R²⁷ is hydrogen or (C₁-C₄)-alkyl,

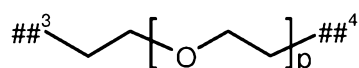
R^{36} is hydrogen, (C_1-C_4) -alkylcarbonyl, tert-butyloxycarbonyl or benzyl-oxy carbonyl,

R^{37} is hydrogen or methyl,

or

5 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

10 p is a number from 2 to 6,

$##^3$ marks the linkage site with the group B,

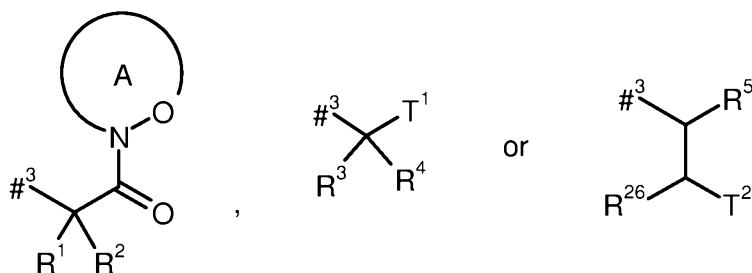
$##^4$ marks the linkage site with the nitrogen atom,

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
15 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,

20 D is a group of the formula



in which

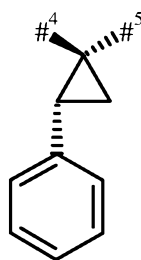
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

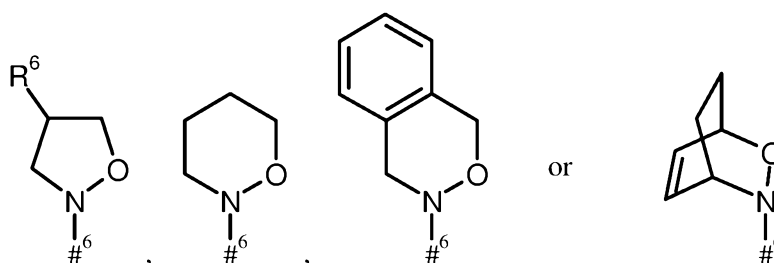


in which

#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,

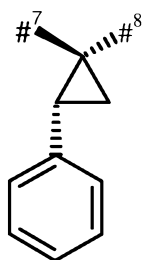
R⁶ is hydrogen, hydroxy or benzyloxy,

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, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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,

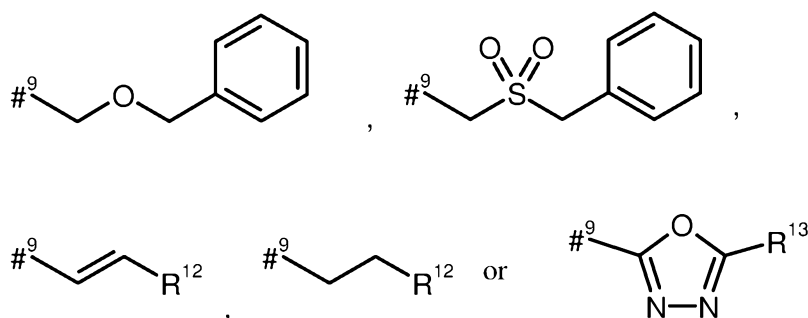
or

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



5 in which

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

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

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

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

15 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,

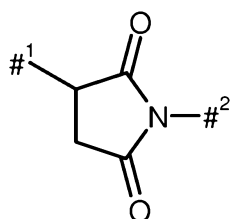
AK is AK_1 or AK_2

where

20 AK_1 is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK₂ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when AK = AK₁, is a group of the formula



5

in which

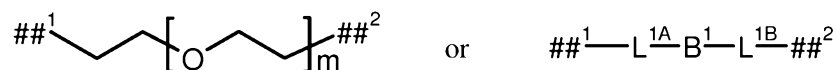
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

or

10 when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



where

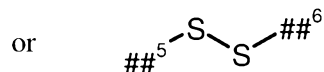
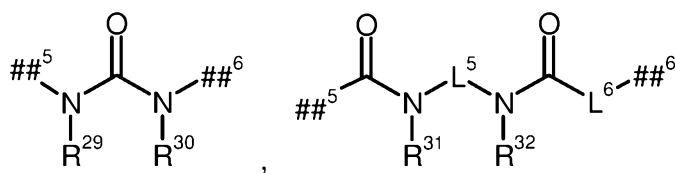
m is a number from 2 to 6,

15 ##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₆)-alkanediyl,

B¹ is a group of the formula



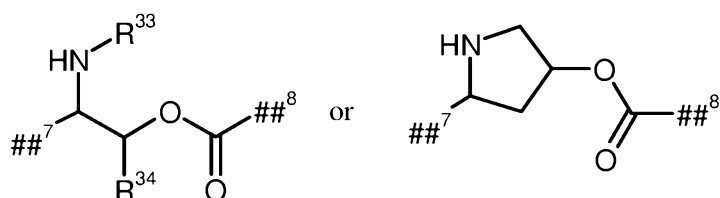
in which

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

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

5 L⁵ is a bond,

L⁶ is a bond or a group of the formula



in which

##⁷ marks the linkage site with the carbonyl group,

10 ##⁸ marks the linkage site with L^{1B},

R³³ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R³⁴ is hydrogen or methyl,

R²⁹ is hydrogen,

R³⁰ is hydrogen,

15 R³¹ is hydrogen or methyl,

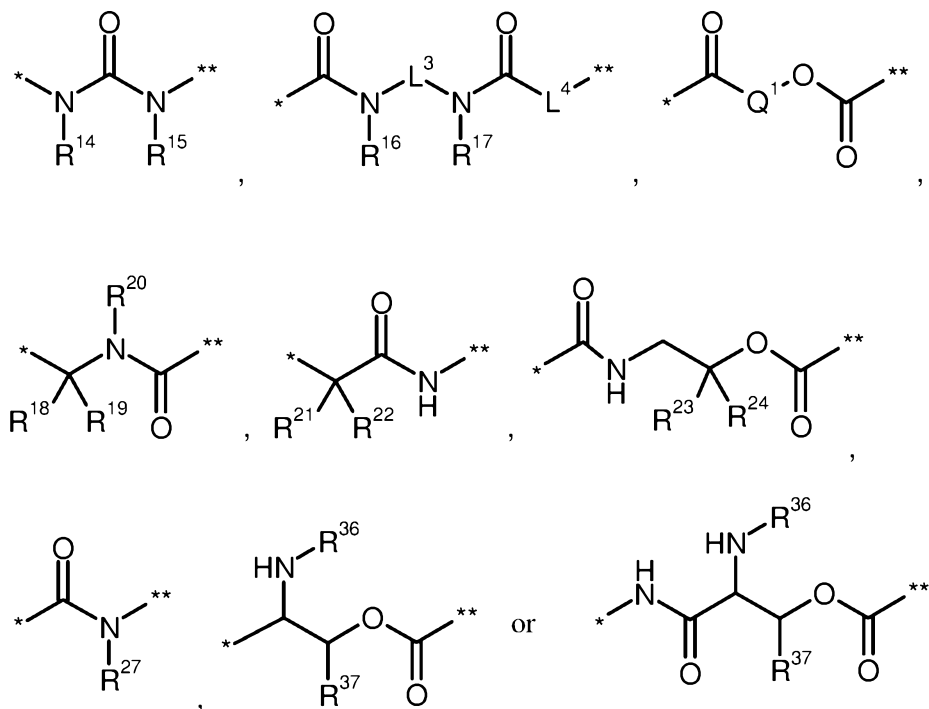
R³² is hydrogen or methyl,

L^{1B} is linear (C₂-C₆)-alkanediyl,

and

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



5

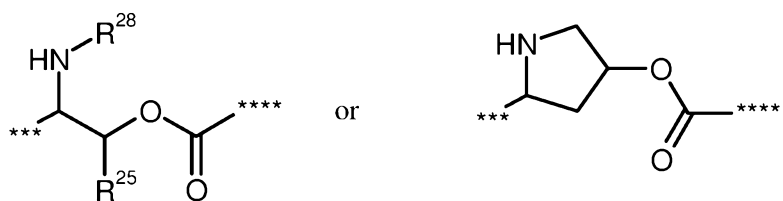
where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



10

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

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,

5 R^{15} is hydrogen,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

10 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,

15 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,

20 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,

25 R^{27} is hydrogen,

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

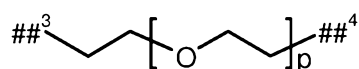
R^{37} is hydrogen or methyl,

or

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

5

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,

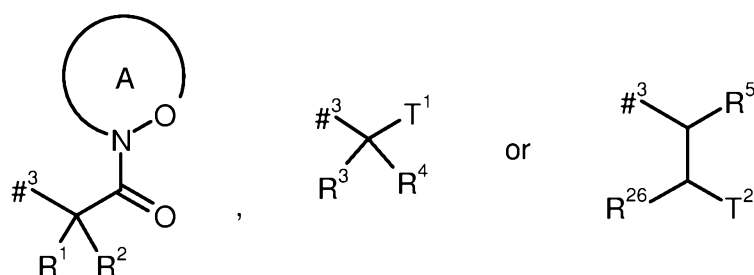
10

$##^3$ 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



15

where

$#^3$ marks the linkage site with the nitrogen atom,

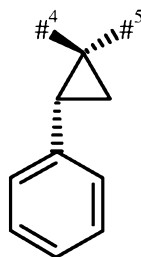
R^1 is hydrogen,

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

20

or

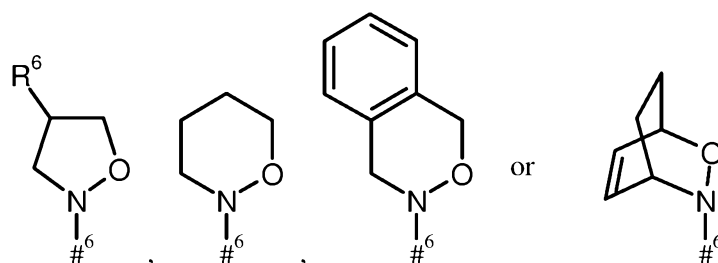
R^1 and R^2 together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

5 $\#^4$ 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



10 in which

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

R^6 is hydrogen, hydroxy or benzyloxy,

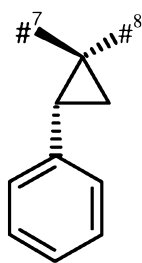
R^3 is hydrogen,

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

15

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

5 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

10 R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

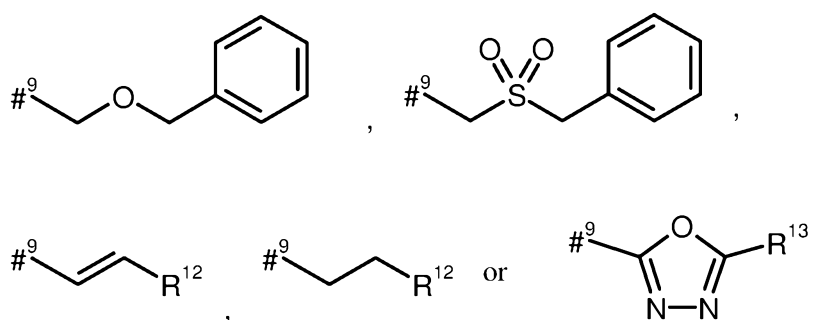
or

R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

15 R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



in which

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

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

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,

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,

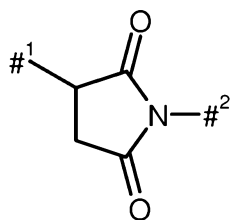
AK is AK_1 or AK_2

where

AK_1 is an antibody which comprises the six CDR sequences of the antibody 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 sulphur atom of a cysteine residue of the binder to the group G,

AK₂ 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 = AK₁, is a group of the formula



in which

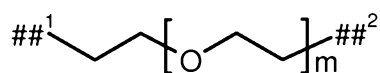
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



where

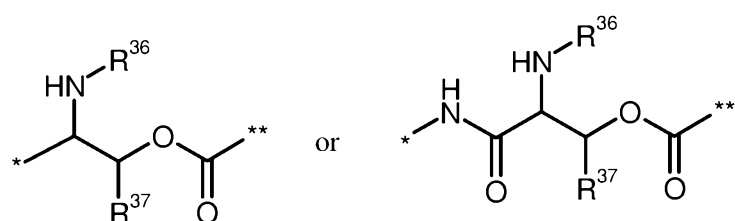
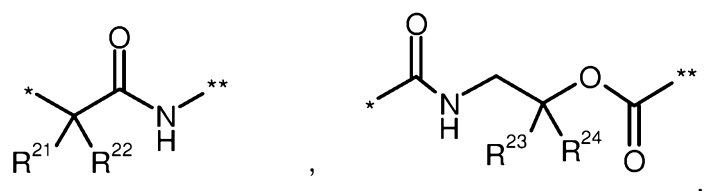
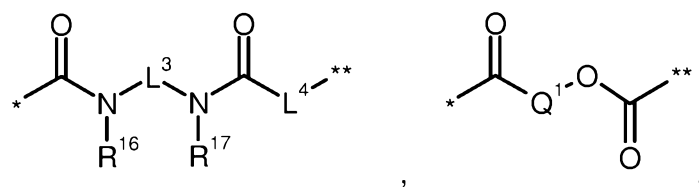
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



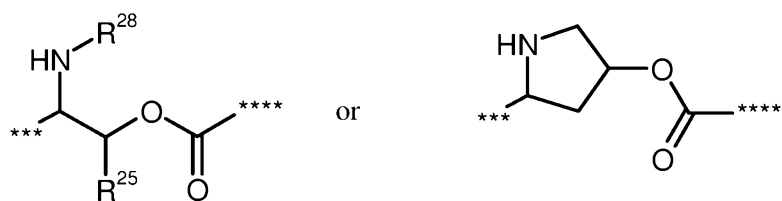
where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

5 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,

10 **** 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,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

R²¹ is hydrogen or methyl,

R²² is hydrogen or methyl,

or

R²¹ and R²² together with the atoms to which they are bonded form a cyclopropyl ring,

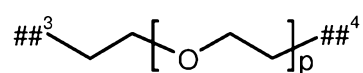
R²³ is methyl,

R^{24} is hydrogen,

R³⁶ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R³⁷ is hydrogen or methyl,

15 L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



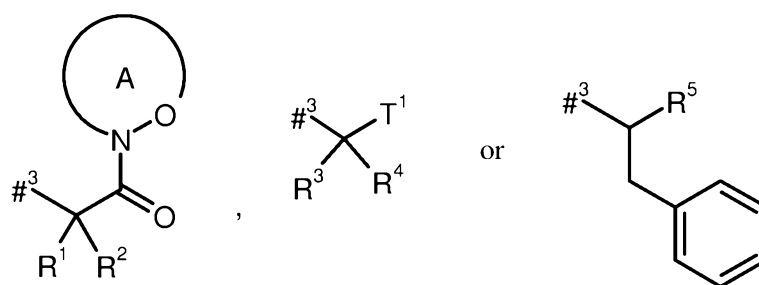
where

p is a number from 2 to 6,

##³ marks the linkage site with the group B,

20 ##⁴ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

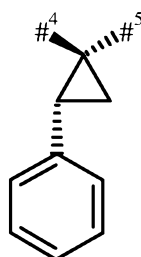
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



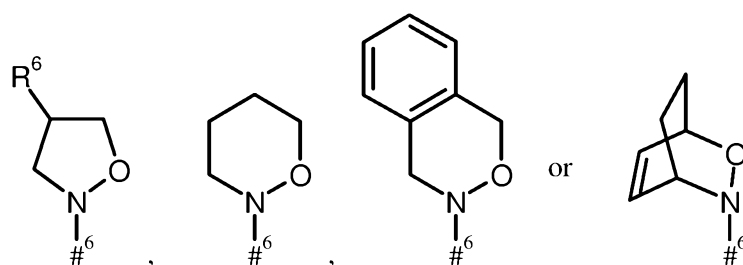
10

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,
15 optionally substituted heterocycle of the formula



in which

#⁶ marks the linkage site with the carbonyl group,

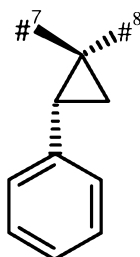
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen,

R⁴ is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, or -CH₂-O-R¹¹,

15

in which

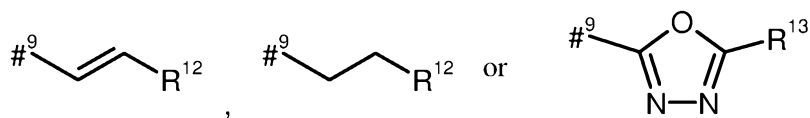
R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ 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 $-\text{CHCH}_2\text{phenyl}$,

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

10 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 15 4, in which

n is a number from 1 to 10,

AK is AK_2

where

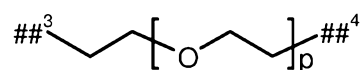
20 AK_2 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10, M31-B01 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6, and is bonded via the NH side group of a lysine residue of the binder to the group G,

25 G is carbonyl,

L^1 is a bond,

B is a bond,

L² is linear (C₃-C₆)-alkanediyl or is a group of the formula



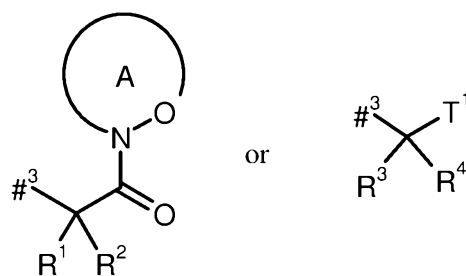
where

5 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



10 where

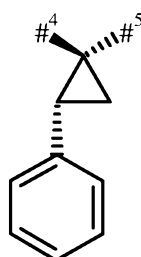
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

15 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



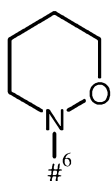
in which

#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

5



in which

#⁶ marks the linkage site with the carbonyl group,

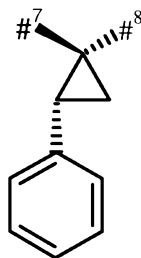
R³ is hydrogen,

10

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹

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,

5 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

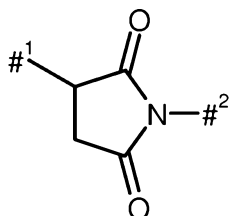
n is a number from 1 to 10,

10 AK is AK_1 ,

where

15 AK_1 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 sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula



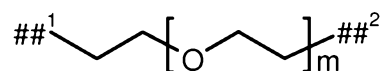
20

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

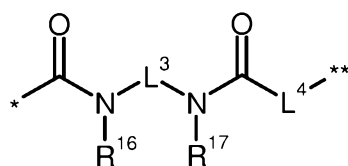
m is a number 2 or 3,

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

5 $\# \#^2$ marks the linkage site with the group B,

where (C₃-C₅)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



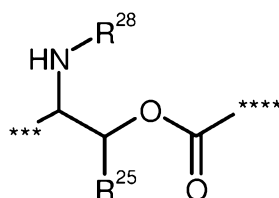
where

10 * marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond or a group of the formula



15 in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is methyl,

R²⁸ is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R^{16} is hydrogen or methyl,

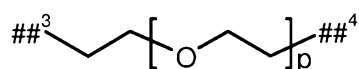
R^{17} is hydrogen or methyl,

or

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

5

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



where

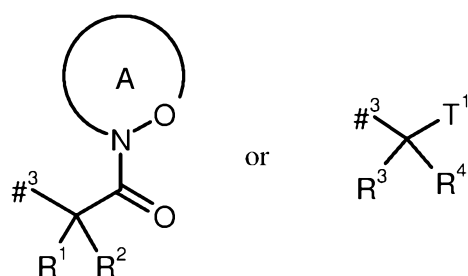
p is a number 2 or 3,

10

$##^3$ 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

15

$##^3$ marks the linkage site with the nitrogen atom,

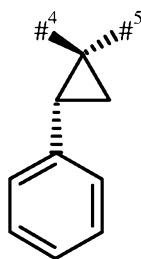
R^1 is hydrogen,

R^2 is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

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

20

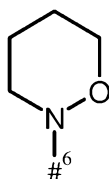


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

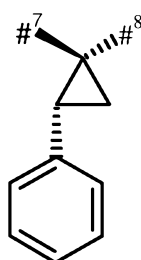
#⁶ marks the linkage site with the carbonyl group,

10 R³ is hydrogen,

R⁴ is 4-hydroxybenzyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

5

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

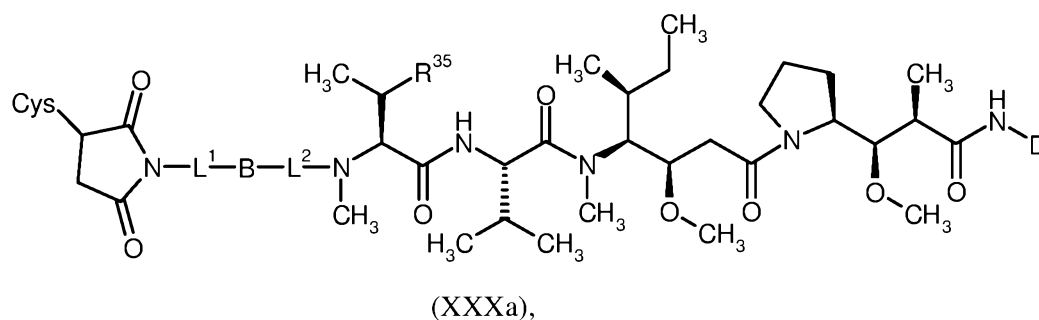
R⁸ is hydrogen,

R⁹ is hydrogen or benzyl,

10 R³⁵ is methyl,

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

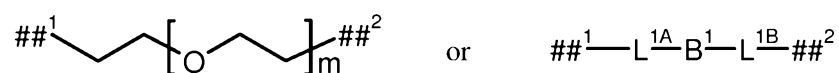
7. Compounds of the formula (XXXa)



15 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,

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl, a group of the formula



20 where

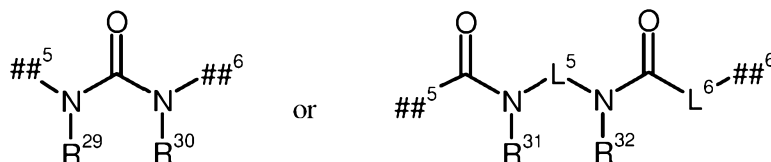
m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₁₀)-alkanediyl,

5 B¹ 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},

10 L⁵ is a bond or (C₂-C₄)-alkanediyl,

L⁶ is a bond,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

15 R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

R³² is hydrogen or (C₁-C₄)-alkyl,

or

20 R³¹ and R³² together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear (C₂-C₁₀)-alkanediyl,

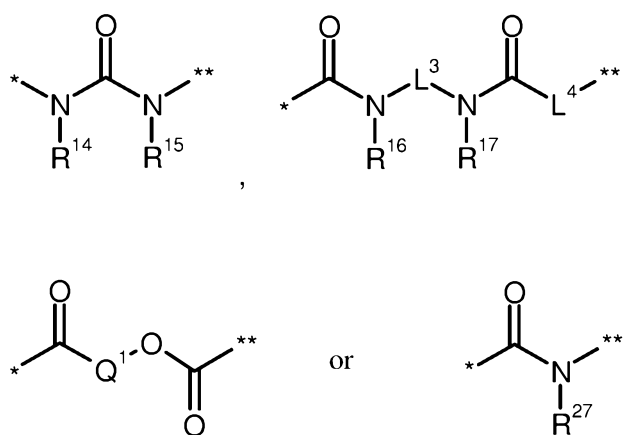
and

where (C₁-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

and

- 5 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



- 10 where

* marks the linkage site with L¹,

** marks the linkage site with L²,

P is O or NH,

L³ is a bond or (C₂-C₄)-alkanediyl,

- 15 L⁴ is a bond,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

5 R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

10 R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

or

15 R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

R²² is hydrogen or (C₁-C₄)-alkyl,

or

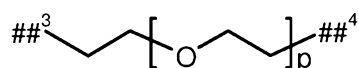
20 R²¹ and R²² together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R²³ is (C₁-C₄)-alkyl,

R²⁴ is hydrogen or (C₁-C₄)-alkyl,

R²⁷ is hydrogen or (C₁-C₄)-alkyl,

L² is linear (C₂-C₁₀)-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,

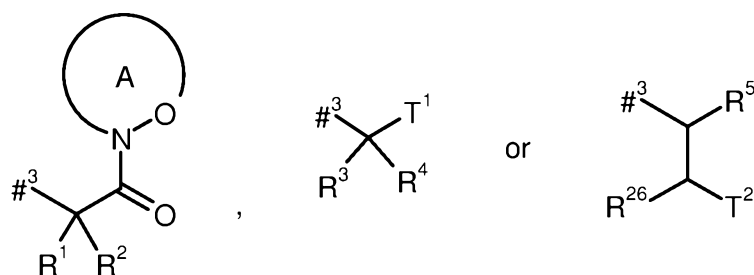
5 ##⁴ marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

and

10 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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

D is a group of the formula



15 where

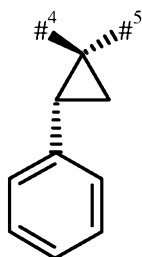
##³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

20 R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

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



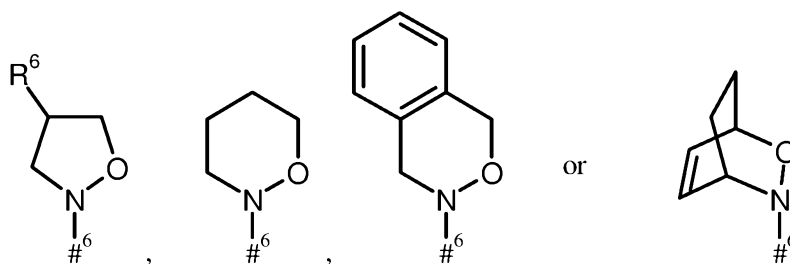
5

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



10

in which

#⁶ marks the linkage site with the carbonyl group,

R^6 is hydrogen, hydroxy or benzyloxy,

15

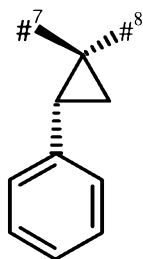
R^3 is hydrogen or methyl,

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, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

20

or

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



in which

5 $\#^7$ 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

10 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,

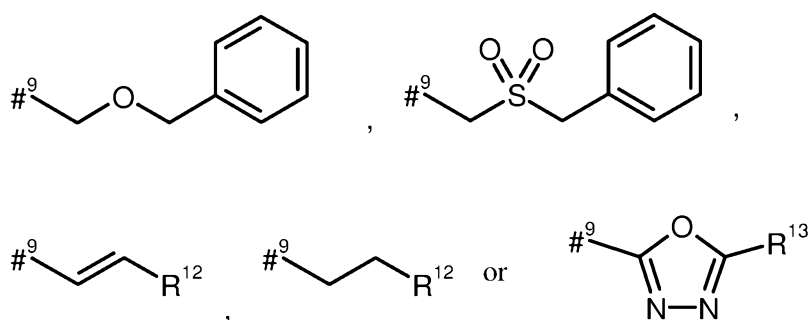
or

15 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,

20 R^5 is hydrogen, methyl or a group of the formula



in which

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

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $-\text{S}(\text{O})_2\text{OH}$,

R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R²⁶ is hydrogen or hydroxy,

T² is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

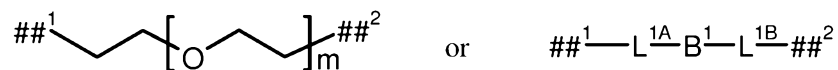
R³⁵ is methyl or hydroxy,

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,

L¹ is a bond, linear (C₂-C₆)-alkanediyl, a group of the formula



where

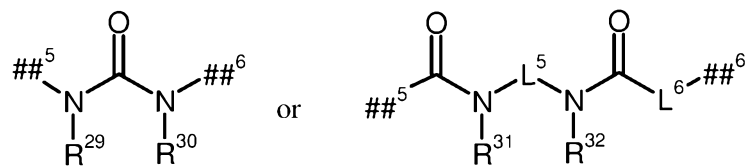
m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₆)-alkanediyl,

B^1 is a group of the formula



in which

5 $##^5$ 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,

10 R^{30} is hydrogen,

R^{31} is hydrogen or methyl,

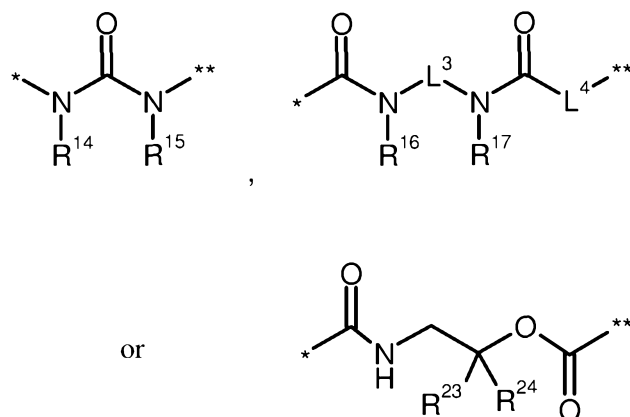
R^{32} is hydrogen or methyl,

L^{1B} is linear (C₂-C₆)-alkanediyl,

and

15 where (C₂-C₆)-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,

5 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,

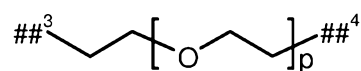
10 or

R^{16} and R^{17} together with the atoms to which they are bonded form piperazinyll ring,

R^{23} is methyl,

R^{24} is hydrogen or methyl,

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



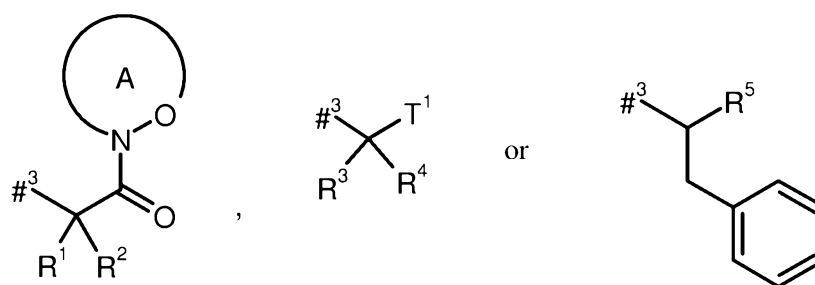
where

p is a number 2 or 3,

$##^3$ marks the linkage site with the group B,

20 $##^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

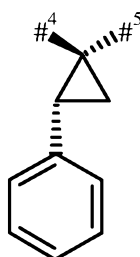
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



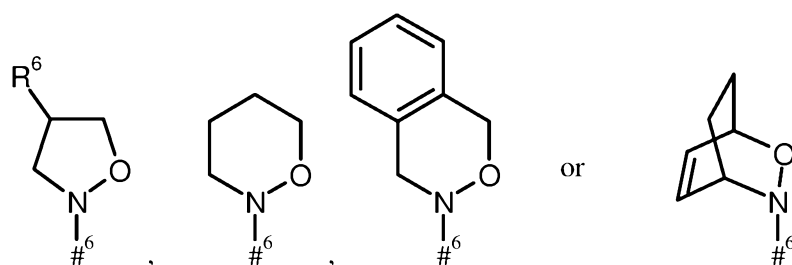
10

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,
15 optionally substituted heterocycle of the formula



in which

#⁶ marks the linkage site with the carbonyl group,

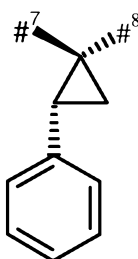
5 R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

10 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

15 #⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or
20 adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

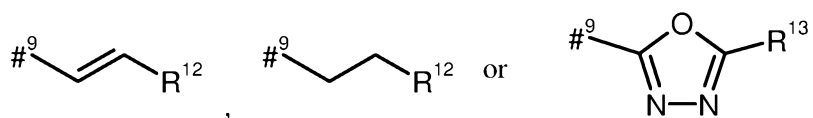
or

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 to $-\text{CHCH}_2\text{phenyl}$,

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

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

R^{35} is methyl or hydroxy,

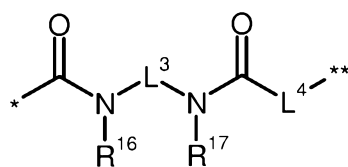
and also their salts, solvates and solvates of the salts.

9. Compounds of the formula (XXXa) according to either of Claims 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 ,

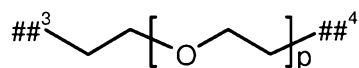
5 L^3 is a bond,

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



10

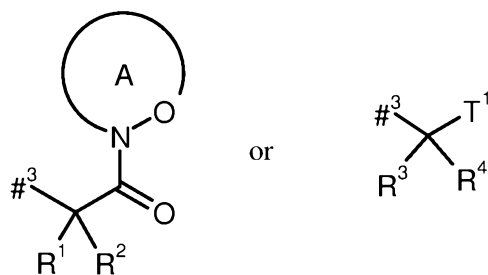
where

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,

15 D is a group of the formula



where

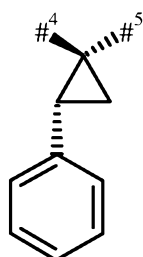
$#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl or 1*H*-indol-3-ylmethyl,

or

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

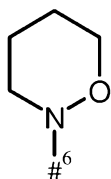


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

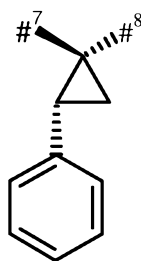
#⁶ marks the linkage site with the carbonyl group,

15 R^3 is hydrogen,

R^4 is benzyl or 1*H*-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

5 T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R⁷ is hydrogen,

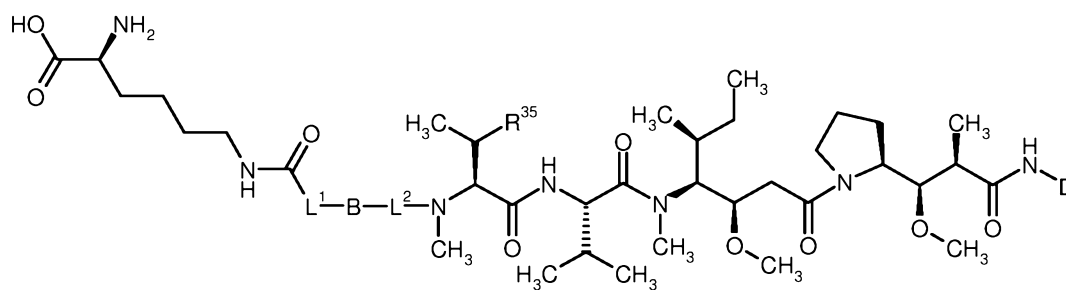
R⁸ is hydrogen,

R⁹ is hydrogen,

10 R³⁵ is methyl,

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

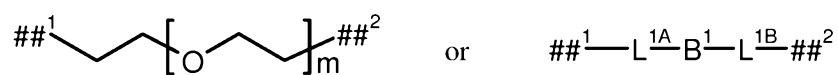
10. Compounds of the formula (XXXI)



(XXXI),

15 in which

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl, a group of the formula



where

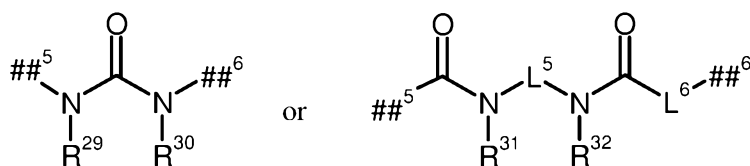
m is a number from 2 to 6,

##¹ marks the linkage site with the group G,

5 ##² marks the linkage site with the group B,

L^{1A} is linear (C₂-C₁₀)-alkanediyl,

B¹ is a group of the formula



in which

10 ##⁵ marks the linkage site with the group L^{1A},

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

L⁵ is a bond or (C₂-C₄)-alkanediyl,

L⁶ is a bond,

R²⁹ is hydrogen or (C₁-C₄)-alkyl,

15 R³⁰ is hydrogen or (C₁-C₄)-alkyl,

or

R²⁹ and R³⁰ together with the atoms to which they are bonded form a 5-
or 6-membered heterocycle,

R³¹ is hydrogen or (C₁-C₄)-alkyl,

20 R³² is hydrogen or (C₁-C₄)-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,

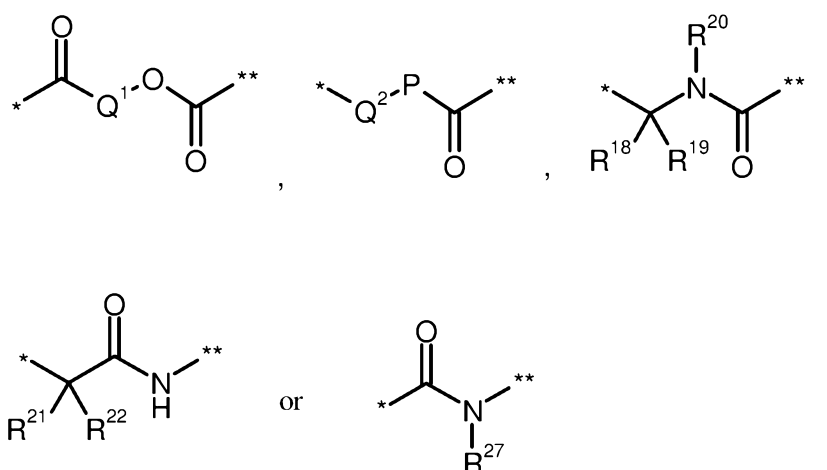
and

5 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

10 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



15 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,

20 Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

5 or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

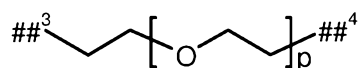
R²² is hydrogen or (C₁-C₄)-alkyl,

10 or

R²¹ and R²² together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R²⁷ is hydrogen or (C₁-C₄)-alkyl,

L² is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



15

where

p is a number from 2 to 6,

##³ marks the linkage site with the group B,

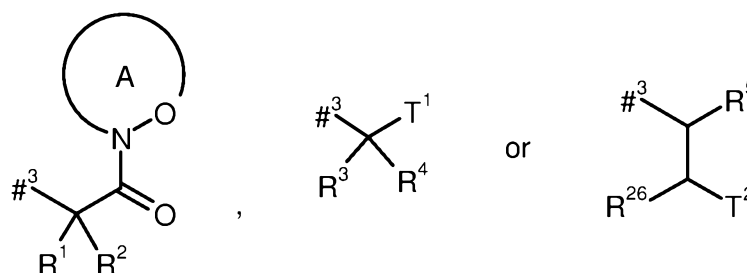
##⁴ marks the linkage site with the nitrogen atom,

20 where (C₂-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

D is a group of the formula



5

in which

#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen or methyl,

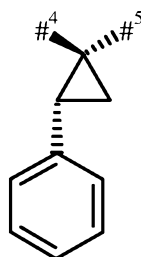
R² is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

10

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

15

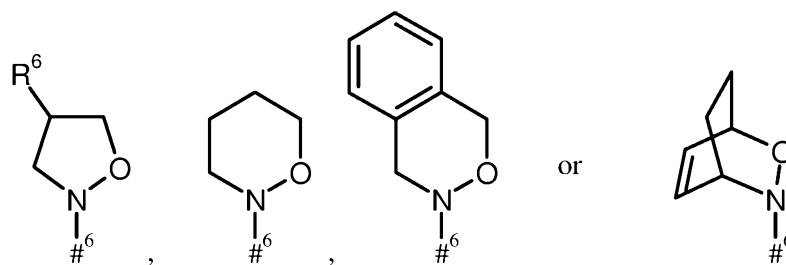


in which

#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,

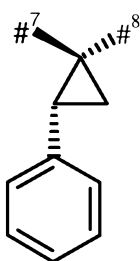
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen or methyl,

R⁴ is isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1*H*-imidazol-4-ylmethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

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

R^8 is hydrogen or methyl,

5 R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

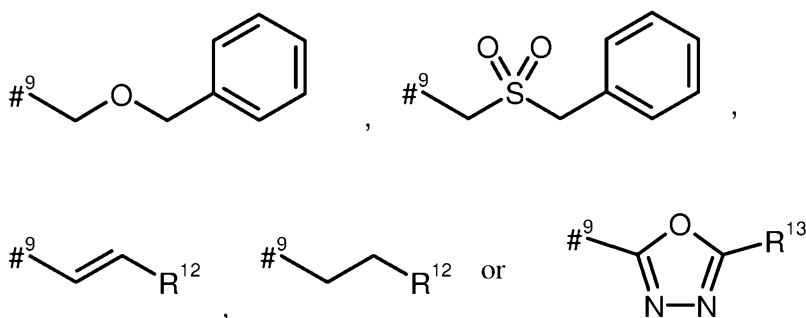
or

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,

10 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



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

15 R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $\text{-S(O)}_2\text{OH}$,

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

R^{26} is hydrogen or hydroxy,

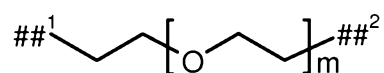
20 T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

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 (C₂-C₆)-alkanediyl or a group of the formula



where

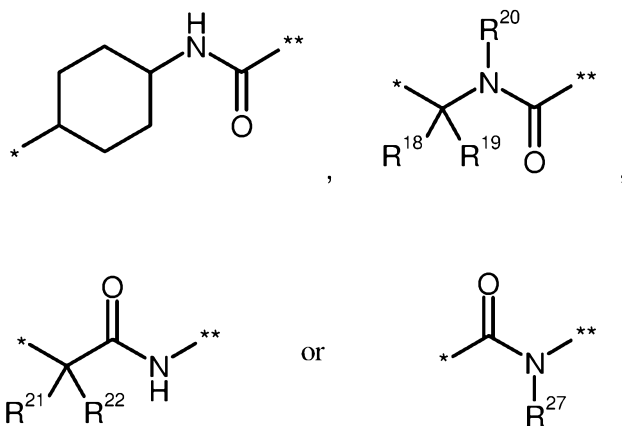
5 m is a number 2 or 3,

##^1 marks the linkage site with the group G,

##^2 marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



10

where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

R^{18} is hydrogen,

15 R^{19} is methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

R^{20} is hydrogen or (C₁-C₄)-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,

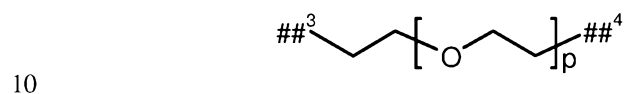
R^{22} is hydrogen or methyl,

5 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,

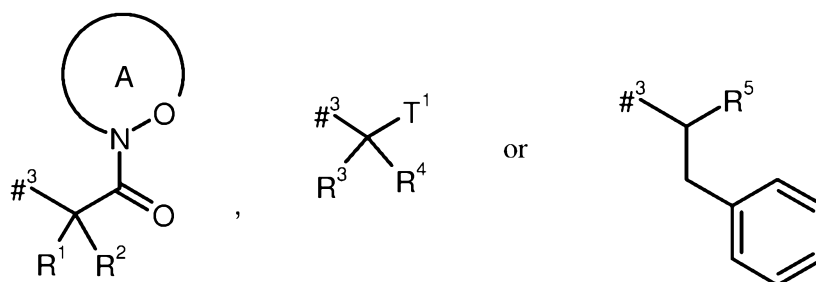
$##^4$ marks the linkage site with the nitrogen atom,

15 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,

20 D is a group of the formula



in which

#³ marks the linkage site with the nitrogen atom,

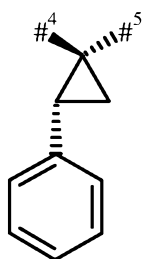
R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

5

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



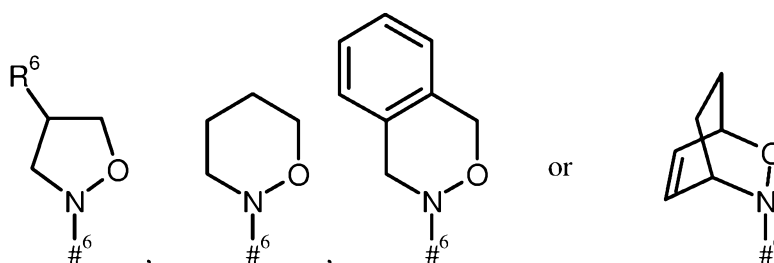
10

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



15

in which

#⁶ marks the linkage site with the carbonyl group,

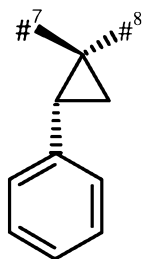
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

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

or

5 R^3 and R^4 together with the carbon atoms to which they are bonded form a (1*S*,2*R*)-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 ,

10 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,

15 R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

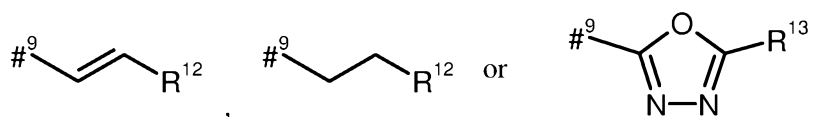
or

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

20 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 $-\text{CHCH}_2\text{phenyl}$,

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula $-\text{S}(\text{O})_2\text{OH}$,

R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R³⁵ is methyl or hydroxy,

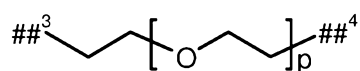
and also their salts, solvates and solvates of the salts.

10 12. Compounds of the formula (XXXI) according to either of Claims 10 or 11, in which

L¹ is a bond,

B is a bond,

L² is linear (C₂-C₆)-alkanediyl or is a group of the formula



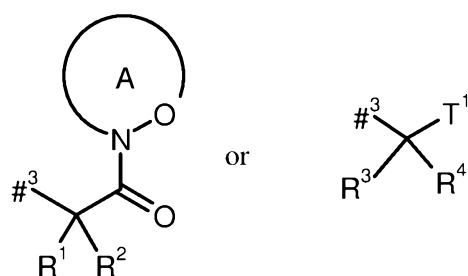
15 where

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

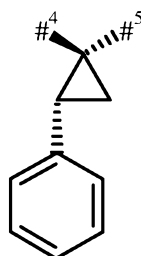
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

5 R² is benzyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



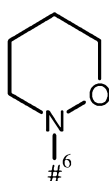
10

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



15

in which

#⁶ marks the linkage site with the carbonyl group,

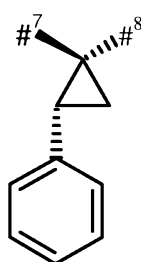
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl or 1*H*-indol-3-ylmethyl,

5 or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

10 #⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷ or -C(=O)-NR⁸R⁹,

in which

R⁷ is hydrogen,

15 R⁸ is hydrogen,

R⁹ is hydrogen,

R³⁵ 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:

20 *N*-[6-(3-{[(2*R*)-2-amino-2-carboxyethyl]sulphonyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-*N*-methyl-L-valyl-*N*-[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*)-1-carboxy-2-(1*H*-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,

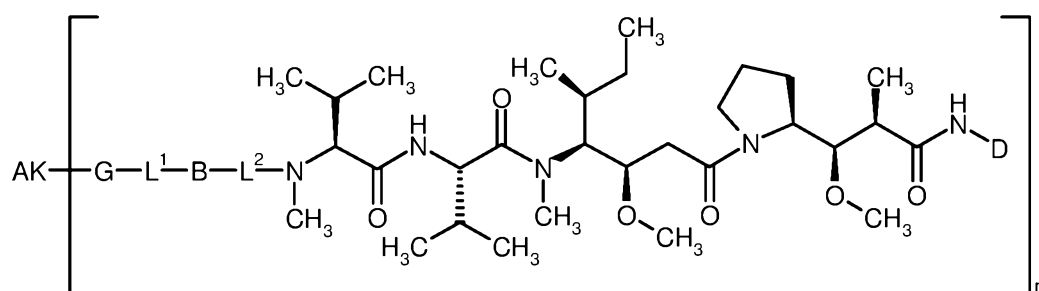
N-[6-(3-[(*2R*)-2-amino-2-carboxyethyl]sulphonyl)-2,5-dioxopyrrolidin-1-yl]hexyl]-*N*-methyl-L-valyl-*N*-[(*3R,4S,5S*)-1-{(*2S*)-2-[(*1R,2R*)-3-[(*2S*)-3-(*1H*-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide,

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.

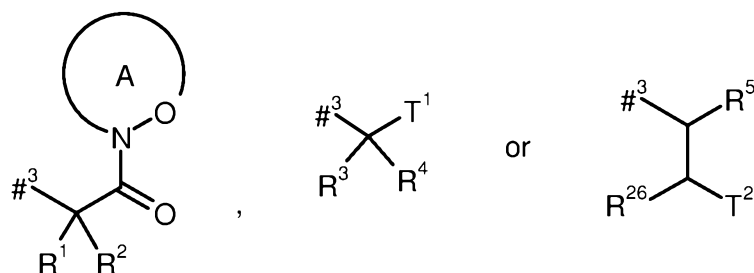
the group §-G-L¹-B-L²-§§ is a linker,

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

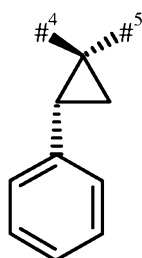
5 #³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

10 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

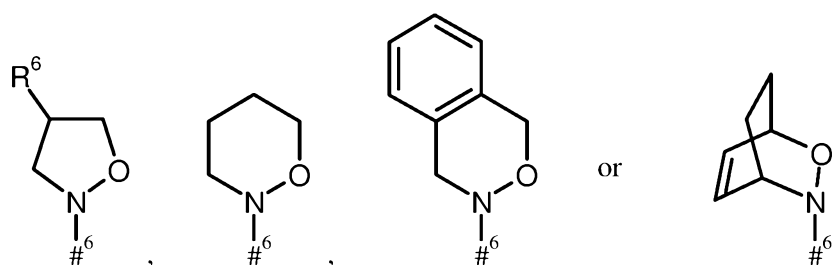


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

15 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,

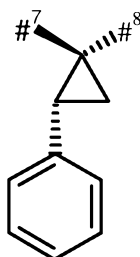
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen,

R⁴ 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

15 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰
or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

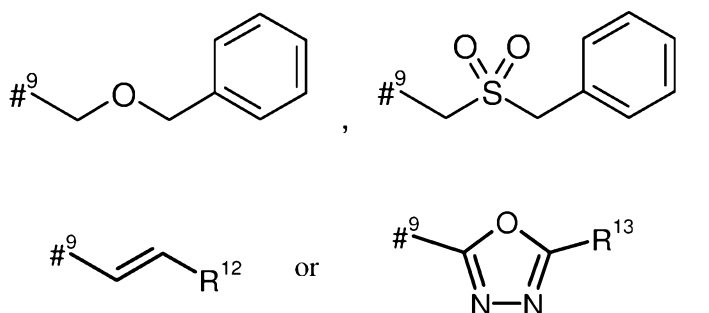
or

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

5 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



10 in which

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

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

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

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-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),

20 in which

n is a number from 1 to 50,

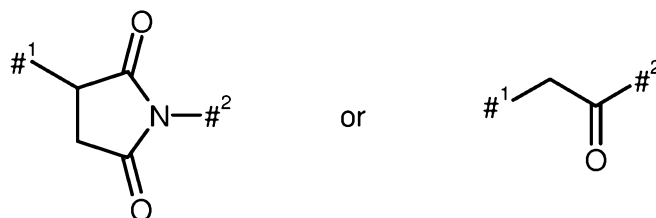
AK is AK_1 or AK_2

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,

5 G when $AK = AK_1$, is a group of the formula



where

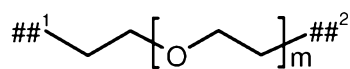
$\#^1$ marks the linkage site with the sulphur atom of the binder,

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

10 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

15 m is a number from 2 to 6,

$##^1$ marks the linkage site with the group G,

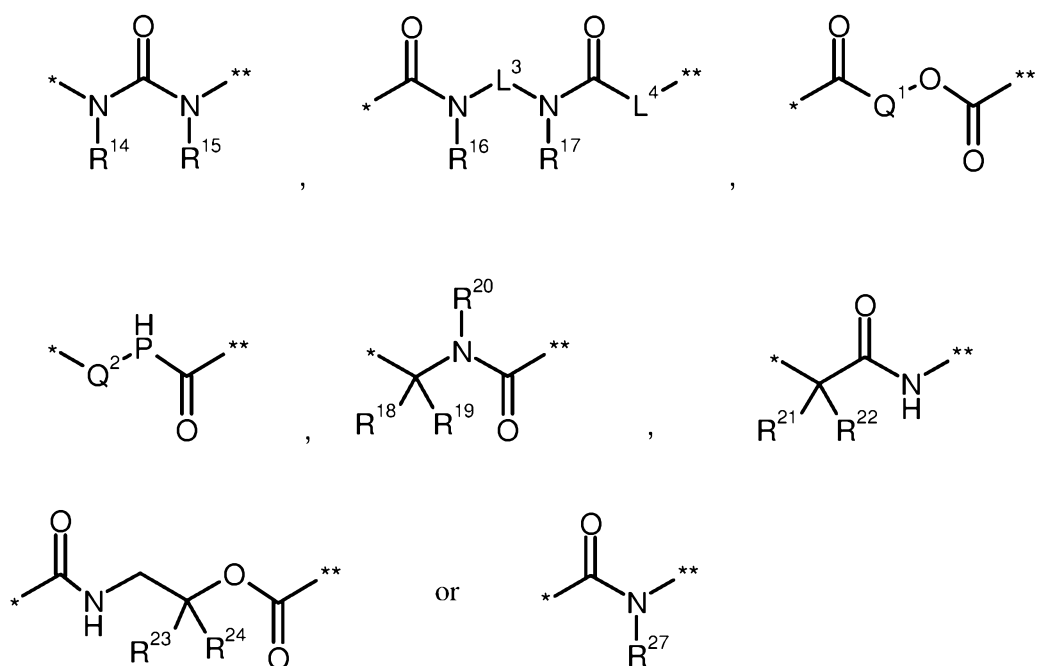
$##^2$ marks the linkage site with the group B,

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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



5

where

* marks the linkage site with L¹,

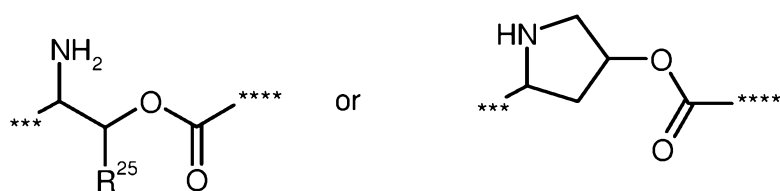
** marks the linkage site with L²,

P is O or NH,

10

L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is hydrogen or methyl,

Q¹ is a 4- to 7-membered heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

5 R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

10 R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

15 R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

R¹⁹ is hydrogen or the side group of a natural α -amino acid or of its homologues or isomers,

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

or

20 R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or (C₁-C₄)-alkyl,

R²² is hydrogen or (C₁-C₄)-alkyl,

or

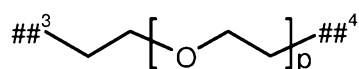
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

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

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

5 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,

10 $##^3$ 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

15 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),

20 in which

n is a number from 1 to 50,

AK is AK_1 or AK_2

where

AK₁ is an antibody or an antigen-binding antibody fragment and are bonded via a sulphur atom to the group G,

AK₂ is an antibody or an antigen-binding antibody fragment and are bonded via a nitrogen atom to the group G,

5 G, L¹, B, L² and D have the definitions indicated in the Claims 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,

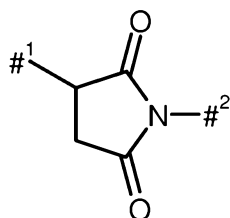
10 AK is AK₁ or AK₂

where

AK₁ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

15 AK₂ is an antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when AK = AK₁, is a group of the formula



20 in which

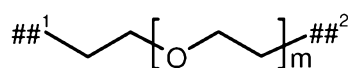
#¹ marks the linkage site with the cysteine residue of the binder,

#² marks the linkage site with the group L¹,

or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl or is a group of the formula



where

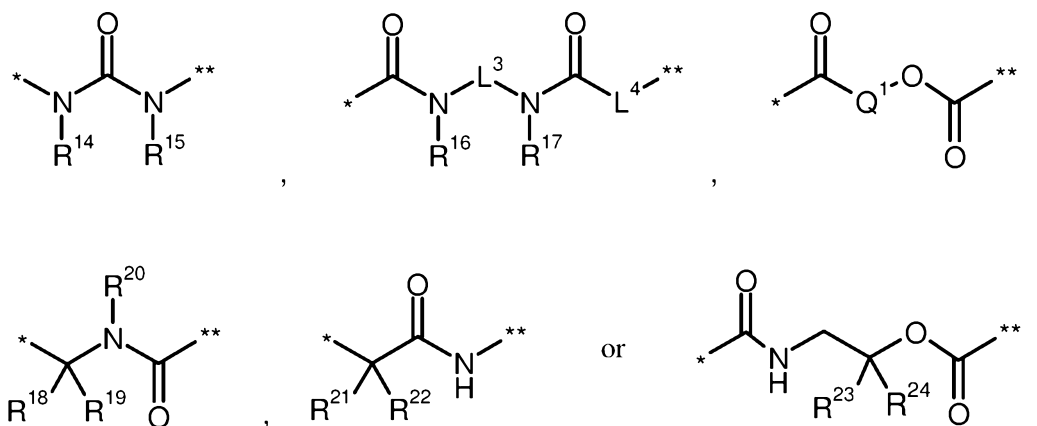
m is a number from 2 to 6,

5 ##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



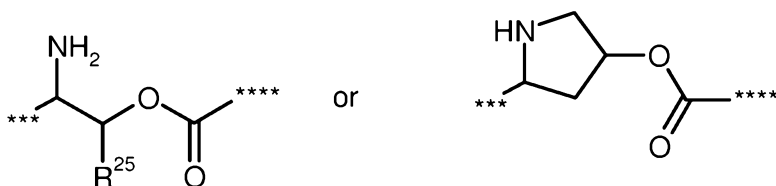
10 where

* marks the linkage site with L^1 ,

** marks the linkage site with L^2 ,

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

L⁴ is a bond or a group of the formula



15

in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L²,

R²⁵ is methyl,

Q¹ is a 4- to 6-membered carbocycle or piperidine-1,4-diyl,

5 R¹⁴ is hydrogen,

R¹⁵ is hydrogen,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

or

10 R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a piperazinyl ring,

R¹⁸ is hydrogen,

R¹⁹ is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

15 R²⁰ is hydrogen or methyl,

or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidinyl ring,

R²¹ is hydrogen or methyl,

20 R²² is hydrogen or methyl,

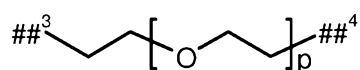
or

R²¹ and R²² together with the atoms to which they are bonded form a cyclopropyl ring,

R²³ is methyl,

25 R²⁴ is hydrogen or methyl,

L^2 is linear (C₂-C₆)-alkanediyl or is a group of the formula



where

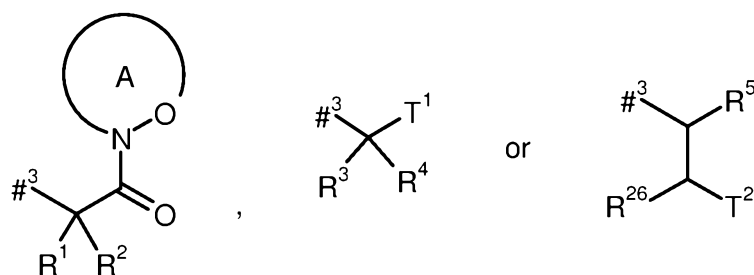
p is a number from 2 to 6,

5 $\#^3$ marks the linkage site with the group B,

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

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

D is a group of the formula



10 where

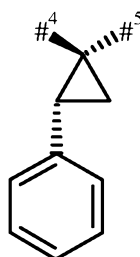
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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



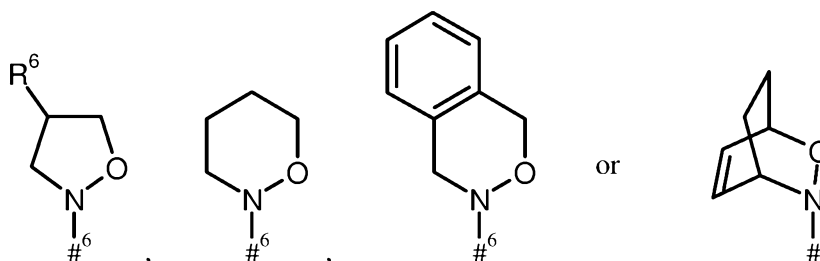
in which

#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

5



in which

#⁶ marks the linkage site with the carbonyl group,

R⁶ is hydrogen, hydroxy or benzyloxy,

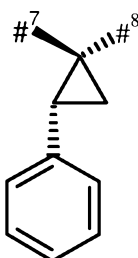
10

R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



15

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

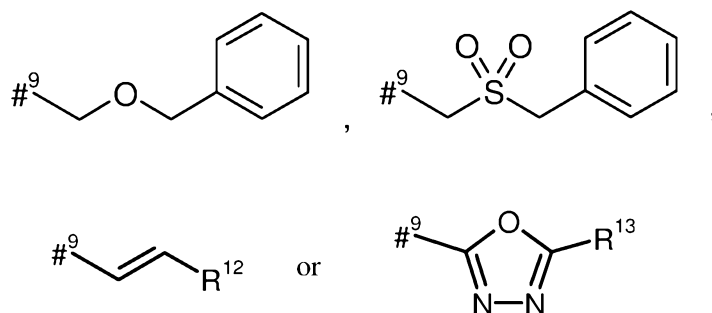
or

R⁸ and R⁹ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen, methyl or a group of the formula



in which

#⁹ marks the linkage site with -CHC(R²⁶)-T²,

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula -S(O)₂OH,

R¹³ is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R²⁶ is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-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

5 n is a number from 1 to 10,

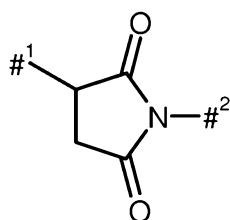
AK is AK_1 or AK_2

where

10 AK_1 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 sulphur atom of a cysteine residue of the binder to the group G,

15 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,

20 G when $AK = AK_1$, is a group of the formula



in which

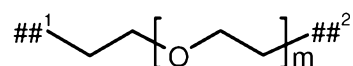
$\#^1$ marks the linkage site with the cysteine residue of the binder,

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

25 or

when AK = AK₂, is carbonyl,

L¹ is a bond, linear (C₂-C₆)-alkanediyl or is a group of the formula



where

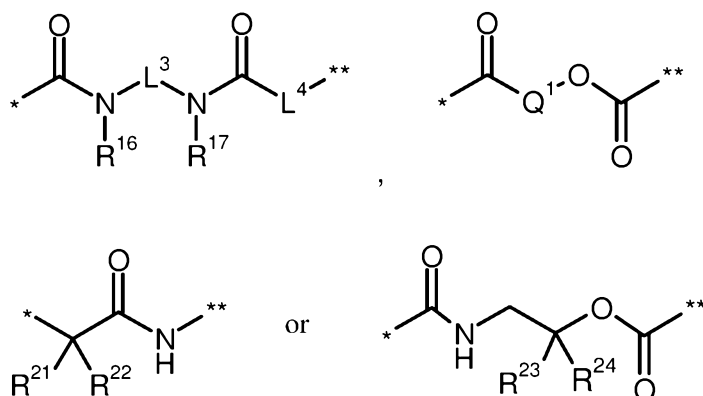
5 m is a number 2 or 3,

##¹ marks the linkage site with the group G,

##² marks the linkage site with the group B,

where (C₂-C₆)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



10

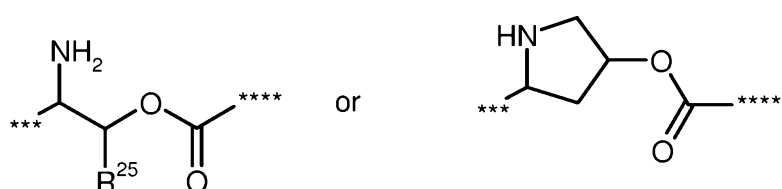
where

* marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

15 L⁴ 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,

5 Q^1 is piperidine-1,4-diyl,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

10 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

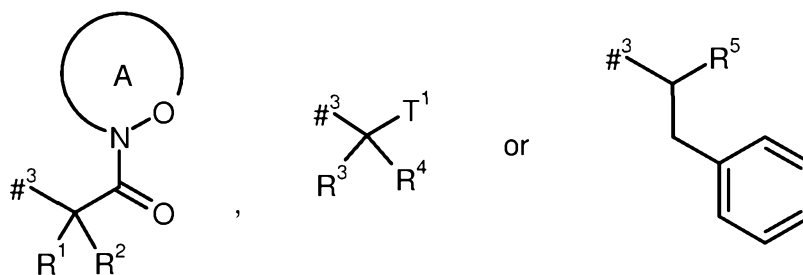
15 R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

R^{23} is methyl,

R^{24} is hydrogen,

L^2 is linear (C_2 - C_6)-alkanediyl,

D is a group of the formula



20

where

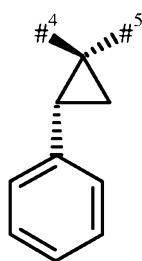
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

5 R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula

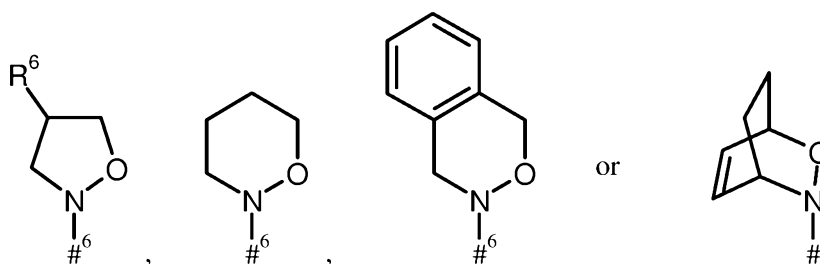


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

10 #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

15 #⁶ marks the linkage site with the carbonyl group,

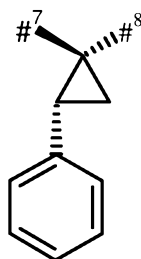
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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



5

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

10

R^7 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or adamantylmethyl,

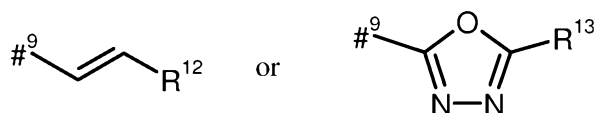
R^8 is hydrogen or methyl,

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,

15

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 $-S(O)_2OH$,

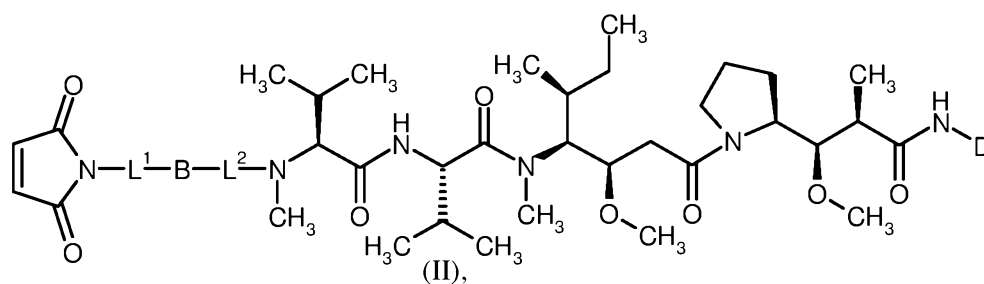
20

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,
5 of the general formula (I), characterized in that a solution of the binder in a buffer

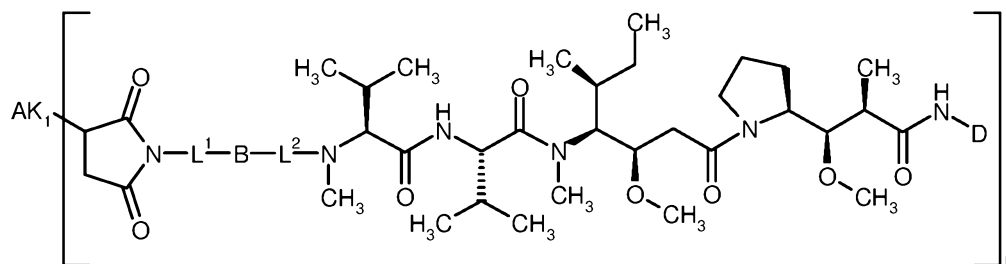
[A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (II)



10

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)

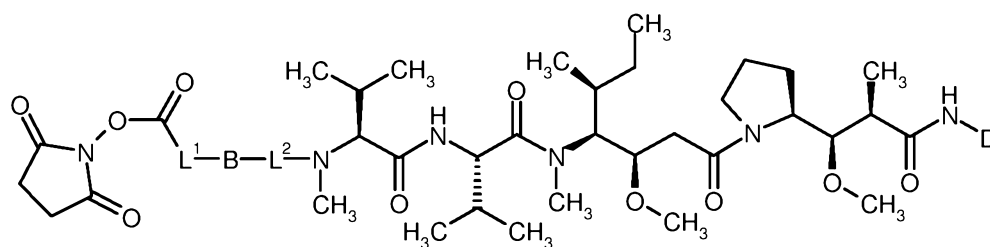


15

in which n, AK_1 , D, L^1 , B and L^2 each have the definitions indicated in Claims 1 to 5,

or

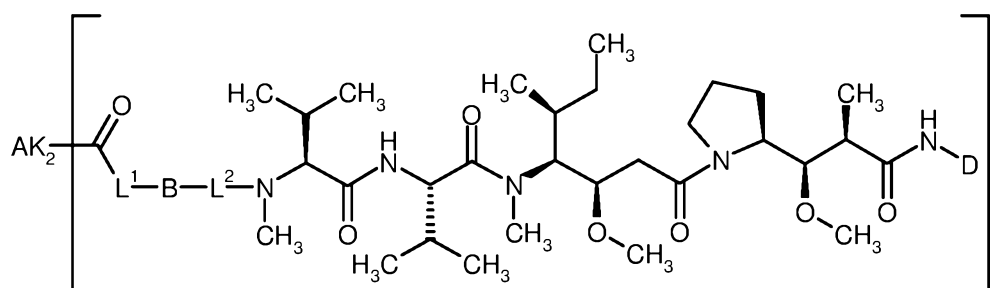
[B] is reacted with a compound of the formula (III)



(III),

in which D, L¹, B and L² each have the definitions indicated in Claims 1 to 5,

5 to give a compound of the formula (I-B)

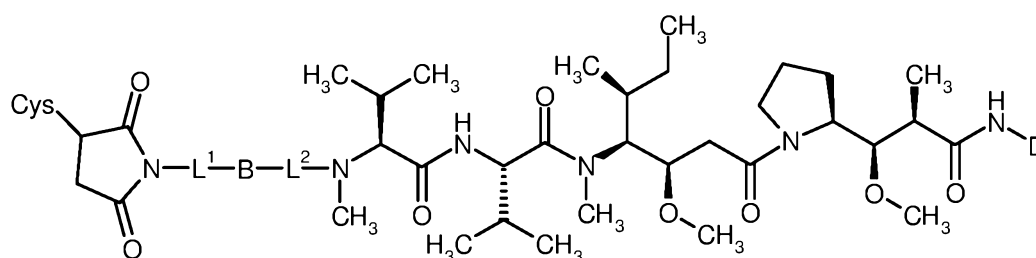


(I-B),

in which n, AK₂, D, L¹, B and L² each have the definitions indicated in
10 Claims 1 to 5.

20. Compounds prepared by the process according to Claim 19 or 50, where AK₁ and AK₂ is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10 or D02-6, and also their salts,
15 solvates and solvates of the salts.

21. Compounds of the formula (XXX)

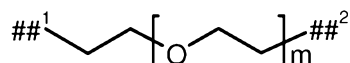


(XXX),

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,

L¹ is a bond, linear (C₁-C₁₀)-alkanediyl or is a group of the formula



5

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,

10

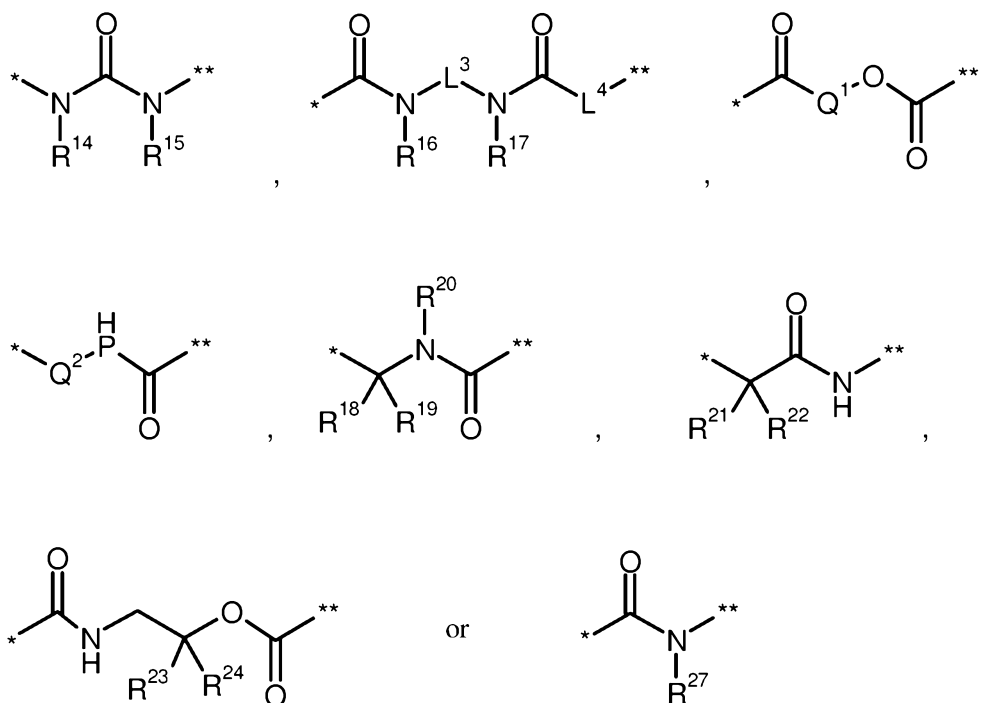
where (C₁-C₁₀)-alkandiyl may be substituted by 1 to 4 methyl substituents,

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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

15

B is a bond or a group of the formula



where

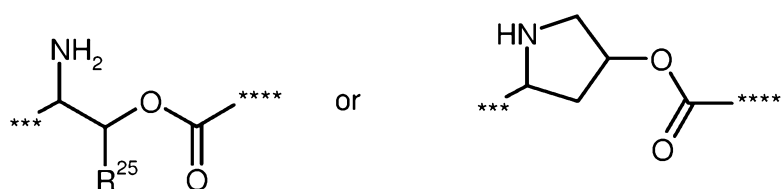
* marks the linkage site with L¹,

** marks the linkage site with L²,

P is O or NH,

5 L³ is a bond or (C₂-C₄)-alkanediyl,

L⁴ is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

10 **** marks the linkage site with L²,

R²⁵ is hydrogen or methyl,

Q¹ is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

Q² is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

R¹⁴ is hydrogen or (C₁-C₄)-alkyl,

15 R¹⁵ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁴ and R¹⁵ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁶ is hydrogen or (C₁-C₄)-alkyl,

20 R¹⁷ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R¹⁸ is hydrogen or (C₁-C₄)-alkyl,

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

R²⁰ is hydrogen or (C₁-C₄)-alkyl,

or

R¹⁹ and R²⁰ together with the atoms to which they are bonded form a pyrrolidiny ring,

10 R²¹ is hydrogen or (C₁-C₄)-alkyl,

R²² is hydrogen or (C₁-C₄)-alkyl,

or

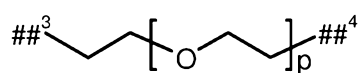
R²¹ and R²² together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

15 R^{23} is (C₁-C₄)-alkyl,

R²⁴ is hydrogen or (C₁-C₄)-alkyl,

R²⁷ is hydrogen or (C₁-C₄)-alkyl,

L^2 is linear (C₂-C₁₀)-alkanediyl or is a group of the formula



20 where

p is a number from 2 to 6,

##³ marks the linkage site with the group B,

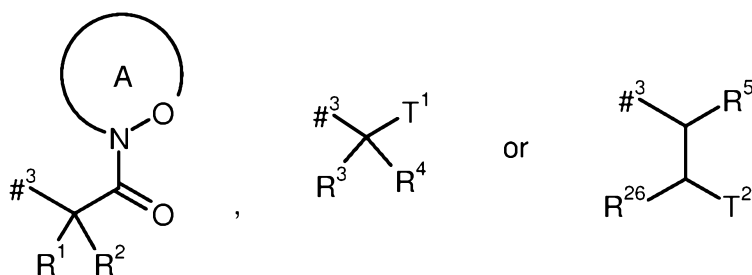
##⁴ marks the linkage site with the nitrogen atom,

where (C₂-C₁₀)-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 (C₃-C₆)-cycloalkyl ring or a phenyl ring,

5 D is a group of the formula



in which

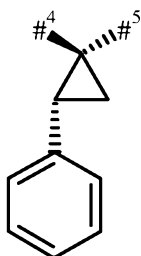
#³ marks the linkage site with the nitrogen atom,

R¹ is hydrogen,

10 R² is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R¹ and R² together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



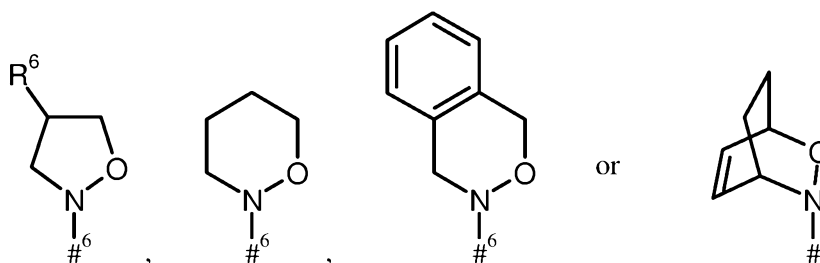
15

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,

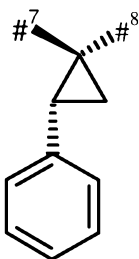
R⁶ is hydrogen, hydroxy or benzyloxy,

5 R³ is hydrogen,

R⁴ is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-2-phenylcyclopropane-1,1-diyl group of the formula



10

in which

#⁷ marks the linkage site with the adjacent nitrogen atom,

#⁸ marks the linkage site with the group T¹,

15 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl or adamantylmethyl,

R⁸ is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

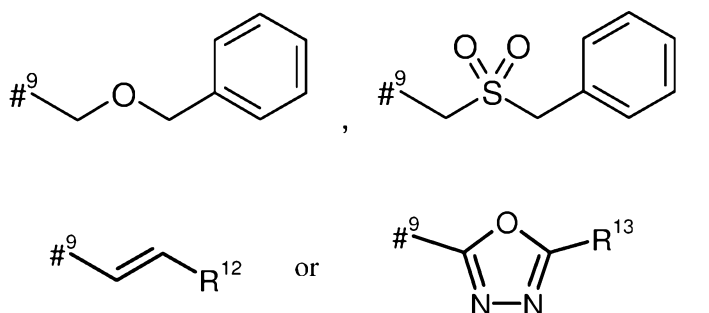
or

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

5 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



10 in which

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

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

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

R^{26} is hydrogen or hydroxy,

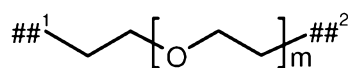
T^2 is phenyl, benzyl, 1*H*-indol-3-yl or 1*H*-indol-3-ylmethyl,

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

22. Compounds of the formula (XXX) according to Claim 21, in which

20 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 ($\text{C}_2\text{-C}_6$)-alkanediyl or is a group of the formula



where

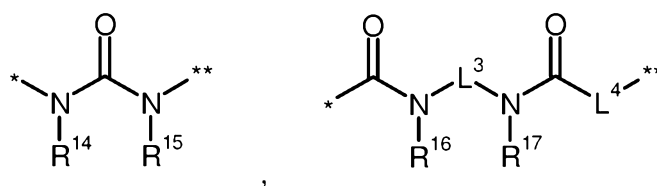
m is a number from 2 to 6,

##^1 marks the linkage site with the group G,

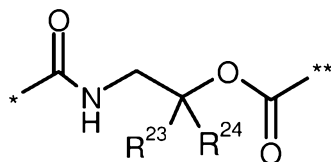
5 ##^2 marks the linkage site with the group B,

where (C₂-C₆)-alkandiyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



or



where

10 * marks the linkage site with L¹,

** marks the linkage site with L²,

L³ is a bond or ethane-1,2-diyl,

L⁴ is a bond,

R¹⁴ is hydrogen,

15 R¹⁵ is hydrogen,

R¹⁶ is hydrogen or methyl,

R¹⁷ is hydrogen or methyl,

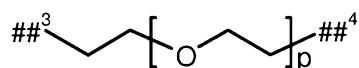
or

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,

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



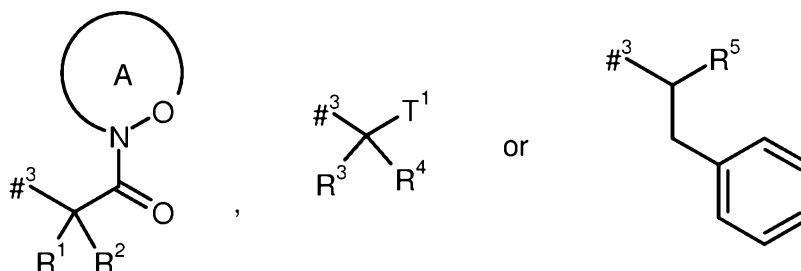
where

p is a number 2 or 3,

$##^3$ marks the linkage site with the group B,

10 $##^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



in which

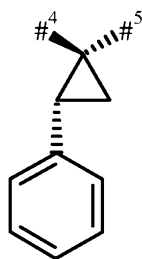
$##^3$ marks the linkage site with the nitrogen atom,

15 R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

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

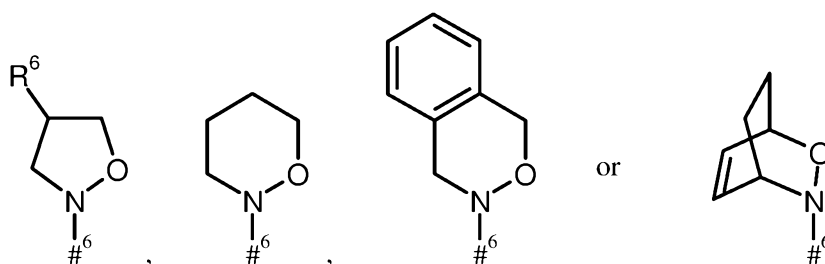


in which

#⁴ marks the linkage site with the adjacent nitrogen atom,

#⁵ marks the linkage site with the carbonyl group,

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



in which

10 #⁶ marks the linkage site with the carbonyl group,

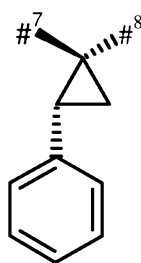
R⁶ is hydrogen, hydroxy or benzyloxy,

R³ is hydrogen,

R⁴ is benzyl, 1-phenylethyl or 1*H*-indol-3-ylmethyl,

or

15 R³ and R⁴ together with the carbon atom to which they are bonded form a (1*S*,2*R*)-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 T¹,

5 T¹ is a group of the formula -C(=O)-OR⁷, -C(=O)-NR⁸R⁹, -C(=O)-NH-NH-R¹⁰ or -CH₂-O-R¹¹,

in which

R⁷ is hydrogen, methyl, ethyl, *n*-propyl, benzyl or adamantylmethyl,

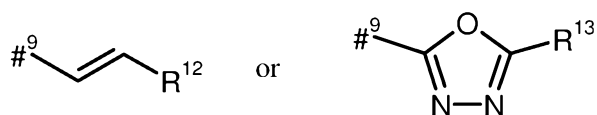
R⁸ is hydrogen or methyl,

10 R⁹ is hydrogen, methyl, ethyl, *n*-propyl or benzyl,

R¹⁰ is benzoyl,

R¹¹ is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R⁵ is hydrogen or a group of the formula



15

in which

#⁹ marks the linkage site with -CHC(R²⁶)phenyl,

R¹² is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula -S(O)₂OH,

20 R¹³ 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 – 6, 14 – 18 where the binder binds to a cancer target molecule.
24. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23, where the binder
5 binds to an extracellular target molecule.
25. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 24, where the binder binds to an extracellular cancer target molecule.
26. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 25, where the target molecule, extracellular target molecule, cancer target molecule or extracellular
10 cancer target molecule is a protein.
27. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 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 – 6, 14 – 18 or 23 – 27, where the
15 binder is a binder protein.
29. Binder-drug conjugate according to any of Claims 1 – 6, 14, 15, 20 or 23 – 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 – 6, 14 – 18 or 23 – 29, where the
20 antibody is a monoclonal antibody.
31. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 30, where the antibody is a human, humanized or chimeric antibody.
32. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 31, where the antibody is an intact or a modified intact antibody.
- 25 33. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 32, where the antibody is an antibody of the IgG class.
34. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 16, 20 or 23 – 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)
30 and carboanhydrase IX (CA IX; NP_001207.2).

35. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 16, 20 or 23 – 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).
- 5 36. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 16, 20 or 23 – 35, where the antibody binds to C4.4a.
37. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 36, where the antibody binds to S1 domains (amino acid position 1-85 of SEQ ID NO: 1) of C4.4a.
- 10 38. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 37, where the antibody binds specifically to C4.4a.
39. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18 or 23 – 38, where the binder is an anti-C4.4a antibody or antigen-binding antibody fragment which competes with antibody M31-B01 and/or with the antibody M20-D02-S-A for binding to C4.4a.
- 15 40. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 16, 20 or 23 – 39, 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 and 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 comprises 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
- 20
- 25
- 30

- 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 the variable light chain represented by the sequences SEQ ID NO: 68-70 (B01-7),
- 5 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
- 10 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
- 15 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
- 20 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).
41. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18, 20 or 23 – 40, where the C4.4a antibody or antigen-binding antibody fragment is selected from the group consisting
- 25 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
- 30 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
- 35 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).
42. Binder-drug conjugate according to any of Claims 1 – 6, 14 – 18, 20 or 23 – 41, where the C4.4a antibody or antigen-binding antibody fragment 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),

5 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

10 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).

43. Binder-drug conjugate or a compound according to any of Claims 1 – 18 or 20 – 42 for the treatment and/or prophylaxis of illnesses.

15 44. Binder-drug conjugate or a compound according to any of Claims 1 – 18 or 20 – 42 for use in a method for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases.

45. Binder-drug conjugate or a compound according to any of Claims 1 – 18 or 20 – 42 for producing a medicament for the treatment and/or prophylaxis of hyperproliferative and/or
20 angiogenic diseases.

46. Medicament comprising a binder-drug conjugate or a compound according to any of Claims 1 – 18 or 20 – 42, in combination with an inert, non-toxic, pharmaceutically suitable excipient.

47. Medicament comprising a binder-drug conjugate or a compound according to any of
25 Claims 1 – 18 or 20 – 42, in combination with one or more anti-hyperproliferative, cytostatic or cytotoxic substances.

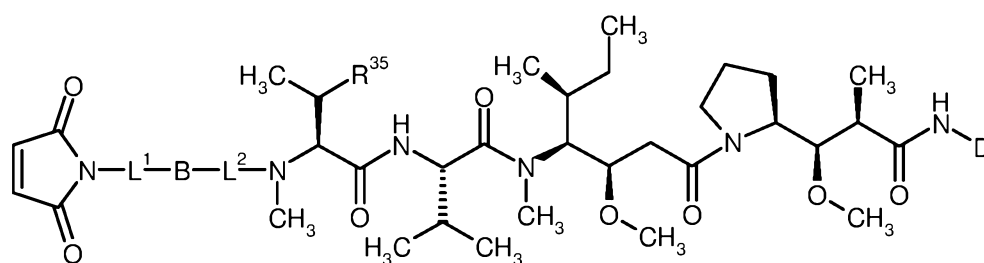
48. Medicament according to Claim 46 – 47 for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases.

49. Method for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic
30 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 – 18 or 20 – 42, or of a medicament as defined in any of Claims 46 to 48.

50. 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

5 [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)

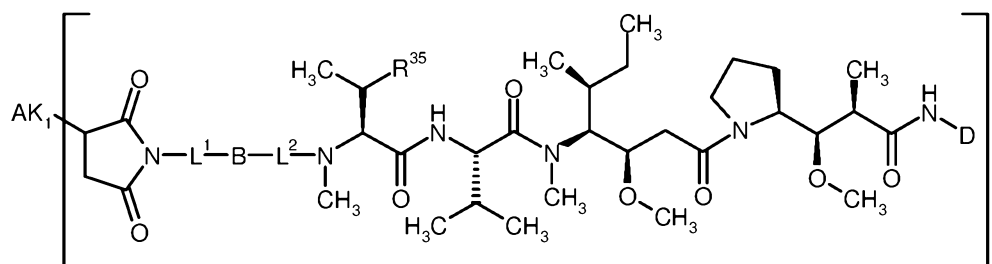


(IIa),

10

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)



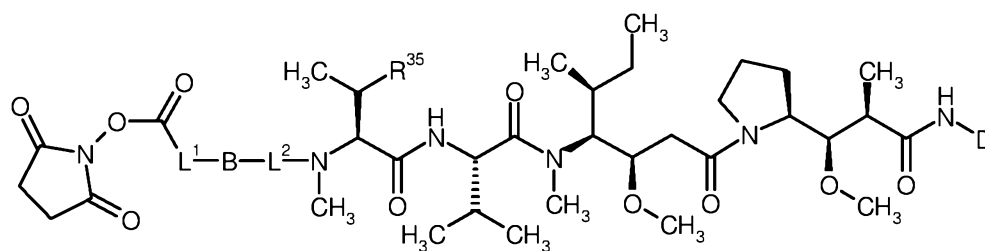
(Ia-A),

15

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

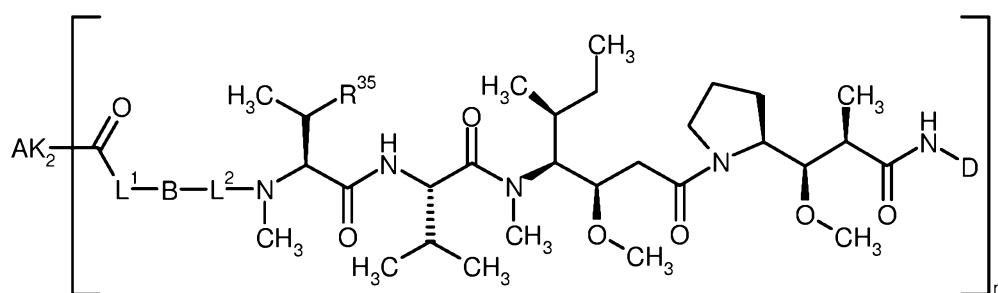
[B] is reacted with a compound of the formula (IIIa)



(IIIa),

in which D, L¹, B, L² and R³⁵ each have the definitions indicated in Claims 1 to 6,

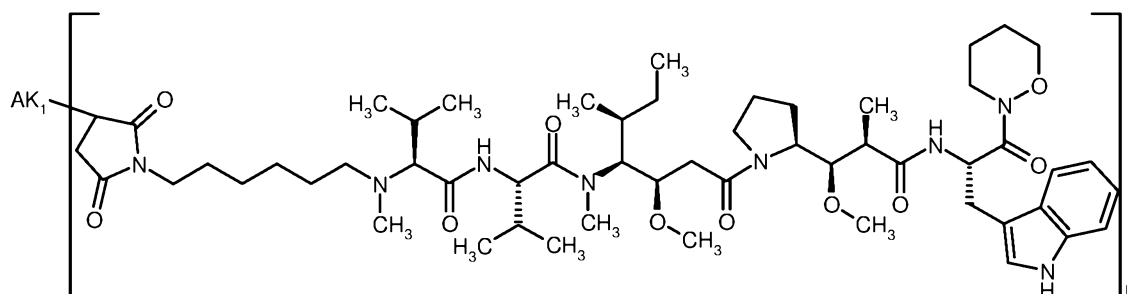
5 to give a compound of the formula (Ia-B)

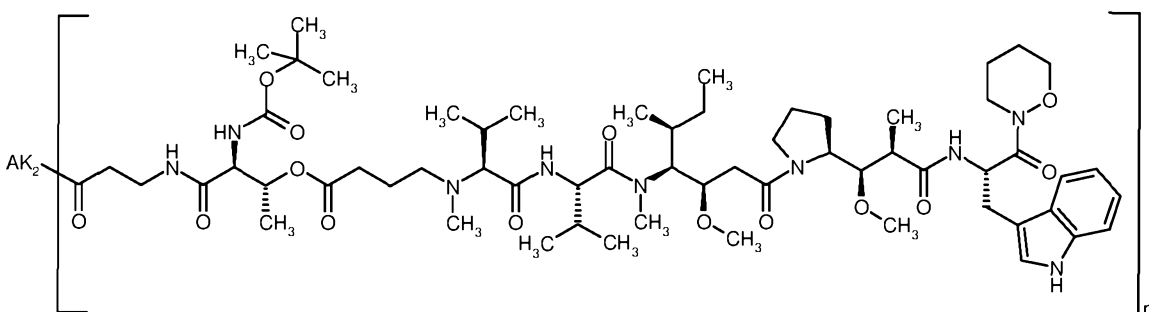
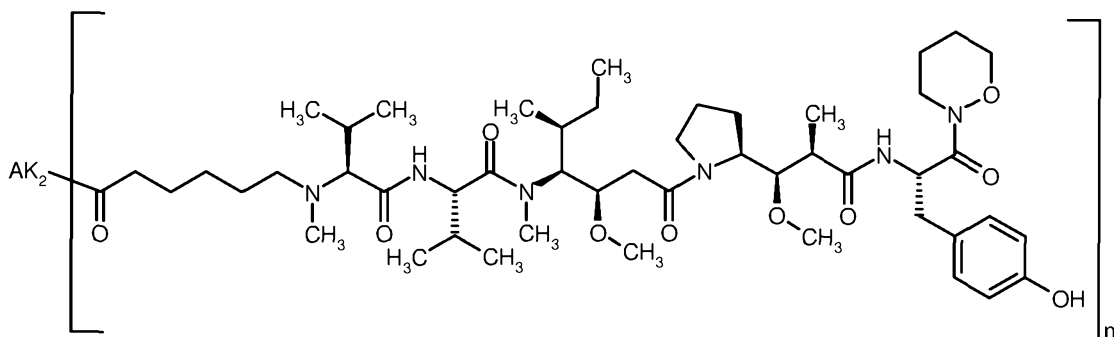
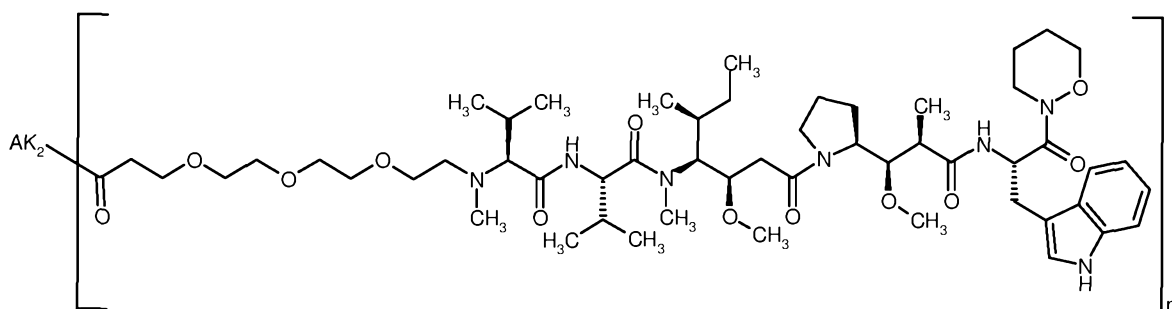
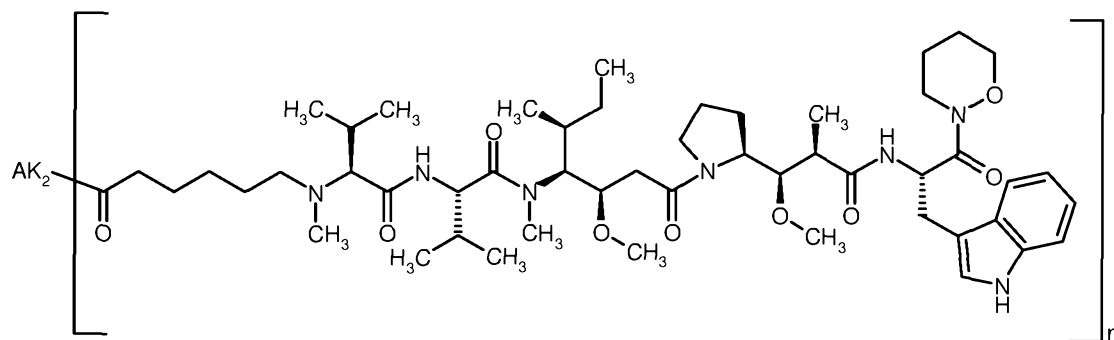


(Ia-B),

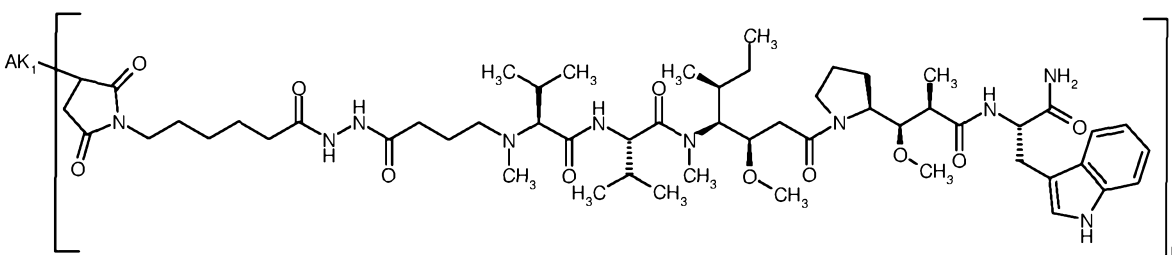
in which n, AK₂, D, L¹, B, L² and R³⁵ each have the definitions indicated in
10 Claims 1 to 6.

51. Binder-drug conjugates selected from the following compounds:





5



where in each case

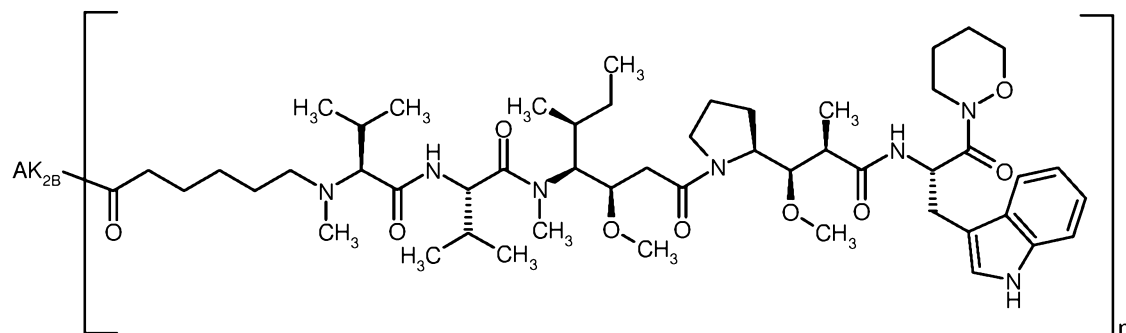
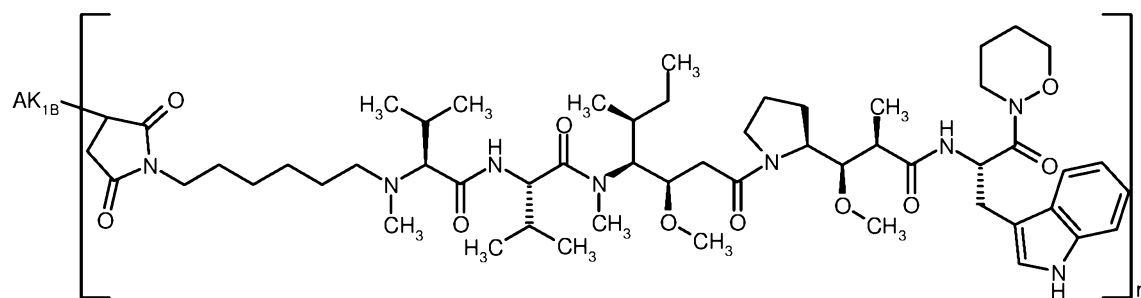
n is a number from 2 to 8, preferably 2 to 5,

and

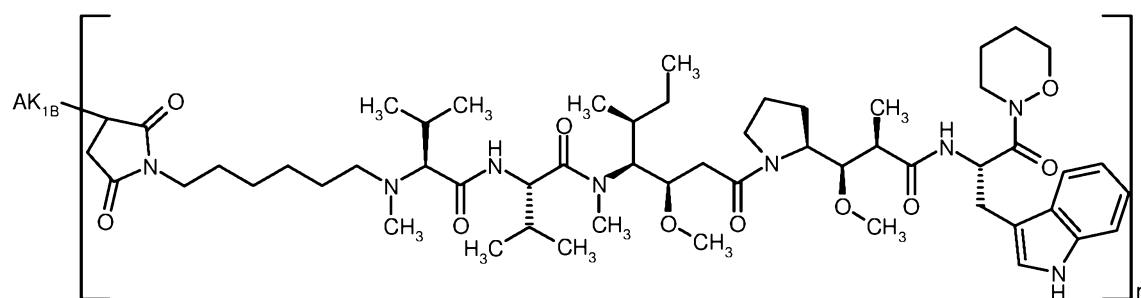
AK₁ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via a cysteine group to the toxophore linker unit, and

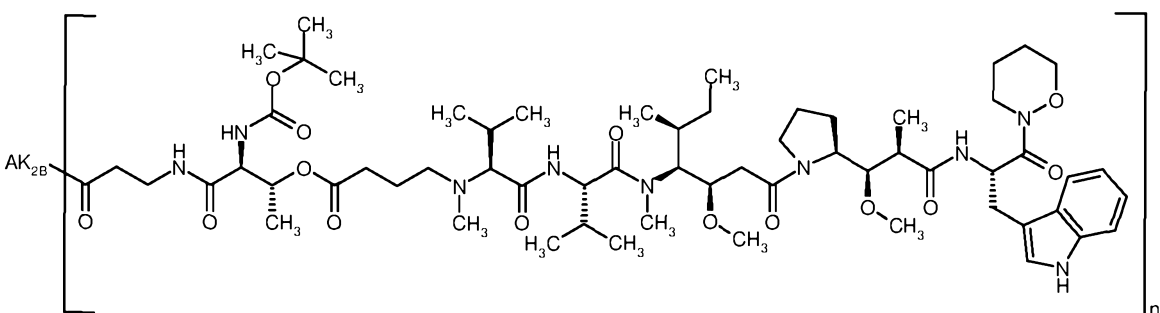
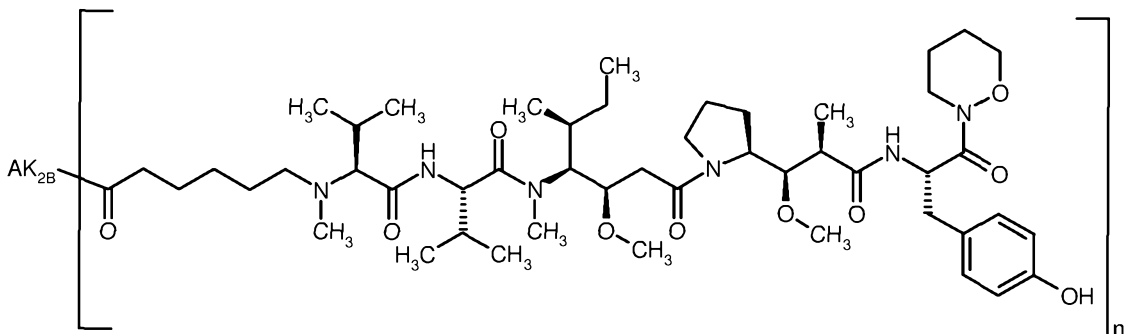
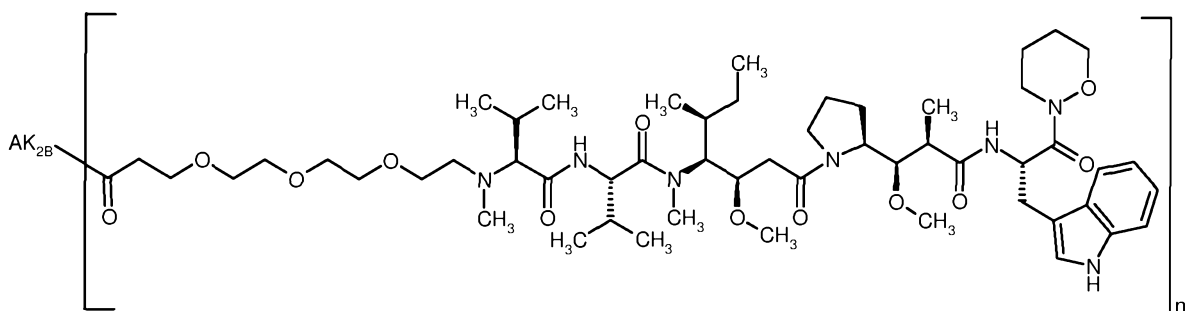
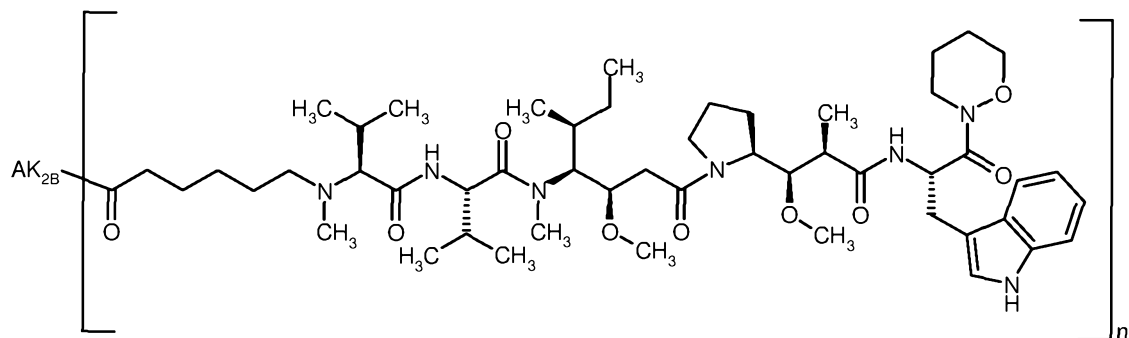
5 AK₂ is a human or humanized antibody or an antigen-binding antibody fragment which binds to C4.4a and is bonded via a lysine group to the toxophore linker unit.

52. Binder-drug conjugates selected from the following compounds:

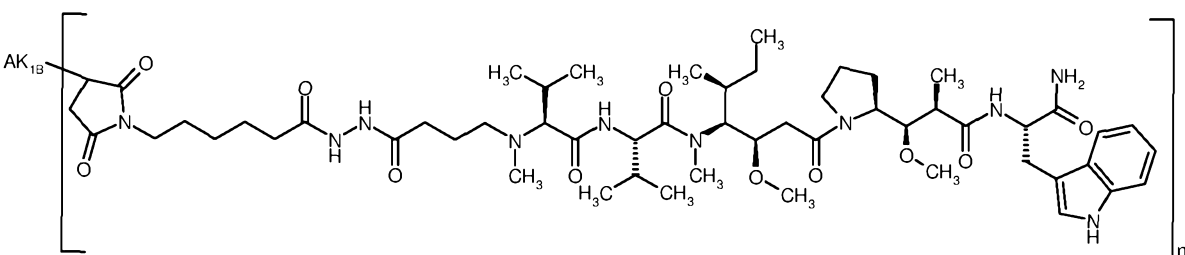


10





5



where in each case

n is a number from 2 to 8, preferably 2 to 5,

and

AK_{1B} and AK_{2B} are B01-3.

PCT-EP2012-057247 Sequence Listing.txt
SEQUENCE LISTING

<110> Seattle Genetics, Inc.

<120> NOVEL BINDER-DRUG CONJUGATES (ADCS) AND USE THEREOF

<130> BHC-00513 / BHC111010

<160> 411

<170> PatentIn version 3.5

<210> 1

<211> 278

<212> PRT

<213> Homo Sapiens

<400> 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
 245 250 255

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

<210> 2
 <211> 293
 <212> PRT
 <213> Mus musculus

<400> 2

Leu Glu Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro
 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

PCT-EP2012-057247 Sequence Listing.txt

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> 3
<211> 346
<212> PRT
<213> Homo Sapiens
<400> 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 Arg Gly Gly Ala Gln Ala Leu Glu
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

PCT-EP2012-057247 Sequence Listing.txt

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> 4
<211> 363
<212> PRT

<213> Mus musculus

<400> 4

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Met Asp Ala Ala Arg Arg Gly Asp Thr Gln Pro Val Met Trp Thr Thr
1      5      10
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
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

```

PCT-EP2012-057247 Sequence Listing.txt

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> 5
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 5

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> 6
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 6

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> 7
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 7

Phe Gly His Tyr Tyr Met Phe Trp Ile
1 5

PCT-EP2012-057247 Sequence Listing.txt

<210> 8
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 8

Phe Ser Ser Asn Tyr Met Ser Trp
 1 5

<210> 9
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 9

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> 10
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 10

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> 11
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 11

Val Ser Ala Ile Ser Gly Ser Gly Tyr Ser Thr His Tyr Ala Asp Ser
 1 5 10 15

Val Lys Gly Arg
 20

PCT-EP2012-057247 Sequence Listing.txt

<210> 12
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 13
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 13

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
 1 5 10

<210> 14
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 14

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
 1 5 10 15

<210> 15
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 15

Ala Arg Leu Pro Tyr Gly Ser Gln Ser Gly Val Asp Tyr
 1 5 10

<210> 16
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 16

Ala Arg Glu Ser Gly Gly Ser Gly Pro Asn Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 17

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 17

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 18

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 18

Ser Gly Ser Ser Ser Asn Val Gly Ser Asn Pro Val Asn
1 5 10

<210> 19

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 19

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 20

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 20

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

PCT-EP2012-057247 Sequence Listing.txt

<210> 21
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 21

Asp Asn Asn Lys Arg Pro Ser
 1 5

<210> 22
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 22

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 23
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 23

Ser Asn Asn Gln Arg Pro Ser
 1 5

<210> 24
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 24

Ser Asn Asn Gln Arg Pro Ser
 1 5

<210> 25
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 25

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
 1 5 10

<210> 26
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 26

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Val
 1 5 10

<210> 27
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 27

Cys Gln Ser Tyr Asp Ser Ser His Val Leu
 1 5 10

<210> 28
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 28

Cys Gln Ser Tyr Asp Arg Ser Leu Arg Gly Trp Val
 1 5 10

<210> 29
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 30
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 31
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 31

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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> 32
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

<210> 33
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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
 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> 34
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 35
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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
115 120

<210> 36
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 36

PCT-EP2012-057247 Sequence Listing.txt

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> 37
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 37
cagtctgtgc tgactcagcc accctcagcg tctgggaccc ctgggcagag ggtcaccatc 60
tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag 120
ctcccaggaa cggcccccaa actcctcatc tatgacaata ataagcgacc ctcagggggtc 180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc 240
cgggtccgagg atgaggctga ttattactgt gcagcatggg atgacaggct gaatgggtccg 300
gtgttcggcg gaggaaccaa gttaaccgtc ctaggtcag 339

<210> 38
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 38
cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60
tcttgttctg gaagcagctc caacgtcggg agtaatcctg taaactggta tcagcagctc 120
ccaggaacgg cccccaaact cctcatctat aggaataatc agcggccctc aggggttcct 180

PCT-EP2012-057247 Sequence Listing.txt

gaccgattct ctgggtccaa gtctggcacc tcagcctccc tggccatcag tggggtccgg	240
tccgaggatg aggctgatta ttactgtgca gcatgggatg acaggctgaa tggttgggtg	300
ttcggcggag gaaccaagct gacggtccta ggtcag	336

<210> 39
 <211> 333
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 39	
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tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag	120
ctcccaggaa cggcccccaa actcctcatc tatagtaata atcagcggcc ctcaggagtc	180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc	240
cgggccgagg atgaggctga ttattactgc cagtcctatg acagcagcca tgttttattc	300
ggcggaggaa ccaagctgac ggtcctaggt cag	333

<210> 40
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 40	
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tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag	120
ctcccaggaa cggcccccaa actcctcatc tatagtaata atcagcggcc ctcaggggctc	180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc	240
cgggccgagg atgaggctga ttattactgc cagtcctatg acagaagcct gcgtgggttg	300
gtgttcggcg gaggaaccaa gctgacggtc ctaggtcag	339

<210> 41
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 41	
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tcctgtgcag cctctggatt caccttcagt aacgcctgga tgagctgggt ccgccaggct	120
ccagggaagg ggctggagtg ggtttcatat attagtagta gtggtagtag catatactac	180
gcagactctg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240

PCT-EP2012-057247 Sequence Listing.txt

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gagagaaggg 300
ttatgggcct ttgactactg gggccagggt accctgggtca ccgtgactag t 351

<210> 42
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 42
gaggtgcagc tggttgagtc tgggggaggc ttggtacagc ctgggggggc 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 actccgata ctactttgac tcctggggcc aggggtaccct ggtcaccgtg 360
actagt 366

<210> 43
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 43
gaggtgcagc tggttgagtc tgggggaggc ttggtacagc ctgggggggc 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 ggccagggtta ccctgggtcac cgtgactagt 360

<210> 44
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 44
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tcctgtgcag cctctggatt caccttcagt agcaactaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtagta gtggtagtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

PCT-EP2012-057247 Sequence Listing.txt

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gagagaatct 300
 ggtgggagcg gaccgaacta ctactacggg atggacgtct ggggccaagg taccctggtc 360
 accgtgacta gt 372

<210> 45
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 45

Phe Ser Asn Ala Trp Met Ser Trp Val
 1 5

<210> 46
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 47
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 47

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
 1 5 10

<210> 48
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 48

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

PCT-EP2012-057247 Sequence Listing.txt

<210> 49
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 49

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 50
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 50

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> 51
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 51

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

PCT-EP2012-057247 Sequence Listing.txt

<210> 52
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder
 <400> 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> 53
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 53
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 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

<210> 54
 <211> 339

PCT-EP2012-057247 Sequence Listing.txt

<212> DNA
 <213> Artificial Sequence
 <220>
 <223> C4.4a binder
 <400> 54
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 agctgcaccg gcagcagcag caacatcgga gccggctacg tgggtgactg gtatcagcag 120
 ctgcccggca ccgcccccaa gctgctgata tacgacaaca acaagcggcc tagcggcgtg 180
 cccgacagat tcagcggcag caagagcggc accagcgcca gcctggccat cagcggcctg 240
 agaagcgagg acgaggccga ctactactgc gccgcctggg acgacagact gaacggccct 300
 gtgttcggcg gaggcaccaa gctgaccgtg ctgggacag 339

<210> 55
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> C4.4a binder
 <400> 55
 Phe Ser Asn Ala Trp Met Ser Trp Val
 1 5

<210> 56
 <211> 20
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> C4.4a binder
 <400> 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> 57
 <211> 10
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> C4.4a binder
 <400> 57
 Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
 1 5 10

<210> 58
 <211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 58

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 59
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 59

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 60
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 60

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
1 5 10

<210> 61
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 62
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

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> 63
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 63

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60

tcctgcgccg ccagcggctt taccttctcc aacgcctgga tgtcctgggt ccgacaggcc 120

PCT-EP2012-057247 Sequence Listing.txt

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> 64
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 64
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tcttgcaccg gtcctccag caacatcggc gctggctacg tgggtgactg gtatcagcag 120
ctgcccggca ccgccccaa gctgctgac tacgacaaca acaagcggcc ctccggcgtg 180
cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg 240
agatctgagg acgaggccga ctactactgc gccgcctacg acgactccct gtccggccct 300
gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> 65
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 65

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> 66
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 67
<211> 10
<212> PRT
<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 67

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> 68

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 68

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 69

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 69

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 70

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 70

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 71

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 71

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

PCT-EP2012-057247 Sequence Listing.txt

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> 72
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

<210> 73
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 73
 gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60
 tcctgcgccg cctccggctt taccttctcc aacgcctgga tgtcctgggt ccgacaggct 120
 cctggcaagg gcctggaatg ggtgtcctac atctctcct ccggctccac catctactac 180
 gccgactccg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac 240
 ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc ccgagagggc 300
 ctgtgggcct tcgataagtg gggccagggc accctggtca ccgtcagctc a 351

<210> 74
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 74
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 tcctgcaccg gtcctccag caacatcggc gctggctacg tggcactg gtatcagcag 120
 ctgcccggca ccgccccaa gctgctgac tacgacaaca acaagcggcc ctccggcgtg 180
 cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg 240
 agatctgagg acgaggccga ctactactgc gccgccttcg acgaccggct gaacggccct 300
 gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> 75
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 75
 Phe Ser Ser Ala Trp Met Ser Trp Val
 1 5

<210> 76
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 77
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 77

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
 1 5 10

<210> 78
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 78

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 79
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 79

Asp Asn Asn Lys Arg Pro Ser
 1 5

<210> 80
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 80

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
 1 5 10

<210> 81
 <211> 117
 <212> PRT
 <213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 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> 82

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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
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> 83
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

<210> 84
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 84
cagtccgtgc tgaccagacc cccttctgtg tctggcgccc ctggccagag agtgaccatc 60
tcttgaccg gtcctccag caacatcggc gctggctacg tgggtgactg gtatcagcag 120
ctgcccggca ccgccccaa gctgctgac tacgacaaca acaagcggcc ctccggcgtg 180
cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg 240
agatctgagg acgaggccga ctactactgc gccgcctacg acgactccct gtccggccct 300
gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 85

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

PCT-EP2012-057247 Sequence Listing.txt

<210> 86
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 87
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 87

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
 1 5 10

<210> 88
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 88

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 89
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 89

Asp Asn Asn Gln Arg Pro Ser
 1 5

<210> 90
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 90

Cys Ala Ala Phe Asp Asp Arg Leu Ser Gly Pro Val
1 5 10

<210> 91

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 91

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> 92

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 93
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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 accctggcca ccgtcagctc a 351

<210> 94
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 94
cagagcgtgc tgaccagcc tcctagcgcc tctggcacc ctggccagag agtgaccatc 60
agctgcagcg gcagcagcag caacatcgga gccggctacg tggtgactg gtatcagcag 120
ctgcccggca ccgccccaa gctgctgac tacgacaaca accagcggcc cagcggcgtg 180
cccagacagat tttccggcag caagagcggc accagcgcca gcctggccat cagcggcctg 240
agaagcgagg acgaggccga ctactactgc gccgccttcg acgacagact gagcggccct 300
gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

PCT-EP2012-057247 Sequence Listing.txt

<210> 95
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 95

Phe Ser Asp Tyr Gln Met Thr Trp Ile
 1 5

<210> 96
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 97
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 97

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
 1 5 10 15

<210> 98
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 98

Ser Gly Ser Ser Ser Asn Val Gly Ser Asn Pro Val Asn
 1 5 10

<210> 99
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 99

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 100

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 100

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Val
1 5 10

<210> 101

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 101

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
100 105 110Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 102

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

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> 103

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 103

gaggtgcagc tgctggaaag cggcggagga ctggtgcagc ctggaggcag cctgagactg 60
tcttgcgccg ccagcggctt caccttcagc gactaccaga tgacctggat ccgacagacc 120
cctggcaagg gcctggaatg ggtgtccggc atcagctgga acggaggcag caccactac 180
gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240
ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300
tacctggtgt acagcgcta ctacttcgac agctggggcc agggcaccct ggtcaccgtg 360
tctagc 366

<210> 104

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 104

gagagcgtgc tgaccagcc tcctagcgcc tctggcacc ctggccagag agtgaccatc 60
agctgctctg gcagcagcag caacatcgga agcaaccccg tgaactggta tcagcagctg 120

PCT-EP2012-057247 Sequence Listing.txt

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> 105
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 105

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> 106
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 107
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 107

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> 108
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 108

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

PCT-EP2012-057247 Sequence Listing.txt

<210> 109
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 109

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 110
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 110

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Ala
 1 5 10

<210> 111
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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
 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> 112
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 113
 <211> 366
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 113

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60
 tcctgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc 120
 cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc caccactac 180
 gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac 240
 ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcdc caagggcgac 300
 tacctggtgt actcctccta ctacttcaag tcctggggcc agggcaccct ggtcaccgtc 360
 agctca 366

<210> 114
 <211> 336

PCT-EP2012-057247 Sequence Listing.txt

<212> DNA
 <213> Artificial Sequence
 <220>
 <223> C4.4a binder
 <400> 114
 cagtccgtgc tgaccagcc tccttcgcc tctggcacc ctggccagag agtgaccatc 60
 tcctgctccg gtcctcctc caacatcggc tccaaccccg tgaactggta tcagcagctg 120
 cccggcaccg cccccaagct gctgatctac cggaacaacc agcggccctc cggcgtgccc 180
 gacagattct ccggctcaa gtccggcacc tccgcctccc tggccatctc cggcctgaga 240
 tctgaggacg aggccgacta ctactgcgcc gcctgggacg accggctgtc tggctgggct 300
 tttggcggcg gaacaaagtt aaccgtgctg ggccag 336

<210> 115
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 115

Phe Ser Asp Tyr Gln Met Thr Trp Ile
 1 5

<210> 116
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 117
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 117

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
 1 5 10 15

<210> 118
 <211> 13

<212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 118

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
 1 5 10

<210> 119
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 119

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 120
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 120

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Ala
 1 5 10

<210> 121
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 122
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

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> 123
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 123

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg	60
tcttgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc	120
cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc caccactac	180
gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac	240

PCT-EP2012-057247 Sequence Listing.txt

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300
tacctggtgt acaagtccta ctacttcaag tcctggggcc agggcaccct ggtcaccgtc 360
agctca 366

<210> 124
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 124
cagtcctgtc tgaccagcc tccttcgcc tctggcacc ctggccagag agtgaccatc 60
tcctgctccg gtcctctc 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> 125
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 125

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> 126
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 127
<211> 15
<212> PRT
<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 127

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> 128

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 128

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> 129

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 129

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 130

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 130

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> 131

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 132
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder
<400> 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> 133
<211> 366
<212> DNA
<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 133
gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60
tcctgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc 120
cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc caccactac 180
gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac 240
ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300
tacctggtgt actcctccta ctacttcaag tcctggggcc agggcacctt ggtcaccgtc 360
agctca 366

<210> 134
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 134
cagtcctgac tgaccagcc tccttccgcc tctggcacc ctggccagag agtgaccatc 60
tcctgctccg gctcctctc 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
tttgcgggcg gaacaaagtt aaccgtgctg ggccag 336

<210> 135
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 135
Phe Ser Ser Tyr Gln Met Thr Trp Ile
1 5

<210> 136
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 137
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 137

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> 138
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 138

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> 139
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 139

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 140
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 140

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Ala
1 5 10

<210> 141
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

PCT-EP2012-057247 Sequence Listing.txt

<400> 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> 142

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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
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> 143
 <211> 366
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 143
 gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ctggcggaag cctgagactg 60
 agctgtgccg ccagcggcctt caccttcagc agctaccaga tgacctggat cagacaggcc 120
 cctggcaagg gcctggaatg ggtgtccggc atcagctgga acggcggcag caccactac 180
 gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240
 ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300
 tacctggtgt acaagagcta ctacttcaag agctggggcc agggcacact ggtcaccgtc 360
 agtca 366

<210> 144
 <211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 144
 cagagcgtgc tgaccagcc tcctagcgcc tctggcacc 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 cggctggggc 300
 tttggcggcg gaacaaagtt aaccgtgctg ggccag 336

<210> 145
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 145

Phe Ser Asn Ala Trp Met Ser Trp Val
 1 5

<210> 146
 <211> 20
 <212> PRT
 <213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 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> 147

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 147

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> 148

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 148

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 149

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 149

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 150

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 150

Cys Ala Ala Tyr Asp Asp Ser Leu Lys Gly Pro Val
1 5 10

PCT-EP2012-057247 Sequence Listing.txt

<210> 151
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 151

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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 Lys Trp Gly Gln Gly Thr Leu
          100          105          110

Val Thr Val Thr Ser
          115
    
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<210> 152
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 152

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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 Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
          50          55          60
    
```

PCT-EP2012-057247 Sequence Listing.txt

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> 153
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 153

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> 154
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 154

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> 155
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 155

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> 156
<211> 14
<212> PRT
<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 156

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 157

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 157

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 158

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 158

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 159

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

PCT-EP2012-057247 Sequence Listing.txt

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> 160
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 161
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 161

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

PCT-EP2012-057247 Sequence Listing.txt

<210> 162
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 163
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 163

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
 1 5 10

<210> 164
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 164

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 165
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 165

Asp Asn Asn Lys Arg Pro Ser
 1 5

<210> 166
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 166

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
 1 5 10

<210> 167

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

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> 168

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 169
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 169

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> 170
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 171
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 171

Ala Arg Glu Gly Leu Trp Ala Phe Asp Trp
1 5 10

PCT-EP2012-057247 Sequence Listing.txt

<210> 172
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 172

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 173
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 173

Asp Asn Asn Gln Arg Pro Ser
 1 5

<210> 174
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 174

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
 1 5 10

<210> 175
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

<210> 176
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 177
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 177

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> 178
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 179
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 179

Ala Arg Glu Gly Leu Trp Ala Phe Asp Asn
1 5 10

<210> 180
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 180

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 181
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 181

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> 182
<211> 12
<212> PRT
<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 182

Cys Ala Ala Tyr Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 183

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 184

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 185
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 185

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> 186
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 187
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 187

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> 188
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 188

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 189
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 189

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> 190
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 190

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> 191
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 192
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 192

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

<210> 193
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 193

Phe Thr Phe Ser Asn Ala Trp Met Ser Trp Val
1 5 10

<210> 194

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 195

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 195

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> 196

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 196

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 197

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 197

Asp Asn Asn Lys Arg Pro Ser
1 5

PCT-EP2012-057247 Sequence Listing.txt

<210> 198
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 198

Cys Ala Ala Tyr Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> 199
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 200
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 200

Glu Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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 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> 201
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 201

Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
1 5 10

<210> 202
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 202

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> 203
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 203

Ala Arg Glu Gly Leu Trp Ala Phe Asp Gly
1 5 10

<210> 204

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 204

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 205

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 205

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> 206

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 206

Cys Ala Ala Tyr Asp Asp Ser Leu Asn Arg Pro Val
1 5 10

<210> 207

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 208
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

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> 209
<211> 11

<212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 209
 Phe Thr Phe Ser Asn Ala Trp Met Ser Trp Val
 1 5 10

 <210> 210
 <211> 20
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 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> 211
 <211> 10
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 211
 Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
 1 5 10

 <210> 212
 <211> 14
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 212
 Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

 <210> 213
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 213

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 214
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 214

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 215
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 216
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

PCT-EP2012-057247 Sequence Listing.txt

<400> 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

Gln

<210> 217

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 217

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> 218

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 219

<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 219

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> 220
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 220

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 221
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 221

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 222
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 222

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 223
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 223

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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> 224
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 225
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 225

Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
 1 5 10

<210> 226
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 227
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 227

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
 1 5 10

<210> 228
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 228

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 229
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 229

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> 230

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 230

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> 231

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 232

<211> 113

<212> PRT

<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 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> 233

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 233

Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
1 5 10

<210> 234

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 235
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 235

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
 1 5 10

<210> 236
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 236

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
 1 5 10

<210> 237
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 237

Asp Asn Asn Gln Arg Pro Ser
 1 5

<210> 238
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 238

Cys Ala Ala Phe Asp Asp Arg Leu Ser Gly Pro Val
 1 5 10

<210> 239
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 240
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 241
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 241

Phe Ser Asp Tyr Gln Met Thr Trp Ile
 1 5

<210> 242
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 243
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 243

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
 1 5 10 15

<210> 244
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 244

Ser Gly Ser Ser Ser Asn Val Gly Ser Asn Pro Val Asn
 1 5 10

<210> 245
 <211> 7

<212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 245

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 246
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 246

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Thr Gly
 1 5 10

<210> 247
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 247

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 Ser Tyr Tyr Phe Lys Ser Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Thr Ser
 115 120

PCT-EP2012-057247 Sequence Listing.txt

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<210> 248
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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

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<210> 249
<211> 11
<212> PRT
<213> Artificial Sequence

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<220>
<223> C4.4a binder

```

```

<400> 249
Phe Thr Phe Ser Ser Tyr Gln Met Thr Trp Ile
1          5          10

```

```

<210> 250
<211> 20
<212> PRT
<213> Artificial Sequence

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<220>
<223> C4.4a binder

```

```

<400> 250
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> 251
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 251

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
 1 5 10 15

<210> 252
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 252

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
 1 5 10

<210> 253
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 253

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 254
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 254

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Gly
 1 5 10

<210> 255
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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

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> 256
 <211> 112
 <212> PRT
 <213> Artificial sequence

<220>
 <223> C4.4a binder

<400> 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> 257
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 257

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
 1 5 10

<210> 258
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 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> 259
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 259

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Tyr
 1 5 10 15

<210> 260
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 260

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
 1 5 10

<210> 261
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 261

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 262

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 262

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Ala
1 5 10

<210> 263

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

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> 264

<211> 112

<212> PRT

<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>

<223> C4.4a binder

<400> 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> 265

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 265

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5 10

<210> 266

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 267

<211> 15

<212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 267

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
 1 5 10 15

<210> 268
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 268

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
 1 5 10

<210> 269
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 269

Arg Asn Asn Gln Arg Pro Ser
 1 5

<210> 270
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 270

Cys Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Gly
 1 5 10

<210> 271
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 271

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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> 272
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder
<400> 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> 273
<211> 11

<212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 273
 Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
 1 5 10

 <210> 274
 <211> 20
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 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> 275
 <211> 15
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 275
 Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
 1 5 10 15

 <210> 276
 <211> 13
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 276
 Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
 1 5 10

 <210> 277
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> C4.4a binder

 <400> 277

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 278
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 278

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> 279
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 280
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

PCT-EP2012-057247 Sequence Listing.txt

<400> 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

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<210> 281
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 281

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Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1          5          10

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<210> 282
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 282

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Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1          5          10          15

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Val Lys Gly Arg
          20

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<210> 283
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 283

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> 284

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 284

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> 285

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 285

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> 286

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 286

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> 287

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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

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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> 288
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder
<400> 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
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> 289
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 289

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5 10

<210> 290

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 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> 291

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 291

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> 292

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 292

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> 293

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 293

Arg Asn Asn Gln Arg Pro Ser
1 5

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<210> 294
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 294

Cys Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Gly
1 5 10

<210> 295
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 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> 296
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 296

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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> 297
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence for M20 D02 S-A derived CDR H1

<220>
<221> VARIANT
<222> (3)..(3)
<223> X = D or S

<400> 297

Phe Ser Xaa Tyr Gln Met Thr Trp Ile
1 5

<210> 298
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence for M20 D02 S-A derived CDRH2

<220>
<221> VARIANT
<222> (4)..(4)
<223> X = V or I

<220>
<221> VARIANT
<222> (9)..(9)
<223> X = A or G

<220>
<221> VARIANT
<222> (10)..(10)

<223> X = R or S

<400> 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> 299

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> consensus for M20 D02 S-A derived CDRH3

<220>

<221> VARIANT

<222> (9)..(9)

<223> X = S, K, or R

<220>

<221> VARIANT

<222> (10)..(10)

<223> X = A, S or R

<220>

<221> VARIANT

<222> (14)..(14)

<223> X = D, K, E or R

<220>

<221> VARIANT

<222> (15)..(15)

<223> X = S or Y

<400> 299

Ala Lys Gly Asp Tyr Leu Val Tyr Xaa Xaa Tyr Tyr Phe Xaa Xaa
1 5 10 15

<210> 300

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> consensus sequence derived from M20 D02 S-A CDRL1

<220>

<221> VARIANT

<222> (7)..(7)

<223> X = V or I

<400> 300

Ser Gly Ser Ser Ser Asn Xaa Gly Ser Asn Pro Val Asn
1 5 10

<210> 301

PCT-EP2012-057247 Sequence Listing.txt

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence derived from M20 D02 S-A derived CDR L3

<220>
<221> VARIANT
<222> (3)..(3)
<223> X = A, Q or R

<220>
<221> VARIANT
<222> (5)..(5)
<223> X = D or G

<220>
<221> VARIANT
<222> (7)..(7)
<223> X = R or S

<220>
<221> VARIANT
<222> (9)..(9)
<223> X = N, W or S

<220>
<221> VARIANT
<222> (12)..(12)
<223> X = V, A or G

<400> 301

Cys Ala Xaa Trp Xaa Asp Xaa Leu Xaa Gly Trp Xaa
1 5 10

<210> 302
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence derived from M31 B01 CDR H1

<220>
<221> VARIANT
<222> (3)..(3)
<223> X = N or S

<220>
<221> VARIANT
<222> (4)..(4)
<223> X = A or Y

<400> 302

Phe Ser Xaa Xaa Trp Met Ser Trp Val
1 5

<210> 303
<211> 20
<212> PRT
<213> Artificial Sequence

PCT-EP2012-057247 Sequence Listing.txt

<220>
<223> consensus sequence derived from M31 B01 CDR H2

<220>
<221> VARIANT
<222> (10)..(10)
<223> X = T or S

<220>
<221> VARIANT
<222> (11)..(11)
<223> X = I or T

<400> 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> 304
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence derived from M31 B01 CDR H3

<220>
<221> VARIANT
<222> (10)..(10)
<223> X = Y, K, G, W or N

<400> 304

Ala Arg Glu Gly Leu Trp Ala Phe Asp Xaa
1 5 10

<210> 305
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> consensus sequence derived from M31 B01 CDR L1

<220>
<221> VARIANT
<222> (1)..(1)
<223> X = T or S

<400> 305

Xaa Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> 306
<211> 7
<212> PRT

<213> Artificial Sequence

<220>

<223> consensus sequence derived from M31 B01 CDR L2

<220>

<221> VARIANT

<222> (4)..(4)

<223> X = K or Q

<400> 306

Asp Asn Asn Xaa Arg Pro Ser
1 5

<210> 307

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> consensus sequence derived from M31 B01 CDR L3

<220>

<221> VARIANT

<222> (4)..(4)

<223> X = W, E, F or Y

<220>

<221> VARIANT

<222> (7)..(7)

<223> X = R, S or M

<220>

<221> VARIANT

<222> (9)..(9)

<223> X = N, K or S

<220>

<221> VARIANT

<222> (10)..(10)

<223> X = G or R

<220>

<221> VARIANT

<222> (11)..(11)

<223> X = P or A

<400> 307

Cys Ala Ala Xaa Asp Asp Xaa Leu Xaa Xaa Xaa Val
1 5 10

<210> 308

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> c4.4a binder

<400> 308

gaggtgcagc tgctggagag cggggggggg ctggtgcagc cggggggggag cctgcgctg

60

PCT-EP2012-057247 Sequence Listing.txt

agctgcgcg	cgagcgggtt	taccttttagc	aacgcgtgga	tgagctgggt	gcgccaggcg	120
ccggggaaaag	ggctggagtg	ggtgagctat	attagcagca	gcgggagcac	cattttattat	180
gcggatagcg	tgaaaggcg	ctttaccatt	agccgcgata	acagcaaaaa	caccctgtat	240
ctgcagatga	acagcctgcg	cgcgaggat	accgcggtgt	attattgcgc	gcgcgagggg	300
ctgtgggcgt	ttgataaatg	ggggcagggg	accctggtga	ccgtgaccag	c	351

<210> 309
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 309	
cagagcgtgc	tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcaccg	ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
ctgccgggga	ccgcgccgaa actgctgatt tatgataaca acaaacgcc gagcgggggtg 180
ccggatcgct	ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgcagcgagg	atgaggcgga ttattattgc gcggcgtatg atgatagcct gaaagggccg 300
gtgtttgggg	gggggaccaa actgaccgtg ctggggcag 339

<210> 310
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 310	
gaggtgcagc	tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgcttg 60
agctgcgcg	cgagcgggtt taccttttagc aacgcgtgga tgagctgggt gcgccaggcg 120
ccggggaaaag	ggctggagtg ggtgagctat attagcagca gcgggagcac cattttattat 180
gcggatagcg	tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga	acagcctgcg cgcgaggat accgcggtgt attattgcgc gcgcgagggg 300
ctgtgggcgt	ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> 311
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 311	
cagagcgtgc	tgaccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60
agctgcaccg	ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120

PCT-EP2012-057247 Sequence Listing.txt

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgcc gagcggggtg	180
ccggatcgct ttagcgggag caaaagcggg accagcgca gcctggcgat tagcgggctg	240
cgagcgagg atgaggcgga ttattattgc gcggcggttg atgatagcct gaacgggccg	300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag	339

<210> 312
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 312 gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg	60
agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg	120
ccggggaaag ggctggagt ggtgagctat attagcagca gcgggagcac cttttattat	180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat	240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg	300
ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c	351

<210> 313
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 313 cagagcgtgc tgaccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt	60
agctgcaccg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag	120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgcc gagcggggtg	180
ccggatcgct ttagcgggag caaaagcggg accagcgca gcctggcgat tagcgggctg	240
cgagcgagg atgaggcgga ttattattgc gcggcggttg atgatagcct gaacgggccg	300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag	339

<210> 314
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 314 gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg	60
agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg	120
ccggggaaag ggctggagt ggtgagctat attagcagca gcgggagcag cacctattat	180

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gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300
ctgtgggcgt ttgattgggt ggggcagggg accctggtga ccgtgaccag c 351

<210> 315
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 315
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg gcggggtatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgca gcctggcgat tagcgggctg 240
cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatagcct gagcgggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 316
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 316
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgcctg 60
agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120
ccggggaaag ggctggagt 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

<210> 317
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 317
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg gcggggtatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgca gcctggcgat tagcgggctg 240

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cgagcgagg atgaggcgga ttattattgc gcggcgatg atgatagcct gaacgggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 318
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 318
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg 60
agctgcgcgg cgagcgggtt taccttttagc agcgcgtgga tgagctgggt gcgccaggcg 120
ccggggaaag ggctggagt 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> 319
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 319
gagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg gcgggggtatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcggcc gagcgggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgagcgagg atgaggcgga ttattattgc gcggcggtgg atgatgcct gaacgggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 320
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 320
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg 60
agctgcgcgg cgagcgggtt taccttttagc aacgcgtgga tgagctgggt gcgccaggcg 120
ccggggaaag ggctggagt ggtgagctat attagcagca gcgggagcac cttttattat 180
gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgagcag c 351

<210> 321
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 321
 gagagcgtgc tgaccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60
 agctgcaccg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
 ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcgggggtg 180
 ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
 cgagcagagg atgaggcgga ttattattgc gcggcgatatg atgatgcct gaacggggccg 300
 gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 322
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 322
 gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg 60
 agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120
 ccgggggaaag ggctggagt ggtgagctat attagcagca gcgggagcag cacctattat 180
 gcggatagcg tgaaaggggc ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
 ctgcagatga acagcctgcg cgcgaggat accgcggtgt attattgcgc gcgcgagggg 300
 ctgtgggcgt ttgatgggtg ggggcagggg accctggtga ccgtgagcag c 351

<210> 323
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 323
 cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
 agctgcagcg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
 ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgcgc gagcgggggtg 180
 ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
 cgagcagagg atgaggcgga ttattattgc gcggcgatatg atgatagcct gaaccgcccg 300
 gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

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<210> 324
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 324
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg 60
agctgcgcg cgagcgggtt taccttttagc aacgcgtgga tgagctgggt gcgccaggcg 120
ccgggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300
ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgagcag c 351

<210> 325
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 325
cagagcgtgc tgaccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60
agctgcaccg ggagcagcag caacattggg gcgggggtatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgcc gagcgggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgcagcagg atgaggcgga ttattattgc gcggcggttg atgatagcct gaacgggccc 300
gtgtttggg gggggaccaa actgaccgtg ctggggcag 339

<210> 326
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 326
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgccctg 60
agctgcgcg cgagcgggtt taccttttagc agcgcgtgga tgagctgggt gcgccaggcg 120
ccgggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300
ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> 327

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<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 327
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcaccg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcgggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgagcagagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacggggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 328
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 328
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgcttg 60
agctgcgcgg cgagcggggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120
ccggggaaag ggctggagt ggtgagctat attagcagca gcgggagcag cacctattat 180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcgaggat accgcggtgt attattgcgc gcgcgagggg 300
ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgagcag c 351

<210> 329
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a

<400> 329
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcggcc gagcgggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgagcagagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacggggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 330
<211> 351
<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 330
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cggggggggag cctgcgccctg 60
agctgcgcgg cgagcggggtt taccttttagc agcgcgtgga tgagctgggt gcgccaggcg 120
ccgggggaaag 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> 331

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 331
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg gcggggatatg tgggtgcattg gtatcagcag 120
ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcgggggtg 180
ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240
cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatcgctt gagcggggccg 300
gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> 332

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 332
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cggggggggag cctgcgccctg 60
agctgcgcgg cgagcggggtt taccttttagc gattatcaga tgacctggat tcgccagacc 120
ccgggggaaag ggctggagtg ggtgagcggg gtgagctgga acggggcgcg caccattat 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> 333

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 333

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt	60
agctgcagcg ggagcagcag caacgtgggg agcaaccggg tgaactggta tcagcagctg	120
ccgggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg	180
gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc	240
agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgctgaa cgggtggggg	300
tttggggggg ggaccaaact gaccgtgctg gggcag	336

<210> 334

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 334

gagcagctgc tggagagcgg gggggggctg 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> 335

<211> 333

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 335

caggtgctga cccagccgcc gagcgcgagc gggaccccg ggcagcgcgt gaccattagc	60
tgacgcggga gcagcagcaa cattgggagc aaccgggtga actggtatca gcagctgccg	120
gggaccgcgc cgaaactgct gatttatcgc aacaaccagc gcccgagcgg ggtgccggat	180
cgcttttagc ggagcaaaag cgggaccagc gcgagcctgg cgattagcgg gctgcgcagc	240
gaggatgagg cggattatta ttgcgcggcg tgggatgatc gcctgaacgg gtgggggttt	300
ggggggggga ccaaactgac cgtgctgggg cag	333

<210> 336

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 336

gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg	60
agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc	120
ccgggggaaag ggctggagt ggtgagcggg attagctgga acgggggggag caccattat	180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat	240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat	300
tatctggtgt atagcagcta ttattttaaa tattgggggc aggggaccct ggtgaccgtg	360
agcagc	366

<210> 337

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 337

cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt	60
agctgcagcg ggagcagcag caacattggg agcaaccgg tgaactggta tcagcagctg	120
ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg	180
gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc	240
agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgctgaa cgggtgggcg	300
tttggggggg ggaccaaact gaccgtgctg gggcag	336

<210> 338

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> C4.4a binder

<400> 338

gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg	60
agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc	120
ccgggggaaag ggctggagt ggtgagcggg attagctgga acgggggggag caccattat	180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat	240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat	300
tatctggtgt atagcagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg	360
agcagc	366

<210> 339

PCT-EP2012-057247 Sequence Listing.txt

<211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 339
 cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
 agctgcagcg ggagcagcag caacattggg agcaaccgga tgaactggta tcagcagctg 120
 ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180
 gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240
 agcagagatg aggcggatta ttattgcgcg gcgtgggatg atagcctgaa cgggtggggg 300
 tttggggggg ggaccaaact gaccgtgctg gggcag 336

<210> 340
 <211> 366
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 340
 gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg 60
 agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120
 ccggggaaag ggctggagt ggtgagcggg attagctgga acggggggag caccattat 180
 gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
 ctgcagatga acagcctgcg cgcgaggat accgcggtgt attattgcgc gaaaggggat 300
 tatctggtgt ataaaagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360
 agcagc 366

<210> 341
 <211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 341
 cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
 agctgcagcg ggagcagcag caacattggg agcaaccgga tgaactggta tcagcagctg 120
 ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180
 gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240
 agcagagatg aggcggatta ttattgcgcg gcgtgggatg atgcctgag cgggtggggg 300
 tttggggggg ggaccaaact gaccgtgctg gggcag 336

<210> 342

PCT-EP2012-057247 Sequence Listing.txt

<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 342
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg 60
agctgcgcgg cgagcgggtt taccttttagc gattatcaga tgacctggat tcgccagacc 120
ccgggggaaag ggctggagt ggtgagcggg attagctgga acgggggggag caccattat 180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300
tatctggtgt atagcagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360
agcagc 366

<210> 343
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 343
cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
agctgcagcg ggagcagcag caacattggg agcaaccggg tgaactggta tcagcagctg 120
ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcggccgag cggggtgccg 180
gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240
agcagggatg aggcggatta ttattgcgcg gcgtgggatg atcgctgag cgggtggggg 300
tttggggggg ggaccaaact gaccgtgctg gggcag 336

<210> 344
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> C4.4a binder

<400> 344
gaggtgcagc tgctggagag cggggggggg ctggtgcagc cgggggggag cctgcgctg 60
agctgcgcgg cgagcgggtt taccttttagc gattatcaga tgacctggat tcgccagacc 120
ccgggggaaag ggctggagt ggtgagcggg attagctgga acgggggggag caccattat 180
gcggatagcg tgaaaggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240
ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300
tatctggtgt ataaaagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360
agcagc 366

PCT-EP2012-057247 Sequence Listing.txt

<210> 345
 <211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> C4.4a binder

<400> 345
 cagagcgtgc tgaccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60
 agctgcagcg ggagcagcag caacattggg agcaaccgga tgaactggta tcagcagctg 120
 ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180
 gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240
 agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atagcctgaa cgggtggggg 300
 tttggggggg ggaccaaact gaccgtgctg gggcag 336

<210> 346
 <211> 217
 <212> PRT
 <213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 347
<211> 447
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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 Lys
435 440 445

PCT-EP2012-057247 Sequence Listing.txt

<210> 348
 <211> 217
 <212> PRT
 <213> Homo Sapiens

<400> 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> 349
 <211> 446
 <212> PRT
 <213> Homo Sapiens

PCT-EP2012-057247 Sequence Listing.txt

<400> 349

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
 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> 350

<211> 217

<212> PRT

<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 351
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 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

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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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
385 390 400

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> 352
<211> 217
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 353
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 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

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

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> 354
 <211> 217
 <212> PRT
 <213> Homo Sapiens

<400> 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

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> 355
 <211> 446

PCT-EP2012-057247 Sequence Listing.txt

<212> PRT
<213> Homo Sapiens

<400> 355

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10
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

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PCT-EP2012-057247 Sequence Listing.txt

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> 356
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 357
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 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
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65

80

Leu Gln Met Asn Ser₈₅ Leu Arg Ala Glu Asp₉₀ Thr Ala Val Tyr Tyr₉₅ Cys

Ala Arg Glu Gly₁₀₀ Leu Trp Ala Phe Asp₁₀₅ Tyr Trp Gly Gln Gly₁₁₀ Thr Leu

Val Thr Val₁₁₅ Ser Ser Ala Ser Thr₁₂₀ Lys Gly Pro Ser Val₁₂₅ Phe Pro Leu

Ala Pro₁₃₀ Ser Ser Lys Ser Thr₁₃₅ Ser Gly Gly Thr Ala₁₄₀ Ala Leu Gly Cys

Leu Val₁₄₅ Lys Asp Tyr Phe₁₅₀ Pro Glu Pro Val Thr₁₅₅ Val Ser Trp Asn Ser₁₆₀

Gly Ala Leu Thr Ser₁₆₅ Gly Val His Thr Phe₁₇₀ Pro Ala Val Leu Gln Ser₁₇₅

Ser Gly Leu Tyr₁₈₀ Ser Leu Ser Ser Val₁₈₅ Val Thr Val Pro Ser₁₉₀ Ser Ser

Leu Gly Thr₁₉₅ Gln Thr Tyr Ile Cys₂₀₀ Asn Val Asn His Lys₂₀₅ Pro Ser Asn

Thr Lys₂₁₀ Val Asp Lys Lys Val₂₁₅ Glu Pro Lys Ser Cys₂₂₀ Asp Lys Thr His

Thr₂₂₅ Cys Pro Pro Cys Pro₂₃₀ Ala Pro Glu Leu Leu₂₃₅ Gly Gly Pro Ser Val₂₄₀

Phe Leu Phe Pro₂₄₅ Lys Pro Lys Asp Thr₂₅₀ Leu Met Ile Ser Arg₂₅₅ Thr

Pro Glu Val Thr₂₆₀ Cys Val Val Val Asp₂₆₅ Val Ser His Glu Asp₂₇₀ Pro Glu

Val Lys Phe₂₇₅ Asn Trp Tyr Val Asp₂₈₀ Gly Val Glu Val His₂₈₅ Asn Ala Lys

Thr Lys₂₉₀ Pro Arg Glu Glu Gln₂₉₅ Tyr Asn Ser Thr Tyr₃₀₀ Arg Val Val Ser

Val₃₀₅ Leu Thr Val Leu His₃₁₀ Gln Asp Trp Leu Asn₃₁₅ Gly Lys Glu Tyr Lys₃₂₀

Cys Lys Val Ser Asn₃₂₅ Lys Ala Leu Pro Ala₃₃₀ Pro Ile Glu Lys Thr₃₃₅ Ile

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
Page 130

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> 358
 <211> 217
 <212> PRT
 <213> Homo Sapiens
 <400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 359
<211> 446
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 360
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

<210> 361
 <211> 446
 <212> PRT
 <213> Homo Sapiens

<400> 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

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> 362
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 363
 <211> 446
 <212> PRT
 <213> Homo Sapiens
 <400> 363
 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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> 364
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 365
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 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

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
Page 140

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> 366
 <211> 217
 <212> PRT
 <213> Homo Sapiens

<400> 366

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

PCT-EP2012-057247 Sequence Listing.txt

<210> 367
 <211> 446
 <212> PRT
 <213> Homo Sapiens

<400> 367

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
      20      25
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
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
    
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PCT-EP2012-057247 Sequence Listing.txt

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>	368
<211>	217
<212>	PRT
<213>	Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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 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> 369
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 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
Page 145

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
 Page 146

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> 370
<211> 216
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 371
<211> 452
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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> 372
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

PCT-EP2012-057247 Sequence Listing.txt

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> 373
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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
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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> 374
 <211> 216
 <212> PRT
 <213> Homo Sapiens

<400> 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

<210> 375

<211> 451

<212> PRT

<213> Homo Sapiens

<400> 375

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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> 376
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 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> 377
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 377

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
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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
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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> 378
 <211> 216
 <212> PRT
 <213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 379
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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
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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly
450

<210> 380
<211> 216
<212> PRT
<213> Homo Sapiens
<400> 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> 381
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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
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
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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> 382
<211> 216
<212> PRT
<213> Homo sapiens

<400> 382

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

PCT-EP2012-057247 Sequence Listing.txt

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> 383
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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> 384
 <211> 216
 <212> PRT
 <213> Homo Sapiens
 <400> 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
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
 65 70 75 80

PCT-EP2012-057247 Sequence Listing.txt

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> 385
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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
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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> 386
 <211> 216
 <212> PRT
 <213> Homo Sapiens

<400> 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
 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

PCT-EP2012-057247 Sequence Listing.txt

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> 387
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

Ser Pro Gly
450

<210> 388
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 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
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

PCT-EP2012-057247 Sequence Listing.txt

<210> 389
 <211> 451
 <212> PRT
 <213> Homo Sapiens

<400> 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

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> 390
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 391
<211> 451
<212> PRT
<213> Homo Sapiens
<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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> 392
<211> 216
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 393
<211> 451
<212> PRT
<213> Homo Sapiens

<400> 393

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
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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> 394
<211> 216
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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> 395
<211> 451
<212> PRT
<213> Homo Sapiens
<400> 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

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

PCT-EP2012-057247 Sequence Listing.txt

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

PCT-EP2012-057247 Sequence Listing.txt

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<210> 396
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 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

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<210> 397
<211> 451
<212> PRT
<213> Homo Sapiens

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PCT-EP2012-057247 Sequence Listing.txt

<400> 397

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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 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 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

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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> 398
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 398

Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
 1 5 10

<210> 399
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 399

PCT-EP2012-057247 Sequence Listing.txt

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> 400
<211> 11
<212> PRT
<213> Homo sapiens

<400> 400

Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly
1 5 10

<210> 401
<211> 14
<212> PRT
<213> Homo sapiens

<400> 401

Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> 402
<211> 11
<212> PRT
<213> Homo sapiens

<400> 402

Leu Met Ile Tyr Gly Val Asn Asn Arg Pro Ser
1 5 10

<210> 403
<211> 10
<212> PRT
<213> Homo sapiens

<400> 403

Ser Ser Tyr Asp Ile Glu Ser Ala Thr Pro
1 5 10

<210> 404
<211> 120
<212> PRT
<213> Homo sapiens

<400> 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
20 25 30

PCT-EP2012-057247 Sequence Listing.txt

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> 405
<211> 113
<212> PRT
<213> Homo sapiens

<400> 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> 406
<211> 360
<212> DNA
<213> Homo sapiens

PCT-EP2012-057247 Sequence Listing.txt

<400> 406
caggtggaat tggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcctttact tcttattgga ttggttgggt gcgccaggcc 120
cctgggaagg gtctcgagt gatgggcatt atcgatccgg gtgatagccg tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcgga aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtggctag 300
ctttatggtg gtacttatat ggatggttgg ggccaaggca ccctggtgac ggttagctca 360

<210> 407
<211> 339
<212> DNA
<213> Homo sapiens

<400> 407
gatatgcac tgaccagcc agcttcagt agcggctcac caggtcagag cattaccatc 60
tcgtgtacgg gtactagcag cgatattggt gggtataatt ctgtgtcttg gtaccagcag 120
catcccgga aggcgccgaa acttatgatt tatggtgtta ataatcgtcc ctcaggcgtg 180
agcaaccgtt ttagcggatc caaaagcggc aacaccgca gcctgaccat tagcggcctg 240
caagcggaag acgaagcgga ttattattgc tcttcttatg atattgagtc tgctactcct 300
gtgtttggcg gcggcacgaa gttaaccgtc ctaggtcag 339

<210> 408
<211> 450
<212> PRT
<213> Homo sapiens

<400> 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

PCT-EP2012-057247 Sequence Listing.txt

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
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> 409
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 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
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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> 410
<211> 1353
<212> DNA
<213> Homo sapiens

<400> 410
caggtggaat tgggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcctttact tcttattgga ttggttggtt gcgccaggcc 120
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PCT-EP2012-057247 Sequence Listing.txt

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