

COMPOUNDS FOR TREATMENT OF CANCER

The present invention relates to novel compounds of formula (I) having anti-cancer activity, pharmaceutically acceptable salts thereof as well as pharmaceutical compositions comprising the same and the use of such compounds for the treatment of cancer.

5 RELATED ART

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 or nearly one in six deaths (WHO Cancer Fact Sheet 2022). The most common in 2020, in terms of new cases of cancer, were: breast cancer, lung cancer, colon and rectum cancer, prostate cancer, skin cancer, in particular non-melanoma cancer, and stomach cancer, which in
10 addition to liver cancer also caused the most vases of cancer death. Despite the enormous activities, development and achievements, new treatment options are highly needed.

A majority of the anticancer drugs used clinically are natural products or are derived from compounds found in nature. Leucinostatins, lipophilic peptide antibiotics produced as microbial metabolites, has generated interest in exploring their applications in human health and
15 agriculture. The leucinostatins are noted to exhibit antimicrobial activities against several types of bacteria and fungi as well as trypanosomes (Kil Y-S et al., J Nat Prod. 2020, 83(6):2010–2024; and references cited therein). Moreover, leucinostatin A has reported to inhibit the growth of DU-145 human prostate cancer cells *in vitro* and *in vivo* only when co-cultured with prostate stromal cells through a proposed mechanism of reduced insulin-like growth factor signaling
20 (Momose I et al., Biochem. Biophys. Res. Commun 2010, 392:460–466).

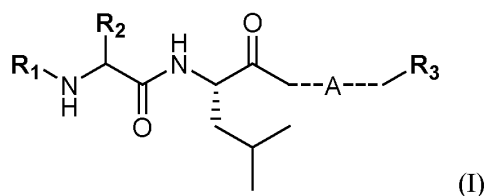
A new class of synthetic leucinostatin derivatives and its use for the treatment of protozoan infections, and further in particular for treatment of skin diseases associated with a protozoan disease, a bacterial infection or a fungal infection, has been described (EP3345917A1, WO2022/167656A1), while synthetic peptide compounds and its assessment
25 for antiproliferative activity against 3 breast cancer cell lines (MDA-MB-468, SKBR3 and T47D), as well as a non-small cell lung cancer line NCI-H460 are disclosed in WO 2020/095253A1.

SUMMARY OF THE INVENTION

We have surprisingly found that the inventive compounds show strong activity against a
30 plurality of different cancer cells including skin cancer cells such as cutaneous squamous cell

carcinoma cells, epithelial skin cancer cells and melanoma skin cancer cells as well as breast cancer cells, colorectal cancer cells, hematopoietic cancer cell lines, cancer cells of the female genitourinary (GU) system, lung cancer cells, head and neck cancer cells, pancreas cancer cells, prostate cancer cells, bladder cancer cells, CNS cancer cells, stomach cancer cells, endocrine cancer cells and kidney cancer cells. This strong activity of the inventive compounds has been demonstrated not only over a structurally similar prior art reference compound but in addition it has been compared to staurosporine which typically serves as a suitable and very potent comparator for those skilled in the art. In particular, it has been surprisingly found that the combination of structural modifications of the inventive compounds, namely the substitution of the pyrrolidine ring system, as present in the inventive compounds, and the substitution of the amino acid *threo*- β -hydroxy-L-leucine, as being present, for example, in naturally occurring leucino-statins, by leucine preferably (*S*)-leucine, and thus by omitting the hydroxyl group at the specific position and replacement with hydrogen, resulted not only in a substantial increase of the activity of the inventive compounds, but further to a highly reduced toxicity thereby overcoming one of the main challenges that has been hampering the development to commercialization of such compounds. Moreover, the tailoring and reduction of the amino acid chain length of the inventive compounds to preferred compounds of an amino acid chain length of a total of eight, while reducing costs of goods of such compounds and drugs, respectively, additionally further led to an additional increase in efficacy. These findings have further been confirmed by the significant efficacy of a preferred inventive compound in experiments using fresh *ex vivo* infiltrative cSCC patient materials.

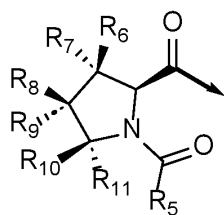
Thus, in a first aspect, the present invention provides a compound of formula (I)



wherein

--A-- represents a peptide chain, wherein said peptide chain consists of 4 to 9 amino acids, wherein preferably said amino acids are selected from α -aminoisobutyric acid (Aib), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala);

R₁ is



, wherein the arrow indicates the attachment to the NH-moiety depicted in formula (I), and wherein

R_5 is selected from H, C_1 - C_{16} alkyl, C_1 - C_{16} alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl or C_1 - C_3 alkylene-heterocyclyl, wherein said C_1 - C_{16} alkyl and said C_1 - C_{16} alkenyl each independently optionally substituted with halogen, OR_{18} , $NR_{19}R_{20}$, $-[O-C_2H_4]_n-OCH_3$ wherein $n=2-20$; and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C_1 - C_4 alkyl, halogen, oxo, CF_3 , OR_{18} , $NR_{19}R_{20}$, C_6H_5 , C_6H_5 substituted with halogen, C_1 - C_3 alkyl, OR_{18} , $NR_{19}R_{20}$, wherein R_{18} , R_{19} , R_{20} are independently at each occurrence H, C_1 - C_3 alkyl, and wherein

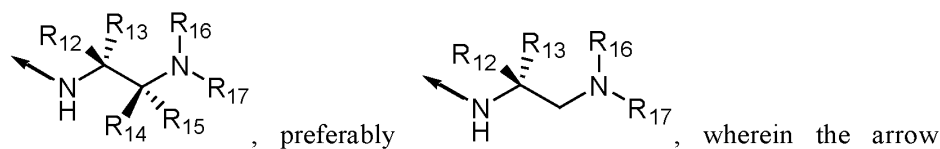
R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} are independently at each occurrence selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl, C_1 - C_3 alkylene-heterocyclyl, halogen, C_1 - C_2 haloalkyl, OR_{21} or $NR_{22}R_{23}$, wherein said R_{21} , R_{22} , R_{23} are independently at each occurrence selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, $C(O)O$ - C_1 - C_6 alkyl, $C(O)$ - C_1 - C_6 alkyl, $C(O)O$ - C_1 - C_6 alkenyl, $C(O)$ - C_1 - C_6 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl or C_1 - C_3 alkylene-heterocyclyl, wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C_1 - C_3 alkyl, halogen, oxo, C_1 - C_2 haloalkyl, OR_{18} , $NR_{19}R_{20}$, C_6H_5 , C_6H_5 substituted with halogen, C_1 - C_3 alkyl, OR_{18} , $NR_{19}R_{20}$; or wherein two of said R_6 , R_7 , R_8 , R_9 , R_{10} , and R_{11} together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle; said carbocycle and said heterocycle optionally substituted with C_1 - C_3 alkyl, halogen, CF_3 , OR_{18} , $NR_{19}R_{20}$; and

wherein at least one of said R_6 , R_7 , R_8 , R_9 , R_{10} , and R_{11} is not H; and

R_2 is selected from C_4 - C_{12} alkyl, C_4 - C_{10} alkoxy, C_1 - C_3 alkylene-cycloalkyl, C_1 - C_3 alkylene-aryl or C_1 - C_3 alkylene-heteroaryl, wherein independently in said C_1 - C_3 alkylene one $-CH_2-$ moiety is optionally replaced by $-CH(NH)-$ or $-O-$; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more, preferably one or two, substituents selected from C_1 - C_2 alkyl, C_1 -

C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl;

R₃ is



indicates the attachment to the A-moiety in formula (I), and wherein

R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

R₁₆ and R₁₇ are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀;

or a pharmaceutically acceptable salt of said compound of formula (I).

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, and a pharmaceutically acceptable carrier or adjuvant.

In another aspect, the present invention provides a compound of formula (I) for use in a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound to said mammal, preferably to said human.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, and a pharmaceutically acceptable carrier or adjuvant, for use in a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said pharmaceutical composition to said mammal, preferably to said human.

In another aspect, the present invention provides a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt thereof, to said mammal, preferably to said human, and wherein preferably said

method comprises administration of an effective amount of said compound to said mammal, preferably to said human.

In a further aspect, the present invention provides for the use of a compound of formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound of formula (I), or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition of the invention, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition, to said mammal, preferably to said human.

Further aspects and embodiments of the present invention will become apparent as this description continues.

DESCRIPTION OF THE FIGURES

FIG. 1A: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in SCC13 skin squamous cell carcinoma cell line as reported in Example 4 showing a statistically significant increase in efficacy (P value: 0.005).

FIG. 1B: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in A31 skin squamous cell carcinoma cell line as reported in Example 4 showing a statistically significant increase in efficacy (P value: 0.03).

FIG. 1C: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in KERTr immortalized keratinocyte cell line as reported in Example 4 showing a statistically significant increase in efficacy (P value: 0.03).

FIG. 2A: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in M150672 melanoma cell line as reported in Example 6 showing a statistically significant increase in efficacy (P value: 0.0039).

FIG. 2B: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in M010817 melanoma cell line as reported in Example 6 showing a statistically significant increase in efficacy (P value: 0.01).

FIG. 2C: Half maximal inhibitory concentrations (IC₅₀) of the preferred inventive compound 23526 as compared to reference compound 6027 in B16 F10 melanoma cell line as reported in Example 6 showing a statistically significant increase in efficacy (P value: 0.004).

FIG. 3A: *Ex vivo* example Immunohistochemistry stainings (HE, ki67) of patient
5 derived cSCC tumor treated for 4 days with 500 nM of 23526 or with DMSO as negative control.

FIG. 3B: Quantification of ki67 positive cells is indicated. A significant reduction in proliferative tumor cells was observed compared to negative control (DMSO) after treatment with inventive compound 23526 (500 nM; **p<0.0035) in *ex vivo* infiltrative cSCC patient
10 material.

FIG. 4A: *Ex vivo* example Immunohistochemistry stainings (HE, panCK, ki67) of patient derived cSCC tumor treated for 4 days with 500 nM of 6027 or 23526 or with DMSO as negative control..

FIG. 4B: Quantification of panCK and ki67 positive cells are indicated. Significant
15 reduction of proliferative tumor cells compared to negative control (DMSO) after treatment with the reference compound 6027 (500 nM; *p<0.03) but in particular after treatment with the inventive compound 23526 (500 nM; **p<0.004) in *ex vivo* infiltrative cSCC patient material was observed.

DETAILED DESCRIPTION OF THE INVENTION

20 Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. The herein described and disclosed embodiments, preferred embodiments and very preferred embodiments should apply to all aspects and other embodiments, preferred
25 embodiments and very preferred embodiments irrespective of whether is specifically again referred to. The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly dictates otherwise. By way of example, “an element” means one element or more than one element. The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

Each alkyl moiety either alone or as part of a larger group such as alkoxy, aminoalkyl or
30 haloalkoxy refers to a monovalent saturated acyclic (i.e., non-cyclic) hydrocarbon group which may be straight or branched. Accordingly, an “alkyl” group does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. A “C₁₋₆alkyl” denotes an alkyl group

having 1 to 6 carbon atoms. Examples include methyl, ethyl, *n*-propyl, prop-2-yl, *n*-butyl, but-2-yl, 2-methyl-prop-1-yl or 2-methyl-prop-2-yl. Examples of an alkoxy include methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, *n*-pentoxy, *neo*-pentoxy, *n*-hexoxy. Examples of aminoalkyl include aminomethyl, aminoethyl, dimethylaminomethyl, dimethylaminoethyl. Haloalkoxy refers to alkoxy with further substitution of halogen.

As used herein, the terms "alkylene" or "alkylenyl," refer to an alkanediyl group, i.e. a straight or branched hydrocarbon chain bi-radical derived from alkyl, as defined herein, wherein one hydrogen of said alkyl is cleaved off generating the second radical of said alkylene. A "C₁₋₆alkylene" denotes an alkylene group having 1 to 6 carbon atoms. Preferred exemplary alkylene groups are methylene (-CH₂-), ethylene (e.g., -CH₂-CH₂- or -CH(-CH₃)-), propylene (e.g., -CH₂-CH₂-CH₂-, -CH(-CH₂-CH₃)-, -CH₂-CH(-CH₃)-, or -CH(-CH₃)-CH₂-), or butylene (e.g., -CH₂-CH₂-CH₂-CH₂-).

Each haloalkyl moiety either alone or as part of a larger group such as haloalkoxy is an alkyl group substituted by one or more of the same or different halogen atoms. Haloalkyl include for example 1 to 5 halo substituents, or 1 to 3 halo substituents. Examples include in particular fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl and 2,2,2-trifluoro-ethyl.

Each alkenyl moiety either alone or as part of a larger group such as alkenyloxy or alkenylene refers to a straight or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having (*E*)- or (*Z*)-configurations, wherein preferably said alkenyl is a C₂-C₁₆alkenyl, more preferably a C₂-C₁₄alkenyl. Preferred Examples include vinyl and allyl. A compound of the present invention comprising an alkenyl moiety thus may include, if applicable, either said compound with said alkenyl moiety in its (*E*)-configuration, said compound with said alkenyl moiety in its (*Z*)-configuration and mixtures thereof in any ratio.

Halogen is fluorine, chlorine, bromine, or iodine.

As used herein, the terms "carbocyclyl" or "carbocycle" refers to a monovalent hydrocarbon ring group including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. The number of carbon atoms in the carbocyclyl is preferably 3 to 14, more preferably 4 to 12 or 5 to 10. In a preferred embodiment, said carbocyclyl is an aryl, a cycloalkyl or a cycloalkenyl.

As used herein, the term "heterocyclyl" or "heterocycle" refers to a monovalent ring

group including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group comprises one or more (such as, e.g., one, two, three, four or five) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. The number of atoms (including carbon and heteroatoms) in the heterocyclyl group is preferably 5 to 14, more preferably 5 to 12 or 5 to 10. In a preferred embodiment, said heterocyclyl is a heteroaryl, a heterocycloalkyl or a heterocycloalkenyl.

The term "aryl", as used herein, refers to a monovalent aromatic hydrocarbon radical of 6-18 carbon atoms (C₆-C₁₈). Aryl includes monocyclic, bicyclic, tricyclic or tetracyclic, preferably monocyclic or bicyclic, further preferably monocyclic radicals comprising an aromatic ring to which saturated, partially unsaturated or aromatic carbocycle(s) or heterocycle(s) are fused or bridged. Aryl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents, wherein said substituents are typically and preferably independently at each occurrence selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Typical aryl groups include, but are not limited to, phenyl, naphthyl, 1,2-dihydronaphthalenyl, 1,2,3,4-tetrahydronaphthenyl, anthracenyl, phenanthrenyl, biphenyl, indenyl and indanyl. In a preferred embodiment, said aryl is phenyl or phenyl substituted by one or two substituents, preferably by one substituent, said substituents independently selected from C₁-C₄alkyl, halogen, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂.

As used herein, the term "heteroaryl" refers to an aromatic ring group including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic), wherein said aromatic ring group comprises one or more (such as, e.g., one, two, three, four or five) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may

optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). Heteroaryl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents independently selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Unless defined otherwise, a "heteroaryl" preferably has 5 to 14 ring atoms, more preferably 5 to 12 or 5 to 10 ring atoms. In a preferred embodiment, said heteroaryl is a monovalent monocyclic aromatic or bicyclic aromatic ring group, wherein said aromatic ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, and wherein said aromatic ring group is optionally substituted independently with one or more substituents, typically and preferably with one or two substituents independently selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, wherein said monocyclic or bicyclic heteroaryl preferably has 5 to 12, preferably 5 to 10 ring atoms. Examples of heteroaryl groups are pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, thiadiazolyl, furazanyl, benzofurazanyl, benzopyranyl, benzothiophenyl, benzothiazolyl, benzooxazolyl, coumarinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl, wherein said heteroaryl are optionally substituted independently with one or more, preferably one or two substituents independently selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Further examples of such monocyclic heteroaryl radicals include, but are not limited to: 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 2-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 3-triazolyl, 1-triazolyl, 5-tetrazolyl, 1-tetrazolyl, and 2-tetrazolyl, which are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents, wherein said substituents are

independently at each occurrence independently selected from C₁-C₄alkyl, halogen, oxo, CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂.

As used herein, the term "cycloalkyl" refers to a monovalent saturated hydrocarbon ring group including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two, three or four rings; such as, e.g., a fused ring system composed of two or three fused rings). Cycloalkyl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents independently selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Unless defined otherwise, "cycloalkyl" preferably refers to a C₃₋₁₄cycloalkyl. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl.

As used herein, the term "heterocycloalkyl" refers to a monovalent saturated ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). Heterocycloalkyl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents independently selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Unless defined otherwise, "heterocycloalkyl" preferably refers to a 3 to 14 membered saturated ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; more preferably, "heterocycloalkyl" refers to a 5 to 7 membered saturated monocyclic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are

optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized.

As used herein, the term "cycloalkenyl" refers to an unsaturated alicyclic (non-aromatic) hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said hydrocarbon ring group comprises one or more (e.g., one or two) carbon-to-carbon double bonds and does not comprise any carbon-to-carbon triple bond. Cycloalkenyl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents, wherein said substituents are typically and preferably independently at each occurrence selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. "Cycloalkenyl" may, e.g., refer to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, or cycloheptadienyl. Unless defined otherwise, "cycloalkenyl" preferably refers to a C₃₋₁₄cycloalkenyl, and more preferably refers to a C₃₋₇ cycloalkenyl.

As used herein, the term "heterocycloalkenyl" refers to an unsaturated alicyclic (non-aromatic) ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms and carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms. Heterocycloalkenyl groups are optionally substituted independently with one or more substituents, typically and preferably with one or two substituents, wherein said substituents are typically and preferably independently at each occurrence selected from C₁-C₄alkyl, halogen, oxo, C₁-C₂haloalkyl preferably CF₃, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OH, OC₁-C₃alkyl, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂. Unless defined otherwise, "heterocycloalkenyl" preferably refers to a 3 to 14 membered unsaturated alicyclic ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one

or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, wherein one or more carbon ring atoms are optionally oxidized, and wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms.

5 Where a group or a chemical moiety is said to be "optionally substituted" shall mean that said group or said chemical moiety has the potential to contain other (functional) groups or moieties, but does not necessarily have any further (functional) groups or moieties. Where a group or a chemical moiety is said to be "optionally substituted", preferably there are optionally 1-5 substituents, more preferably optionally 1-3 substituents, and again more preferably
10 optionally one or two substituents.

The term "amino acid", as used herein, refers to organic compounds containing the functional groups amine (-NH₂) and carboxylic acid (-COOH) and its zwitterions, typically and preferably, along with a side chain specific to each amino acid. The term "amino acid" typically and preferably includes amino acids that occur naturally, such as proteinogenic amino acids
15 (produced by RNA-translation), non-proteinogenic amino acids (produced by other metabolic mechanisms, e.g. posttranslational modification), standard or canonical amino acids (that are directly encoded by the codons of the genetic code) and non-standard or non-canonical amino acids (not directly encoded by the genetic code). Naturally occurring amino acids include non-eukaryotic and eukaryotic amino acids. The term "amino acid", as used herein, also includes
20 unnatural amino acids that are chemically synthesized. Moreover, the term covers alpha- (α -), beta- (β -), gamma- (γ -) and delta- (δ -) etc. amino acids as well as mixtures thereof in any ratio, and any isomeric form of an amino acid, i.e. D- and L-stereoisomers (alternatively addressed by the (*R*) and (*S*) nomenclature) as well as mixtures thereof in any ratio, preferably in a racemic ratio of 1:1. Amino acids in this invention are preferably in L-configuration. The term "D-stereoisomer", "L-stereoisomer", "D-amino acid" or "L-amino acid" refers to the chiral alpha
25 carbon of the amino acids.

Certain compounds of formula (I) of the present invention may contain one or two or more centers of chirality and such compounds may be provided as pure enantiomers or pure diastereoisomers as well as mixtures thereof in any ratio. The compounds of the invention also
30 include all tautomeric forms of the compounds of formula (I). The compounds of formula (I) may also be solvated, especially hydrated, which are also included in the compounds of formula (I). The term "chiral" refers to compounds, which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to compounds, which are superimposable on their mirror image partner. The term "stereoisomers" refers to compounds,

which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. "Diastereomer" refers to a stereoisomer with two or more centers of chirality in which the compounds are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and chemical and biological reactivities. Mixtures of diastereomers may be separated under high resolution analytical procedures such as electrophoresis and chromatography. "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. Stereochemical definitions and conventions used herein generally follow S.P. Parker, Ed., *McRaw-Hiff Dictionary of Chemical Terms* (1984), McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with (−) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or a scalemic mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies, which are interconvertible via a low energy barrier. For example, proton tautomers include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations.

The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention, in particular acid addition salts. Exemplary salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate,

methanesulfonate (mesylate), ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound.

5 Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion. If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available

10 in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid,

15 such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as *p*-toluenesulfonic acid or ethanesulfonic acid, or the like.

The term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep. The term "mammal", as used herein,

20 preferably refers to humans.

The term "treatment" of a disorder or disease as used herein (e.g., "treatment" of a skin cancer such as melanoma) is well known in the art. "Treatment" of a disorder or disease implies that a disorder or disease is suspected or has been diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific

25 clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease).

The "treatment" of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease (e.g., no deterioration of symptoms) or a delay in the progression of the disorder or disease (in case the halt in progression is of a transient nature only). The

30 "treatment" of a disorder or disease may also lead to a partial response (e.g., amelioration of symptoms) or complete response (e.g., disappearance of symptoms) of the subject/patient suffering from the disorder or disease. Accordingly, the "treatment" of a disorder or disease may also refer to an amelioration of the disorder or disease, which may, e.g., lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease.

Such a partial or complete response may be followed by a relapse. It is to be understood that a subject/patient may experience a broad range of responses to a treatment. The treatment of a disorder or disease may, inter alia, comprise curative treatment (preferably leading to a complete response and eventually to healing of the disorder or disease) and palliative treatment (including symptomatic relief). The "amelioration" of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

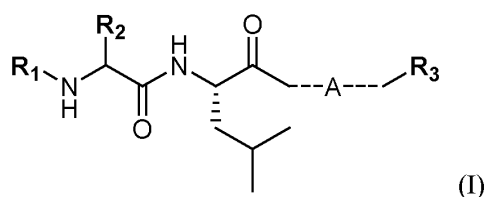
The term "effective amount" means an amount of a compound of the present invention or an inventive pharmaceutical composition that (i) treats the particular disease or disorder or (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease or disorder. In the case of a skin cancer, in particular in case of a cancer is a melanoma or a cutaneous squamous cell carcinoma, the effective amount of the drug may reduce the tumor volume and/or reduce clinical symptoms.

The terms "cancer" and "cancerous" includes the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells.

The term "skin cancer" as used herein, refers to a skin cancer such as a melanoma skin cancer and non-melanoma skin cancer (NMSC) but also refers and includes precancer and pre-invasive neoplastic skin proliferations such as cutaneous squamous cell carcinoma in situ (cSCCis or Bowen's disease) or Actinic Keratosis (AK, also called "solar keratosis" and "senile keratosis"). Moreover, the term "skin cancer" as used herein, shall also include cutaneous lymphomas such as cutaneous T-cell lymphoma (CTCL) or cutaneous B-cell lymphoma (CBCL), or a pre-invasive form thereof. Bowen's disease is a neoplastic skin disease which can be considered as an early stage or intraepidermal form of squamous cell carcinoma. Actinic keratosis is characterized by pre-cancerous patches of thick, scaly, or crusty skin, which are usually formed when skin gets damaged by ultraviolet (UV) radiation from the sun or indoor tanning beds.

The term "non-melanoma skin cancer", (abbreviated as "NMSC") is used herein to refer to a group of diseases in particular including cutaneous squamous cell carcinoma (cSCC), basal cell carcinoma (BCC), Merkel Cell carcinoma (MCC), Bowen's Disease (BD) and Actinic Keratosis (AK), as well as any precancer and pre-invasive forms thereof.

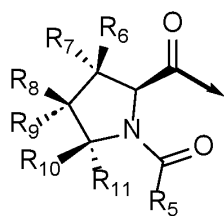
In a first aspect, the present invention provides for a compound of formula (I)



wherein

--A-- represents a peptide chain, wherein said peptide chain consists of 4 to 9 amino acids, wherein preferably said amino acids are selected from α -aminoisobutyric acid (Aib; 2-amino-2-methylpropionic acid), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala);

R₁ is



, wherein the arrow indicates the attachment to the NH-moiety

depicted in formula (I), and wherein

R₅ is selected from H, C₁-C₁₆alkyl, C₁-C₁₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-heterocyclyl, wherein said C₁-C₁₆alkyl and said C₁-C₁₆alkenyl each independently optionally substituted with halogen, OR₁₈, NR₁₉R₂₀, -[O-C₂H₄]_n-OCH₃ wherein n=2-20; and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl, and wherein

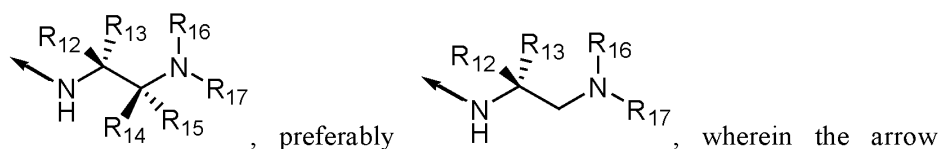
R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl, C₁-C₃alkylene-heterocyclyl, halogen, C₁-C₂haloalkyl, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, C(O)O-C₁-C₆alkyl, C(O)-C₁-C₆alkyl, C(O)O-C₁-C₆alkenyl, C(O)-C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-heterocyclyl, wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, C₁-C₂haloalkyl, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈,

NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle; said carbocycle and said heterocycle optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀; and

5 wherein at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H; and

R₂ is selected from C₄-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-cycloalkyl, C₁-C₃alkylene-aryl or C₁-C₃alkylene-heteroaryl, wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more, preferably one or two, substituents selected from C₁-C₂alkyl, C₁-C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl;

R₃ is



15 indicates the attachment to the A-moiety in formula (I), and wherein

R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

20 R₁₆ and R₁₇ are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocycle, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀;

25 or a pharmaceutically acceptable salt of said compound of formula (I).

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, and a pharmaceutically acceptable carrier or adjuvant.

30 In a further aspect, the present invention provides a compound of formula (I) for use in a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound to said mammal, preferably to said human.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, and a pharmaceutically acceptable carrier or adjuvant, for use in a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of
5 said pharmaceutical composition to said mammal, preferably to said human.

In another aspect, the present invention provides a method of treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically
10 acceptable salt thereof, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound to said mammal, preferably to said human.

In a further aspect, the present invention provides for the use of a compound of formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound of formula (I), or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition of the invention, to said mammal, preferably to said human, and wherein preferably said method comprises
15 administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition, to said mammal, preferably to said human.

In a further aspect, the present invention provides a compound of formula (I) for use in a method of treating a skin cancer of a mammal, preferably of a human, wherein said method comprises administration to said mammal, preferably to said human, of a compound of formula
25 (I), or a pharmaceutically acceptable salt thereof, as defined herein, in particular as in any one of the appended claims, wherein preferably said method comprises administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, to said mammal, preferably to said human.

In a further aspect, the present invention provides a pharmaceutical composition for use
30 in a method of treatment of a skin cancer of a mammal, preferably of a human, wherein said pharmaceutical composition comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein, in particular as in any one of the appended claims, and a pharmaceutically acceptable carrier or adjuvant, and wherein said method comprises administration of said pharmaceutical composition to said mammal, preferably to said human,

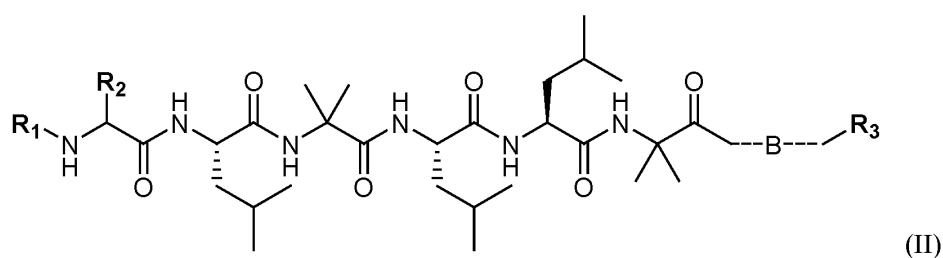
and wherein preferably said pharmaceutical composition comprises an effective amount of said compound.

Thus, in particular, the present invention provides compounds and pharmaceutical compositions for use in methods of treatment of skin cancer of a mammal, preferably of a human, in particular for use in methods of treatment of melanoma and non-melanoma skin cancer, and preferably for melanoma and cutaneous squamous cell carcinoma, wherein said methods comprise administration of an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I), or a pharmaceutically acceptable salt thereof, to said mammal, preferably to said human.

In another aspect, the present invention provides a method for treating a skin cancer of a mammal, preferably of a human, wherein said method comprises administration of a compound of formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I), or a pharmaceutically acceptable salt thereof, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition to said mammal, preferably to said human.

In a further aspect, the present invention provides for the use of a compound of formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a skin cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound of formula (I), or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition of the invention, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition, to said mammal, preferably to said human.

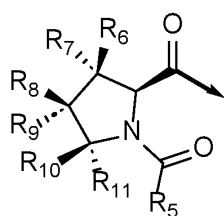
In another aspect, the present invention provides a compound of formula (II)



wherein

--B-- represents a peptide chain, wherein said peptide chain consists of 0 to 5 amino acids, wherein preferably said amino acids are selected from α -aminoisobutyric acid (Aib; 2-amino-2-methylpropionic acid), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala);

R₁ is



, wherein the arrow indicates the attachment to the NH-moiety depicted in formula (I), and wherein

R₅ is selected from H, C₁-C₁₆alkyl, C₁-C₁₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-heterocyclyl, wherein said C₁-C₁₆alkyl and said C₁-C₁₆alkenyl each independently optionally substituted with halogen, OR₁₈, NR₁₉R₂₀, -[O-C₂H₄]_n-OCH₃ wherein n=2-20; and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl, and wherein

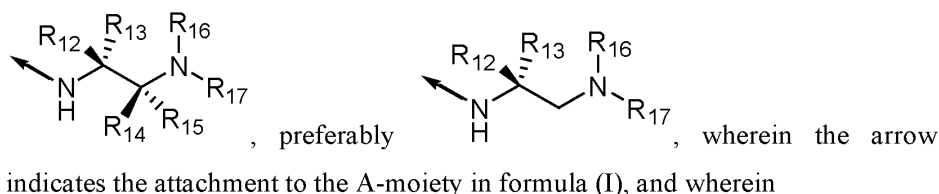
R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl, C₁-C₃alkylene-heterocyclyl, halogen, C₁-C₂haloalkyl, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, C(O)O-C₁-C₆alkyl, C(O)-C₁-C₆alkyl, C(O)O-C₁-C₆alkenyl, C(O)-C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-heterocyclyl, wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, C₁-

C₂haloalkyl, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle; said carbocycle and said heterocycle optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀; and

wherein at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H; and

R₂ is selected from C₄-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-cycloalkyl, C₁-C₃alkylene-aryl or C₁-C₃alkylene-heteroaryl, wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more, preferably one or two, substituents selected from C₁-C₂alkyl, C₁-C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl;

R₃ is



R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

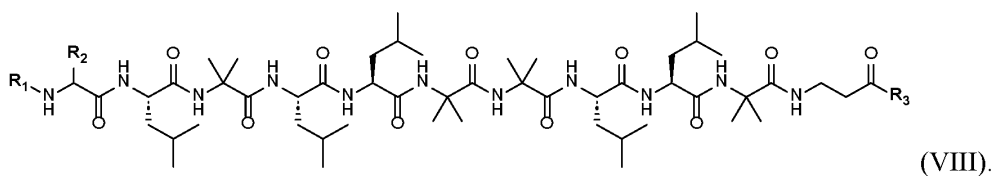
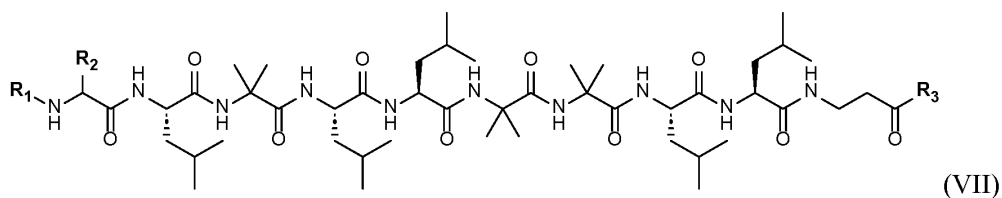
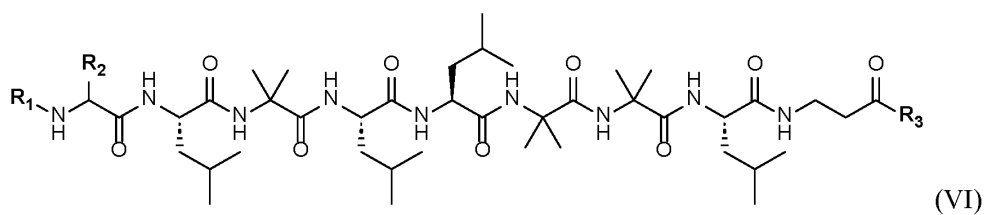
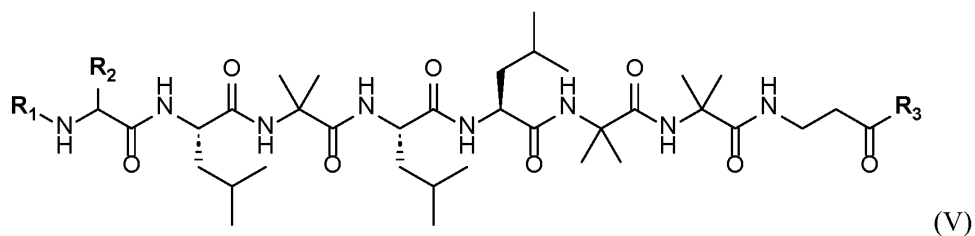
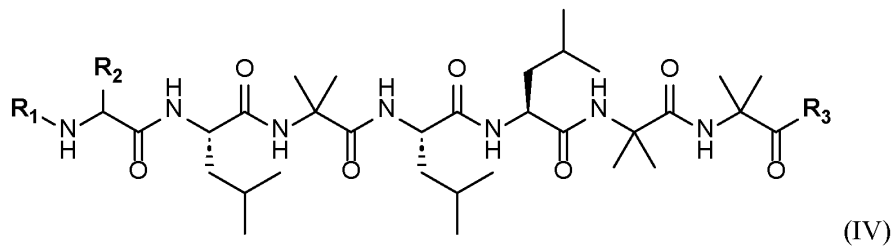
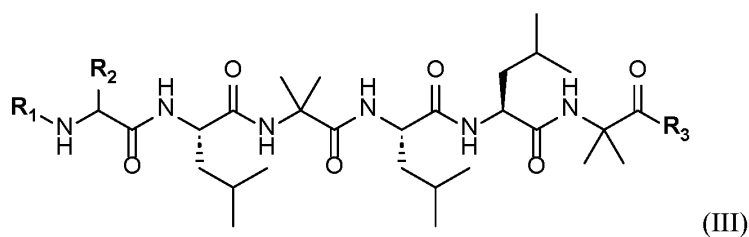
R₁₆ and R₁₇ are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀;

or a pharmaceutically acceptable salt of said compound of formula (I).

In a preferred embodiment, said compound of formula (I) is a compound of formula (II).

In another preferred embodiment, said compound of formula (I) is a compound selected from any one of the formulas (III) to (VIII) as depicted below.

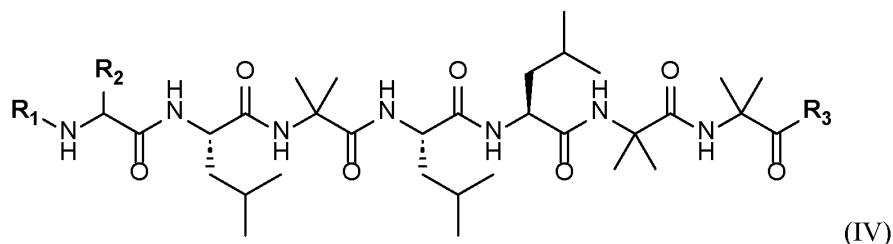
In another preferred embodiment, said compound of formula (II) is a compound selected from any one of the formulas (III) to (VIII)



In another preferred embodiment, said compound of formula (II) is a compound selected from any one of the formulas (IV) to (VI). In another preferred embodiment, said compound of formula (II) is a compound selected from any one of the formulas (IV) to (V). In another preferred embodiment, said compound of formula (II) is a compound of formula (V). In another preferred embodiment, said compound of formula (II) is a compound of formula (VI). In another very preferred embodiment, said compound of formula (II) is a compound of formula

(IV).

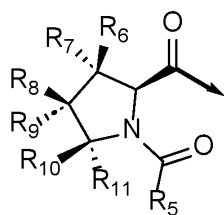
In a further aspect, the present invention provides a compound of formula (IV)



wherein

--B-- represents a peptide chain, wherein said peptide chain consists of 0 to 5 amino acids, wherein preferably said amino acids are selected from α -aminoisobutyric acid (Aib; 2-amino-2-methylpropionic acid), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala);

R₁ is



, wherein the arrow indicates the attachment to the NH-moiety depicted in formula (I), and wherein

R₅ is selected from H, C₁-C₁₆alkyl, C₁-C₁₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-heterocyclyl, wherein said C₁-C₁₆alkyl and said C₁-C₁₆alkenyl each independently optionally substituted with halogen, OR₁₈, NR₁₉R₂₀, -[O-C₂H₄]_n-OCH₃ wherein n=2-20; and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl, and wherein

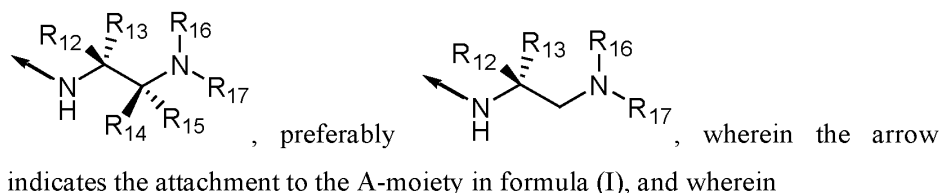
R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl, C₁-C₃alkylene-heterocyclyl, halogen, C₁-C₂haloalkyl, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₆alkyl, C₁-C₆alkenyl, C(O)O-C₁-C₆alkyl, C(O)-C₁-C₆alkyl, C(O)O-C₁-C₆alkenyl, C(O)-C₁-C₆alkenyl, carbocyclyl, heterocyclyl, C₁-C₃alkylene-carbocyclyl or C₁-C₃alkylene-

heterocyclyl, wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, C₁-C₂haloalkyl, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle; said carbocycle and said heterocycle optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀; and

wherein at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H; and

R₂ is selected from C₄-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-cycloalkyl, C₁-C₃alkylene-aryl or C₁-C₃alkylene-heteroaryl, wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more, preferably one or two, substituents selected from C₁-C₂alkyl, C₁-C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl;

R₃ is



R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

R₁₆ and R₁₇ are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀;

or a pharmaceutically acceptable salt of said compound of formula (I).

In another preferred embodiment, said R₅ is selected from cycloalkyl, aryl, heteroaryl, C₅-C₁₂alkyl, C₅-C₁₂alkenyl or C₁-C₄alkylene-[O-C₂H₄]_n-OCH₃ wherein n=5-15, wherein said

aryl, heteroaryl, cycloalkyl each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀.

In another preferred embodiment, said R₅ is selected from C₆-C₇alkyl, C₆-C₇alkenyl, C₁-C₄alkylene-[O-C₂H₄]_n-OCH₃ wherein n=8-12, phenyl or a monocyclic heteroaryl comprising
5 one or two heteroatoms selected from N, O and S, preferably oxazolyl, wherein said phenyl or said monocyclic heteroaryl preferably said oxazolyl, each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀.

In another preferred embodiment, said R₅ is selected from cycloalkyl, aryl, heteroaryl,
10 C₅-C₁₂alkyl, or C₅-C₁₂alkenyl, wherein said aryl, heteroaryl, cycloalkyl each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀. In another preferred embodiment, said R₅ is selected from C₆-C₇alkyl, C₆-C₇alkenyl, phenyl or a monocyclic heteroaryl comprising one or two heteroatoms selected from N, O and S, preferably oxazolyl, wherein said phenyl or said
15 monocyclic heteroaryl preferably said oxazolyl, each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀. In another preferred embodiment, said R₅ is selected from C₅-C₁₂alkyl or C₅-C₁₂alkenyl, preferably from C₆-C₇alkyl or C₆-C₇alkenyl. In another preferred embodiment, said R₅ is ((S,E)-4-methylhex-2-enyl.

In another preferred embodiment, said R₅ is selected from cycloalkyl, aryl or heteroaryl,
20 each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₅ is selected from cycloalkyl, monocyclic or bicyclic aryl or monocyclic or bicyclic heteroaryl, each
25 independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R₅ is selected from phenyl, naphthyl, 1,2-dihydronaphthalenyl, 1,2,3,4-tetrahydronaphthenyl, anthracenyl, phenanthrenyl, biphenyl,
30 indenyl, indanyl, pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, thiadiazolyl, furazanyl, benzofurazanyl, benzopyranyl, benzothiophenyl,

benzothiazolyl, benzooxazolyl, coumarinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, adamantanyl, each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R₅ is selected from cycloalkyl, monocyclic or bicyclic aromatic aryl or monocyclic or bicyclic heteroaryl, each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₅ is selected from phenyl or a monocyclic or bicyclic heteroaryl comprising one or two heteroatoms selected from N, O and S, preferably from phenyl, coumarinyl or oxazolyl, further preferably phenyl or oxazolyl; each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

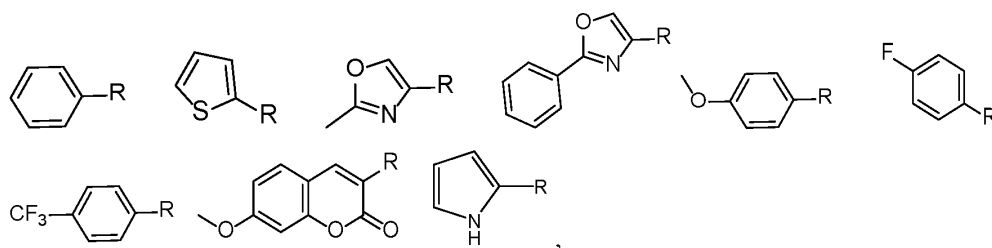
In a further preferred embodiment, said R₅ is selected from phenyl or monocyclic or bicyclic heteroaryl, each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₁ is selected from phenyl or monocyclic or bicyclic aromatic heteroaryl, each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R₅ is selected from phenyl, imidazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, indolyl, benzimidazolyl, benzopyranyl, benzothiophenyl, benzothiazolyl, benzooxazolyl, each independently optionally substituted with C₁-C₄alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₅ is selected from phenyl, imidazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, indolyl, benzimidazolyl, benzopyranyl, benzothiophenyl, benzothiazolyl, benzooxazolyl, coumarinyl, each independently optionally substituted with methyl, ethyl, chlorine, fluorine, oxo, CF₃, OC₁-C₂alkyl, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with

methyl, ethyl, chlorine, fluorine, OC₁-C₂alkyl, NR₁₉R₂₀, wherein R₁₉, R₂₀ are independently at each occurrence H, methyl, ethyl.

In a further preferred embodiment, said R₅ is selected from phenyl, imidazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, coumarinyl, each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₅ is selected from phenyl, thienyl, oxazolyl, pyrrolyl, coumarinyl, each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl. In a further preferred embodiment, said R₅ is selected from phenyl, thienyl, oxazolyl, pyrrolyl, coumarinyl, each independently optionally substituted, preferably mono-substituted, with methyl, ethyl, chlorine, fluorine, CF₃, OC₁-C₂alkyl, NR₅R₆, C₆H₅, C₆H₅ substituted with methyl, ethyl, chlorine, fluorine, OC₁-C₂alkyl, NR₁₉R₂₀, wherein R₁₉, R₂₀ are independently at each occurrence H, methyl, ethyl.

In a further preferred embodiment, said R₅ is selected from the formula



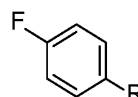
wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

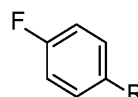
In a further preferred embodiment, said R₅ is phenyl or oxazolyl, each independently optionally substituted with C₁-C₄alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R₅ is phenyl, coumarinyl or oxazolyl, each independently optionally substituted, preferably mono-substituted, with methyl, ethyl, chlorine, fluorine, CF₃, OC₁-C₂alkyl, NR₅R₆, C₆H₅, C₆H₅ substituted with methyl, ethyl, chlorine, fluorine, OC₁-C₂alkyl, NR₁₉R₂₀, wherein R₁₉, R₂₀ are independently at each occurrence H, methyl, ethyl.

In a further preferred embodiment, said R₅ is phenyl, coumarinyl or oxazolyl, each independently optionally substituted, preferably mono-substituted, with methyl, chlorine,

fluorine, CF₃, OCH₃, C₆H₅, C₆H₅ substituted, preferably mono-substituted, with methyl or fluorine.



In a further very preferred embodiment, said R₅ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

5 In a preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₄alkyl, C₁-C₄alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl, C₁-C₂alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₄alkyl, C₁-C₄alkenyl, C(O)O-C₁-C₄alkyl, C(O)-C₁-C₄alkyl, C(O)O-C₁-C₄alkenyl, C(O)-C₁-C₄alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is mono- or bicyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a mono- or bicyclic carbocycle or heterocycle, preferably a mono- or bicyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl,

20 In another preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₄alkyl, C₁-C₄alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl, C₁-C₂alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁ and R₂₂, are independently at each occurrence selected from C₁-C₄alkyl, C₁-C₄alkenyl, C(O)O-C₁-C₄alkyl, C(O)-C₁-C₄alkyl, C(O)O-C₁-C₄alkenyl, C(O)-C₁-C₄alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, and wherein R₂₃ is selected from H, C₁-C₄alkyl, C₁-C₄alkenyl, C(O)O-C₁-C₄alkyl, C(O)-C₁-C₄alkyl, C(O)O-C₁-C₄alkenyl, C(O)-C₁-C₄alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is mono- or bicyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a mono- or bicyclic carbocycle or heterocycle, preferably a mono- or bicyclic carbocycle; wherein said carbocycle

and said heterocycle each independently optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉ are independently at each occurrence C₁-C₃alkyl, and wherein preferably R₂₀ is H or C₁-C₃alkyl.

In another preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each
5 occurrence selected from H, C₁-C₃alkyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl, C₁-C₂alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₃alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₃alkyl, C(O)-C₁-C₃alkyl, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, wherein
10 said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, wherein R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₃alkyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁-
20 C₂alkylene-carbocyclyl, C₁-C₂alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁ and R₂₂ are independently at each occurrence selected from C₁-C₃alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₃alkyl, C(O)-C₁-C₃alkyl, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, and wherein R₂₃ is selected from H, C₁-C₃alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₃alkyl, C(O)-C₁-C₃alkyl, C(O)O-C₁-
25 C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁-C₂alkylene-carbocyclyl or C₁-C₂alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀,
30 and R₁₁ together with the carbon atom to which they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉ are independently at each occurrence C₁-C₃alkyl, and wherein preferably R₂₀ is H or C₁-C₃alkyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₂alkyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl, C₁alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, C₁-C₂alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₂alkyl, C(O)-C₁-C₂alkyl, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl or C₁alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₂alkyl, halogen preferably F, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen preferably F, C₁-C₂alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with C₁-C₂alkyl, halogen preferably F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉ are independently at each occurrence C₁-C₂alkyl, and wherein preferably R₂₀ is H or C₁-C₂alkyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, C₁-C₂alkyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl, C₁alkylene-heterocyclyl, halogen, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁ and R₂₂ are independently at each occurrence selected from C₁-C₂alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₂alkyl, C(O)-C₁-C₂alkyl, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl or C₁alkylene-heterocyclyl, and wherein R₂₃ is selected from H, C₁-C₂alkyl, C₁-C₃alkenyl, C(O)O-C₁-C₂alkyl, C(O)-C₁-C₂alkyl, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, Calkylene-carbocyclyl or C₁alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₂alkyl, halogen preferably F, oxo, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen preferably F, C₁-C₂alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with C₁-C₂alkyl, halogen preferably F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉ are independently at each occurrence C₁-C₂alkyl, and wherein preferably R₂₀ is H or C₁-C₂alkyl.

In a preferred embodiment, said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a preferred embodiment, said R₁₈ and R₁₉ are independently at each occurrence C₁-C₃alkyl, and wherein preferably R₂₀ is H or C₁-C₃alkyl.

In a preferred embodiment, said R₁₈ and R₁₉ are independently at each occurrence C₁-C₂alkyl, and wherein preferably R₂₀ is H or C₁-C₂alkyl.

5 In a preferred embodiment, said R₁₈ and R₁₉ are independently at each occurrence methyl, and wherein preferably R₂₀ is H or methyl.

In a preferred embodiment, at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is H, and at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H.

10 In a preferred embodiment, at least two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is H, and at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H.

In a preferred embodiment, at least three of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is H, and at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H.

In a preferred embodiment, at least four of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is H, and at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H.

15 In a preferred embodiment, at least five of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is H, and at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H.

In a preferred embodiment, said R₁₀ is H. In a preferred embodiment, said R₁₁ is H. In a further preferred embodiment, said R₁₀ and said R₁₁ is H.

20 In a preferred embodiment, said R₆ is not H. In a preferred embodiment, said R₇ is not H. In a preferred embodiment, said R₈ is not H. In a preferred embodiment, said R₉ is not H. In a further preferred embodiment, said R₈ and said R₉ is not H. In a further preferred embodiment, at least two of said R₆, R₇, R₈ and R₉ are not H. In a further preferred embodiment, said R₆ and said R₈ are not H. In a further preferred embodiment, said R₇ and said R₉ are not H.

25 In a preferred embodiment, one of said R₈ or said R₉ is not H, wherein the stereochemistry at the carbon atom substituted by either R₈ or R₉ has the (*S*)-stereochemistry.

30 In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, methyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl, C₁alkylene-heterocyclyl, F, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl or C₁alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with F, methyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁, preferably

R₈ and R₉, R₇ and R₉ or R₆ and R₈, further preferably R₈ and R₉ or R₆ and R₈, together with the carbon atom to which they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably
5 R₁₈ and R₁₉ are independently at each occurrence methyl, and wherein preferably R₂₀ is H or methyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, methyl, C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl, C₁alkylene-heterocyclyl, F, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁ and R₂₂ are
10 independently at each occurrence selected from methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl or C₁alkylene-heterocyclyl, and wherein said R₂₃ is selected from H, methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, carbocyclyl, heterocyclyl, C₁alkylene-carbocyclyl or C₁alkylene-heterocyclyl, wherein said carbocyclyl and said
15 heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with F, methyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁, preferably R₈ and R₉, R₇ and R₉ or R₆ and R₈, further preferably R₈ and R₉ or R₆ and R₈, together with the carbon atom to which they are attached form a monocyclic carbocycle
20 or heterocycle, preferably a monocyclic carbocycle; wherein said carbocycle and said heterocycle each independently optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉ are independently at each occurrence methyl, and wherein preferably R₂₀ is H or methyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each
25 occurrence selected from H, methyl, C₁-C₃alkenyl, phenyl, benzyl, C₃-C₆cycloalkyl, C₁alkylene-C₃₋₆cycloalkyl, F, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁, R₂₂, R₂₃ are independently at each occurrence selected from H, methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, phenyl, benzyl, C₃-C₆cycloalkyl, C₁alkylene-C₃₋₆cycloalkyl, and wherein each of said phenyl, benzyl, C₃-C₆cycloalkyl independently at each
30 occurrence optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with F, methyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁, preferably R₈ and R₉, R₇ and R₉ or R₆ and R₈, further preferably R₈ and R₉ or R₆ and R₈, together with the carbon atom to which they are attached form a C₃-C₆cycloalkyl; wherein said C₃-C₆cycloalkyl is optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉

are independently at each occurrence methyl, and wherein preferably R₂₀ is H or methyl.

In a further preferred embodiment, said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are independently at each occurrence selected from H, methyl, C₁-C₃alkenyl, phenyl, benzyl, C₃-C₆cycloalkyl, C₁alkylene-C₃-C₆cycloalkyl, F, CF₃, OR₂₁ or NR₂₂R₂₃, wherein said R₂₁ and R₂₂ are
5 independently at each occurrence selected from methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, phenyl, benzyl, C₃-C₆cycloalkyl, C₁alkylene-C₃-C₆cycloalkyl, and wherein R₂₃ is selected from H, methyl, C₁-C₃alkenyl, C(O)O-CH₃, C(O)-CH₃, C(O)O-C₁-C₃alkenyl, C(O)-C₁-C₃alkenyl, phenyl, benzyl, C₃-C₆cycloalkyl, C₁alkylene-C₃-C₆cycloalkyl, and wherein each of said phenyl, benzyl, C₃-C₆cycloalkyl independently at each
10 occurrence optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with F, methyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁, preferably R₈ and R₉, R₇ and R₉ or R₆ and R₈, further preferably R₈ and R₉ or R₆ and R₈, together with the carbon atom to which they are attached form a C₃-C₆cycloalkyl; wherein said C₃-C₆cycloalkyl is optionally substituted with methyl, F, CF₃, OR₁₈, NR₁₉R₂₀, wherein preferably R₁₈ and R₁₉
15 are independently at each occurrence methyl, and wherein preferably R₂₀ is H or methyl.

In a preferred embodiment, one, two, three or four of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are methyl, wherein the other five, four, three or two of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, one or two of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are methyl, wherein the other five or four of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

20 In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is methyl, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, two of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are methyl, wherein the other four of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

25 In a very preferred embodiment, said R₆ and R₇ are methyl, wherein said R₈, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₈ and R₉ are methyl, wherein said R₆, R₇, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₁₀ and R₁₁ are methyl, wherein said R₆, R₇, R₈ and R₉ are H.

30 In a preferred embodiment, said R₆ is methyl, wherein R₇, R₈, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₇ is methyl, wherein R₆, R₈, R₉, R₁₀ and R₁₁ are H.

In a very preferred embodiment, said R₈ is methyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is methyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₁₀ is methyl, wherein R₆, R₇, R₈, R₉ and R₁₁ are H.

In a preferred embodiment, said R₁₁ is methyl, wherein R₆, R₇, R₈, R₉ and R₁₀ are H.

In a preferred embodiment, said R₈ is OH, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is OH, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

5 In a preferred embodiment, said R₆ and R₈ together with the carbon atom to which they are attached form a cyclohexyl, wherein R₇, R₉, R₁₀ and R₁₁ are H. In a preferred embodiment, said R₇ and R₉ together with the carbon atom to which they are attached form a cyclohexyl, wherein R₆, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is O-phenyl optionally substituted with methyl, F, CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

10 In a preferred embodiment, said R₈ is O-phenyl, optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is O-phenyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

15 In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is O-phenyl, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is O-phenyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is O-phenyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

20 In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is benzyl optionally substituted with methyl, F, CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is benzyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is benzyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

25 In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is benzyl substituted with F, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is benzyl substituted with F, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

30 In a preferred embodiment, said R₉ is benzyl substituted with F, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₈ is benzyl substituted with F at the para position, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is benzyl substituted with F at the para position, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one or two of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are F, wherein the other five or four of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is F, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

5 In a preferred embodiment, two of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are F, wherein the other four of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is F, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is F, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₈ and said R₉ are F, wherein R₆, R₇, R₁₀ and R₁₁ are H.

10 In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₆ and R₇ together with the carbon atom to which they are attached form a cyclopropyl, wherein R₈, R₉, R₁₀ and R₁₁ are H. In a preferred embodiment, said R₈ and R₉ together with the carbon atom to which they are attached form a cyclopropyl, wherein R₆, R₇, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is phenyl optionally substituted with methyl, F, CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

20 In a preferred embodiment, said R₈ is phenyl, optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a very preferred embodiment, said R₉ is phenyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is phenyl, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is phenyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a very preferred embodiment, said R₉ is phenyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is phenyl substituted with F, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

30 In a preferred embodiment, said R₈ is phenyl optionally substituted with F, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a very preferred embodiment, said R₉ is phenyl substituted with F, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₈ is phenyl, optionally substituted with F at the para

position, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is phenyl substituted with F at the para position, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is cyclohexyl optionally substituted with methyl, F, CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

In a preferred embodiment, said R₈ is cyclohexyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is cyclohexyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

10 In a preferred embodiment, said R₈ is cyclohexyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is cyclohexyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is O-benzyl optionally substituted with methyl, F, CF₃, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

15 In a preferred embodiment, said R₈ is O-benzyl, optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

In a preferred embodiment, said R₉ is O-benzyl optionally substituted with methyl, F, CF₃, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is O-benzyl, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

20 In a preferred embodiment, said R₈ is O-benzyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

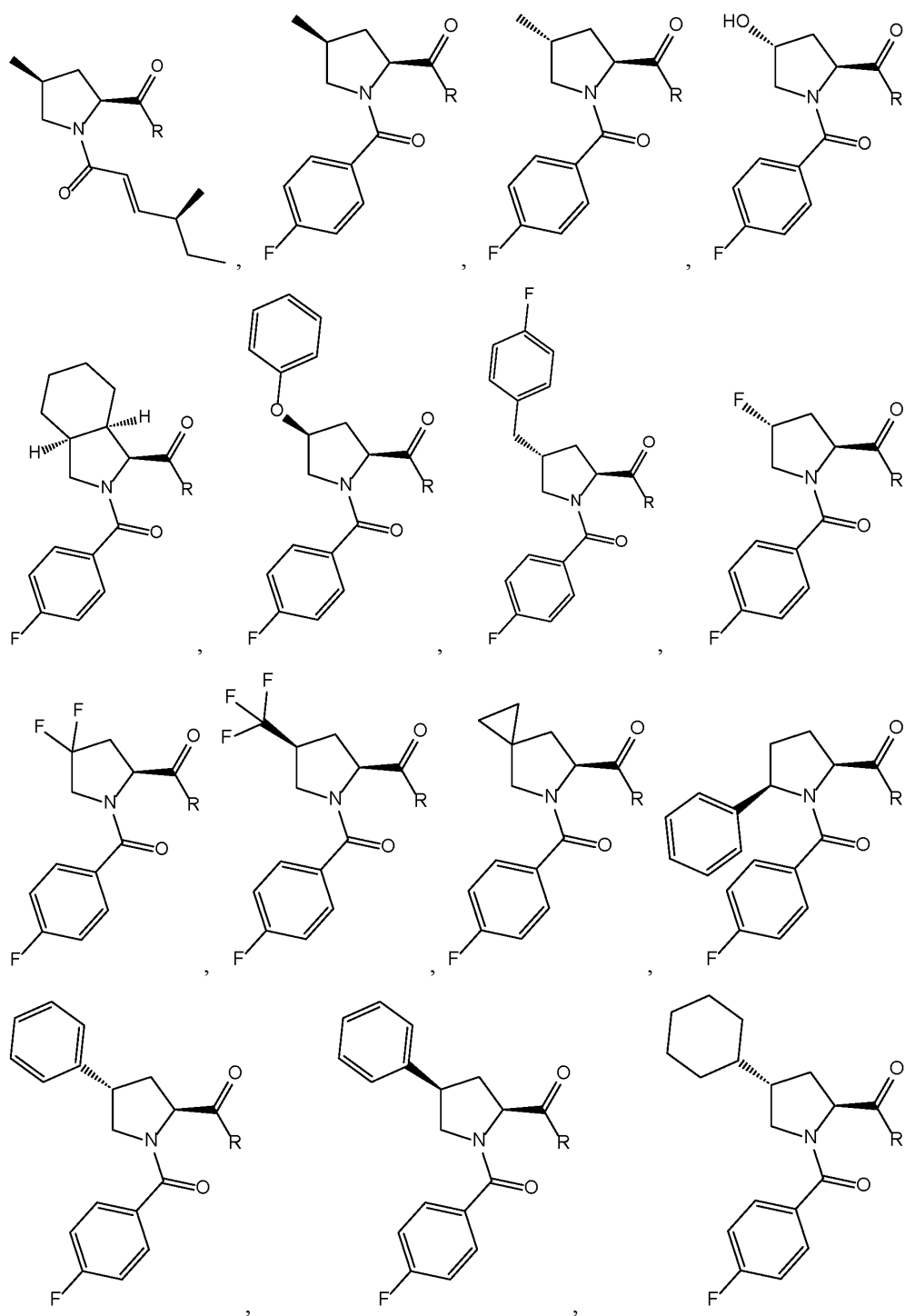
In a preferred embodiment, said R₉ is O-benzyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

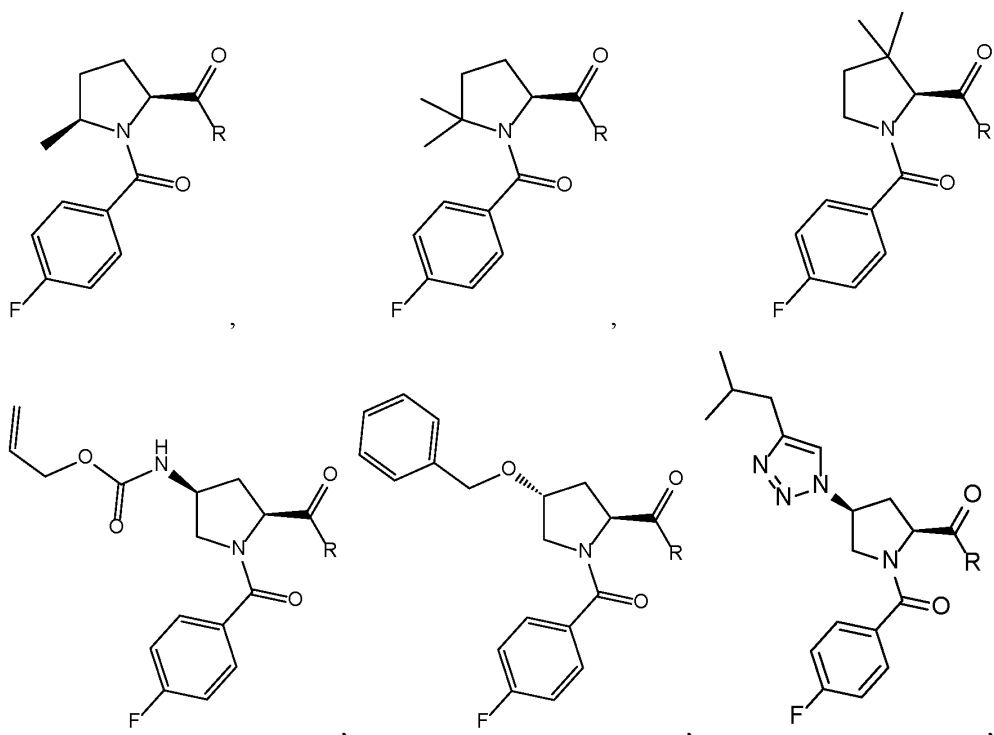
In a preferred embodiment, one of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ is NHC(O)O-allyl, wherein the other five of said R₆, R₇, R₈, R₉, R₁₀, R₁₁ are H.

25 In a preferred embodiment, said R₈ is NHC(O)O-allyl, wherein R₆, R₇, R₉, R₁₀ and R₁₁ are H.

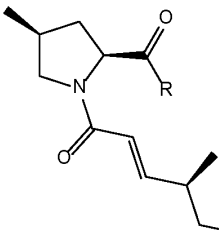
In a preferred embodiment, said R₉ is NHC(O)O-allyl, wherein R₆, R₇, R₈, R₁₀ and R₁₁ are H.

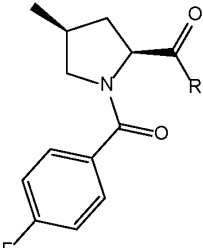
In a preferred embodiment, said R₁ is selected from the formula

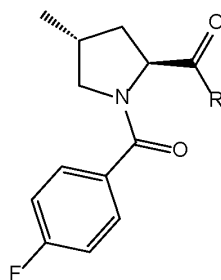


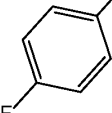


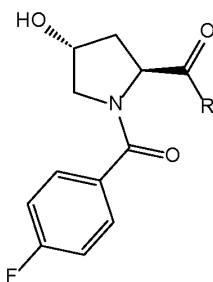
wherein R indicates the attachment to the NH-moiety depicted in formula (I).

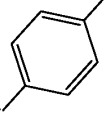
- 5 In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

In another very preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

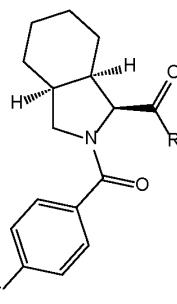


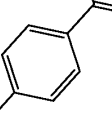
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

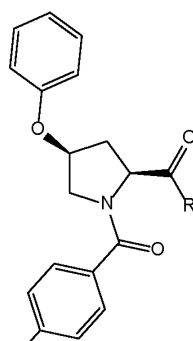


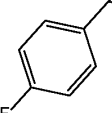
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

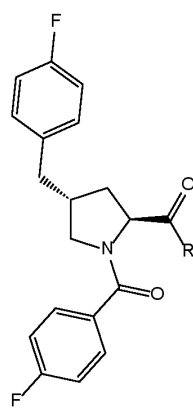
5



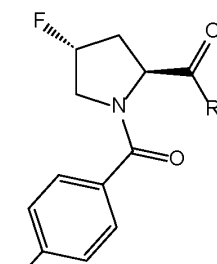
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



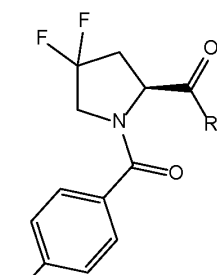
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



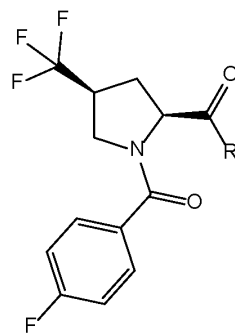
In another preferred embodiment, said R_1 is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



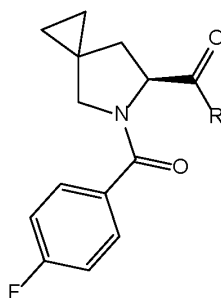
In another preferred embodiment, said R_1 is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

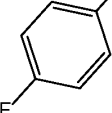


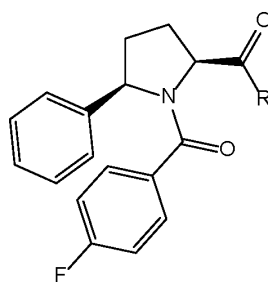
5 In another preferred embodiment, said R_1 is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

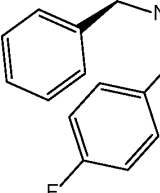


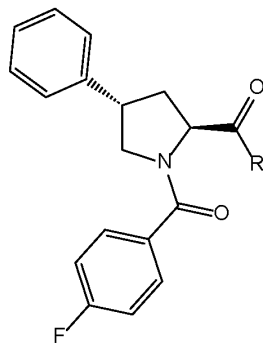
In another preferred embodiment, said R_1 is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



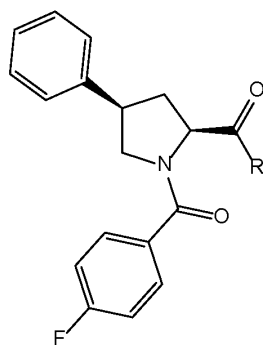
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



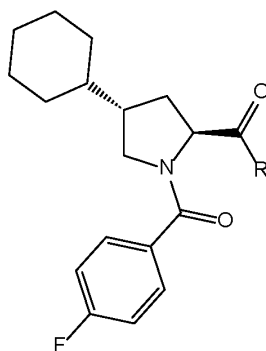
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

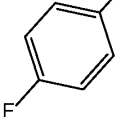


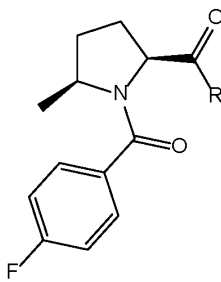
5 In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

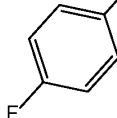


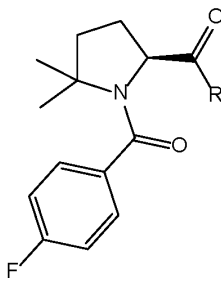
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

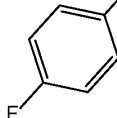


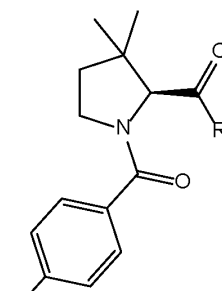
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

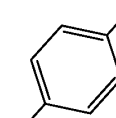


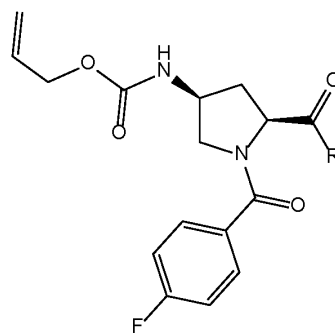
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

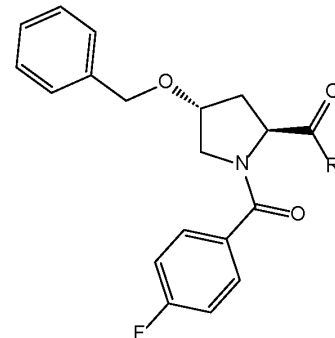


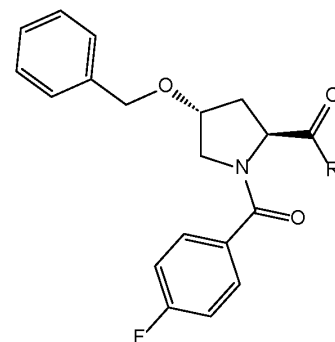
5 In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

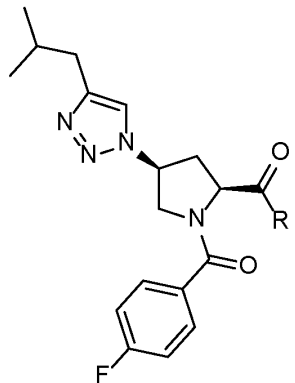


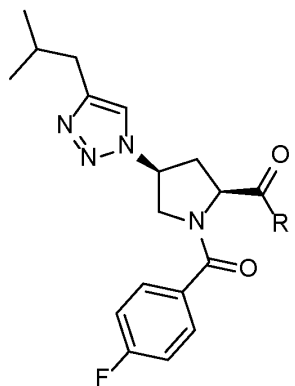
In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

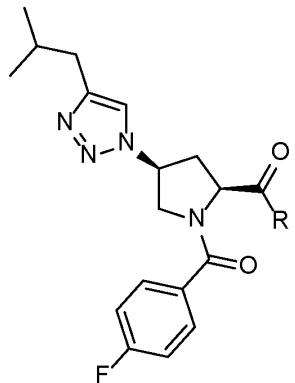


In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).



5 In another preferred embodiment, said R₁ is , wherein R indicates the attachment to the NH-moiety depicted in formula (I).

In a further preferred embodiment, said R₂ is selected from C₅-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-cycloalkyl, C₁-C₃alkylene-aryl, C₁-C₃alkylene-heteroaryl, wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or
 10 -O-; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally and preferably substituted with one or more, typically and preferably one or two, substituents selected from C₁-C₂alkyl, C₁-C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl.

In a further preferred embodiment said R₂ is selected from C₅-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-C₅-C₆cycloalkyl, C₁-C₃alkylene-phenyl, C₁-C₃alkylene-biphenyl, C₁-C₃alkylene-(mono- or bicyclic-heteroaryl), wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-, and wherein said phenyl, biphenyl, 5 C₅-C₆-cycloalkyl, and mono- or bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably one or two, substituents selected from methyl, ethyl, fluorine, chlorine, methoxy, wherein preferably said mono- or bicyclic-heteroaryl is selected from imidazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzopyranyl, benzothiophenyl, 10 benzothiazolyl, benzooxazolyl.

In a further preferred embodiment said R₂ is selected from C₅-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₂alkylene-C₅-C₆cycloalkyl, C₁-C₂alkylene-phenyl, C₁-C₂alkylene-biphenyl, C₁-C₂alkylene-(mono- or bicyclic-heteroaryl), wherein independently in said C₁-C₂alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-, and wherein said phenyl, biphenyl, 15 C₅-C₆-cycloalkyl, and mono- or bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably one or two, substituents selected from methyl, ethyl, fluorine, chlorine, methoxy, wherein preferably said mono- or bicyclic-heteroaryl is selected from imidazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzopyranyl, benzothiophenyl, 20 benzothiazolyl, benzooxazolyl, and wherein further preferably said mono- or bicyclic-heteroaryl is selected from isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, indolyl, benzimidazolyl, benzothiazolyl, benzooxazolyl.

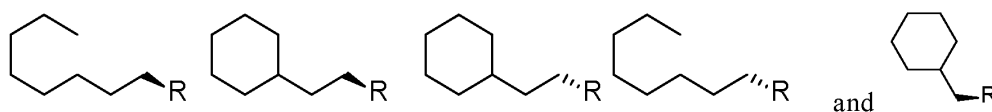
In a further preferred embodiment said R₂ is selected from C₅-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₂alkylene-C₅-C₆cycloalkyl, C₁-C₂alkylene-phenyl, C₁-C₂alkylene-biphenyl, C₁-C₂alkylene-(mono- or bicyclic-heteroaryl), wherein independently in said C₁-C₂alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-, and wherein said phenyl, biphenyl, C₅-C₆-cycloalkyl, and mono- or bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably one or two, substituents selected from methyl, ethyl, fluorine, chlorine, methoxy, wherein said mono- or bicyclic-heteroaryl is selected 25 from isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, indolyl, benzimidazolyl, benzothiazolyl, benzooxazolyl. 30

In a further preferred embodiment said R₂ is selected from C₅-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₂alkylene-C₅-C₆cycloalkyl, CH₂-phenyl, CH₂-biphenyl, CH₂-O-biphenyl, CH₂-(mono- or bicyclic-heteroaryl), wherein said phenyl, biphenyl, C₅-C₆-cycloalkyl, and mono- or

bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably one or two, substituents selected from methyl, ethyl, fluorine, chlorine, methoxy, wherein preferably said mono- or bicyclic-heteroaryl is selected from isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, indolyl, benzimidazolyl, benzothiazolyl, benzooxazolyl, and wherein
 5 further preferably said mono- or bicyclic-heteroaryl is selected from, thiazolyl, indolyl, benzothiazolyl and benzooxazolyl.

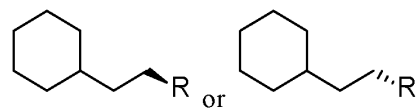
In a further preferred embodiment said R_2 is selected from C_5 - C_{12} alkyl, C_4 - C_{10} alkoxy, C_1 - C_2 alkylene- C_5 - C_6 cycloalkyl, CH_2 -phenyl, CH_2 -biphenyl, CH_2 -O-biphenyl, CH_2 -(mono- or bicyclic-heteroaryl), wherein said phenyl, biphenyl, C_5 - C_6 -cycloalkyl, and mono- or
 10 bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably one or two, substituents selected from methyl, ethyl, fluorine, chlorine, methoxy, wherein said mono- or bicyclic-heteroaryl is selected from, thiazolyl, indolyl, benzothiazolyl and benzooxazolyl. In a further preferred embodiment, said R_2 is selected from C_5 - C_{12} alkyl, C_1 - C_2 alkylene- C_5 - C_6 cycloalkyl, CH_2 -biphenyl and CH_2 -O-biphenyl and a bicyclic-heteroaryl
 15 selected from benzothiazolyl and benzooxazolyl.

In a further very preferred embodiment, said R_2 is selected from

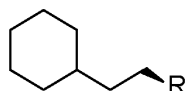


and wherein R indicates the attachment to the CH-moiety depicted in formula (I).

In a further very preferred embodiment, said R_2 is
 20 wherein R indicates the attachment to the CH-moiety depicted in formula (I).

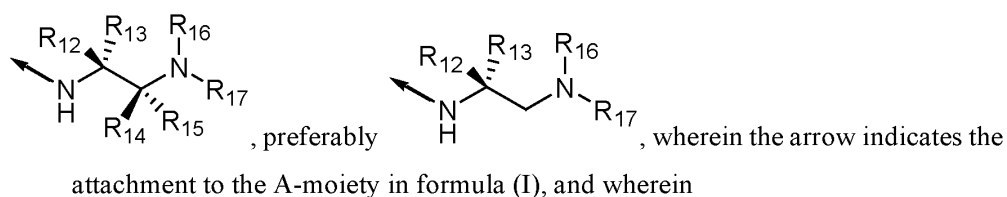


In a further very preferred embodiment, said R_2 is
 wherein R indicates the attachment to the CH-moiety depicted in formula (I).



In a further very preferred embodiment, said R_2 is
 the attachment to the CH-moiety depicted in formula (I).

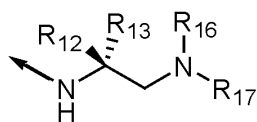
25 In a further preferred embodiment, said R_3 is



R_{12} , R_{13} , R_{14} and R_{15} are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R_{12} , R_{13} , R_{14} and R_{15} together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

R_{16} and R_{17} are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R_{18} , R_{19} , R_{20} are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, said R_3 is



In a further preferred embodiment, said R_{12} , R_{13} , R_{14} and R_{15} are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R_{12} , R_{13} , R_{14} and R_{15} together with the carbon atom to which they are attached form a carbocyclic or heterocyclic ring, preferably a carbocyclic ring, and wherein R_{16} and R_{17} are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a mono- or bicyclic heteroaryl or a mono- or bicyclic heterocyclyl, preferably selected from a pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, tetrahydroisoquinoliny, indolyl, benzimidazolyl, indazolyl, indoliziny, pyridazinyl, triazinyl, isoindolyl, purinyl, pyrrolidinyl, piperidinyl, morpholiny, thiomorpholiny, piperazinyl, homopiperazinyl, 2-pyrroliny, 3-pyrroliny, indoliny, dihyrooxazolyl, pyrazoliny, pyrazolidiny, imidazoliny, imidazolidiny, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein R_{18} , R_{19} , R_{20} are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R_{12} , R_{13} , R_{14} and R_{15} are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two

of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a mono- or bicyclic heteroaryl or a mono- or bicyclic heterocyclyl, preferably selected from a pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, indazolyl, indolizynyl, pyridazinyl, triazinyl, isoindolyl, purinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolynyl, dihyrooxazolyl, pyrazolynyl, pyrazolidinyl, imidazolynyl, imidazolidinyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heteroaryl or a monocyclic heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic

carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heteroaryl or a monocyclic heterocyclyl, wherein said monocyclic heteroaryl or said monocyclic heterocyclyl comprise one or two heteroatoms (including said nitrogen atom to which R₁₆ and R₁₇ are attached) selected from nitrogen, oxygen and sulphur, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heteroaryl or a monocyclic heterocyclyl selected from a pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, 2-pyrrolinyl, 3-pyrrolinyl, dihyrooxazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolidinyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclic ring, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are

independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclyl, wherein said monocyclic heterocyclyl comprise one or two heteroatoms (including said nitrogen atom to which R₁₆ and R₁₇ are attached) selected from nitrogen, oxygen and sulphur, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

In a further preferred embodiment, R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or independently at each occurrence two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R₁₆ and R₁₇ are independently of each other H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclic ring selected from imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, 2-pyrrolinyl, 3-pyrrolinyl, dihyrooxazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolidinyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀; wherein said R₁₈, R₁₉, R₂₀ are independently at each occurrence H, C₁-C₃alkyl.

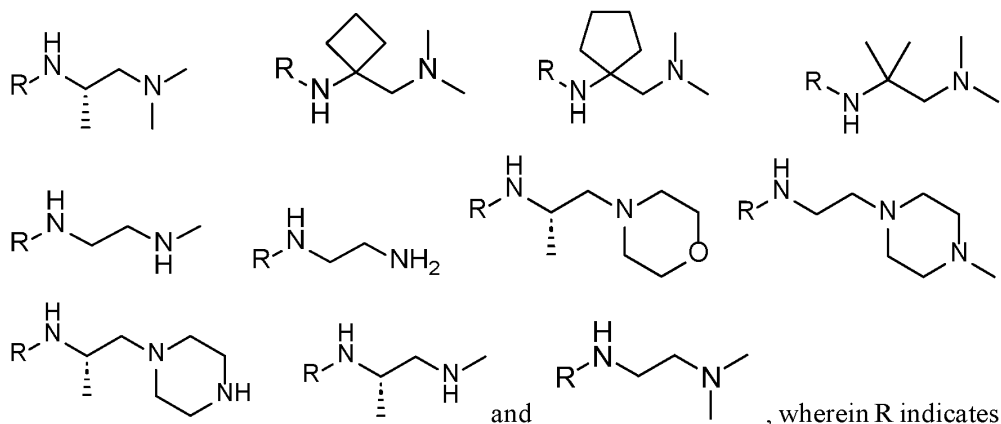
In a further preferred embodiment, said R₁₄ and R₁₅ are H, and said R₁₂ and R₁₃ are independently at each occurrence H or C₁-C₃alkyl, preferably H or methyl, or said R₁₂ and R₁₃, together with the carbon atom to which they are attached form a monocyclic carbocyclic ring, wherein further preferably said monocyclic carbocyclic ring is selected from cyclopropyl,

cyclobutyl, cyclopentyl or cyclohexyl, and wherein again further preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R_{16} and R_{17} are independently of each other H or C_1 - C_4 alkyl optionally substituted with halogen, hydroxyl or C_3 - C_6 cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclic ring selected from imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, 2-pyrrolinyl, 3-pyrrolinyl, dihyrooxazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, each independently optionally substituted with halogen, C_1 - C_4 alkyl, OR_{18} , $NR_{19}R_{20}$; wherein said R_{18} , R_{19} , R_{20} are independently at each occurrence H, C_1 - C_3 alkyl.

In a further preferred embodiment, R_{12} , R_{13} , R_{14} and R_{15} are independently at each occurrence H or C_1 - C_3 alkyl, preferably H or methyl, or independently at each occurrence two of said R_{12} , R_{13} , R_{14} and R_{15} together with the carbon atom to which they are attached form a monocyclic carbocyclic ring selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R_{16} and R_{17} are independently of each other H or C_1 - C_4 alkyl optionally substituted with halogen, hydroxyl or C_3 - C_6 cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, preferably from piperidinyl or morpholinyl, and further preferably from morpholinyl, each independently optionally substituted with halogen, C_1 - C_4 alkyl, OR_{18} , $NR_{19}R_{20}$; wherein said R_{18} , R_{19} , R_{20} are independently at each occurrence H, C_1 - C_3 alkyl.

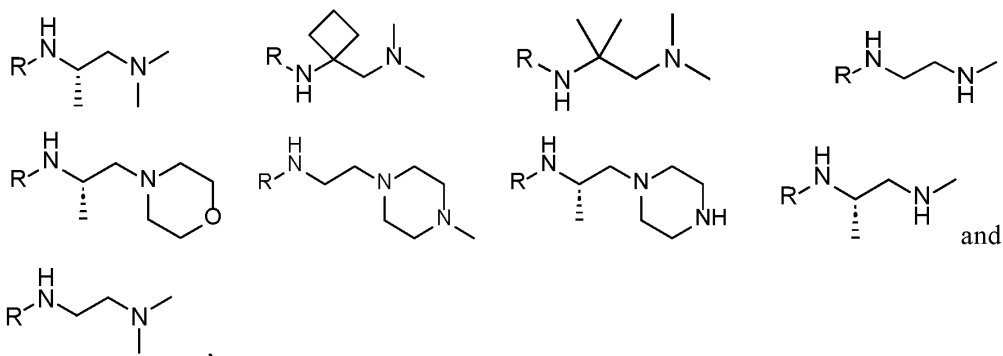
In a further preferred embodiment, said R_{14} and R_{15} are H, and said R_{12} and R_{13} are independently at each occurrence H or C_1 - C_3 alkyl, preferably H or methyl, or said R_{12} and R_{13} , together with the carbon atom to which they are attached form a monocyclic carbocyclic ring selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably said monocyclic carbocyclic ring is cyclobutyl or cyclopentyl, and wherein R_{16} and R_{17} are independently of each other H or C_1 - C_4 alkyl optionally substituted with halogen, hydroxyl or C_3 - C_6 cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, preferably from piperidinyl or morpholinyl, and further preferably from morpholinyl, each independently optionally substituted with halogen, C_1 - C_4 alkyl, OR_{18} , $NR_{19}R_{20}$; wherein said R_{18} , R_{19} , R_{20} are independently at each occurrence H, C_1 - C_3 alkyl.

In a further preferred embodiment, said R_3 is selected from

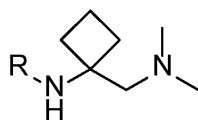


5 the attachment to the A-moiety in formula (I).

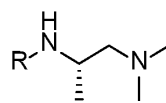
In a further preferred embodiment, said R_3 is selected from



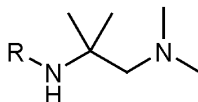
10 wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).



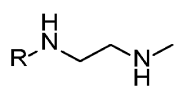
In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

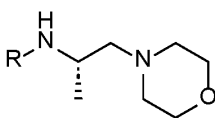


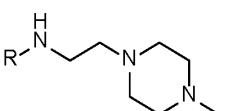
In a further very preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

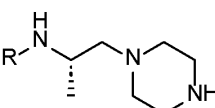


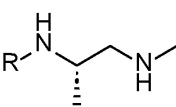
15 In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

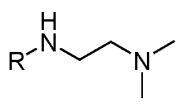
In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

5 In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

10 In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

In a further preferred embodiment, said R₃ is , wherein R indicates the attachment to the C(O)-moiety depicted in formula (I).

In a further very preferred embodiment, said compound of formula (I) is selected from
20762: allyl ((3S,5S)-5-(((12S,15S,21S,24S)-26-cyclohexyl-1-((1-
 15 ((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-
 1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)carbonyl)-1-(4-
 fluorobenzoyl)pyrrolidin-3-yl)carbamate

22178:(2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-
 2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-
 20 nonaazahentriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-
 carboxamide

22179:(2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-
 2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-
 nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

- 23103:**(2S,4S)-N-((12S,15S,21S,24S)-26-cyclohexyl-1-((1-((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide
- 5 **23491:**(2S,4S)-N-((12S,15S,21S,24S)-26-cyclohexyl-1-((1-((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 10 **23525:**(2S,4S)-N-((17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,4,11,11,14,14,23,23-nonamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 15 **23526:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 20 **23538:**(2S,4S)-N-((17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,4,11,11,14,14,23,23-nonamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide
- 25 **23542:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octazaheptacosan-25-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide
- 30 **23549:**(2S,4R)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-hydroxypyrrolidine-2-carboxamide
- 35 **23552:**(1S,3aS,7aR)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octazaheptacosan-25-yl)-2-(4-fluorobenzoyl)octahydro-1H-isindole-1-carboxamide
- 40 **23577:**(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-hydroxypyrrolidine-2-carboxamide
- 45 **23585:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

- 23586:**(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 23594:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenoxy-pyrrolidine-2-carboxamide
- 23595:**(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-4-fluoro-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide
- 23596:**(2S,4R)-4-(benzyloxy)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide
- 23612:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide
- 23687:**(2S,4S)-N-((4S,10S,13S,19S,22S)-24-cyclohexyl-10,13,19-triisobutyl-2,4,7,7,16,16-hexamethyl-6,9,12,15,18,21-hexaaxo-2,5,8,11,14,17,20-heptaazatetracosan-22-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 23692:**(2S,4S)-N-((4S,11S,20S,23S,29S,32S)-34-cyclohexyl-11,20,23,29-tetraisobutyl-2,4,14,14,17,17,26,26-octamethyl-6,10,13,16,19,22,25,28,31-nonaaxo-2,5,9,12,15,18,21,24,27,30-decaazatetratriacontan-32-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 23693:**(2S,4S)-N-((4S,11S,14S,23S,26S,32S,35S)-37-cyclohexyl-11,14,23,26,32-pentaisobutyl-2,4,17,17,20,20,29,29-octamethyl-6,10,13,16,19,22,25,28,31,34-decaaxo-2,5,9,12,15,18,21,24,27,30,33-undecaazaheptatriacontan-35-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 23705:**(2S,4S)-N-((4S,14S,17S,26S,29S,35S,38S)-40-cyclohexyl-14,17,26,29,35-pentaisobutyl-2,4,11,11,20,20,23,23,32,32-decamethyl-6,10,13,16,19,22,25,28,31,34,37-undecaaxo-2,5,9,12,15,18,21,24,27,30,33,36-dodecaazatetracontan-38-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide
- 23717:**(2S,5S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5-methylpyrrolidine-2-carboxamide

- 23718:**(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5,5-dimethylpyrrolidine-2-carboxamide
- 23720:**(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide
- 23736:**(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-3,3-dimethylpyrrolidine-2-carboxamide
- 23738:**(2S,4S)-4-cyclohexyl-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide
- 23739:**(2S,5R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5-phenylpyrrolidine-2-carboxamide
- 23742:**(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-(4-fluorobenzyl)pyrrolidine-2-carboxamide
- 23794:**(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-4,4-difluoro-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide
- 23795:**(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-5-(4-fluorobenzoyl)-5-azaspiro[2.4]heptane-6-carboxamide, or
- 23826:**(2S,4S)-N-((13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-7,7,10,10,19,19-hexamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide.
- 24879:**(2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)-4-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]pyrrolidin-2-yl]formamido]butanamido]-N-(1-[[[(1S)-1-[[[(1S)-1-(1-[[[(2S)-1-(dimethylamino)propan-2-yl]carbamoyl]-1-methylethyl]carbamoyl]-1-methylethyl]carbamoyl]-3-methylbutyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-methylethyl)-4-methylpentanamide
- 25041:**(2S)-2-[(2S)-2-[2-[(2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)

4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(2S)-1-(morpholin-4-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide

25042:(2S)-2-[(2S)-4-cyclohexyl-2-{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methyl-N-(1-methyl-1-[(1S)-3-methyl-1-[(1S)-3-methyl-1-({1-methyl-1-[(1-methyl-1-{2-(4-methylpiperazin-1-yl)ethyl]carbamoyl}ethyl)carbamoyl]ethyl}carbamoyl)butyl]carbamoyl}butyl]carbamoyl}ethyl)pentanamide

25088:(2S)-2-[(2S)-4-cyclohexyl-2-{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-N-(1-{[(1S)-1-[(1S)-1-({1-[(1-{2-(dimethylamino)ethyl]carbamoyl}-1-methylethyl)carbamoyl]-1-methylethyl}carbamoyl)-3-methylbutyl]carbamoyl}-3-methylbutyl]carbamoyl}-1-methylethyl)-4-methylpentanamide

25126:(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(2S)-1-(piperazin-1-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide, and

25157:(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(2S)-1-(methylamino)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide.

In a further very preferred embodiment, said compound of formula (I) is **23526:** (2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide.

In a further very preferred embodiment, said compound of formula (I) is **23542:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide.

In a further very preferred embodiment, said compound of formula (I) is **23612:**(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide.

In a further very preferred embodiment, said compound of formula (I) is **23736**:(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-3,3-dimethylpyrrolidine-2-carboxamide.

5 In a further very preferred embodiment, said compound of formula (I) is **24879**:(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]pyrrolidin-2-yl]formamido}butanamido]-N-(1-{{[(1S)-1-{{[(1S)-1-{{1-[(1-{{(2S)-1-(dimethylamino)propan-2-yl]carbamoyl}-1-methylethyl)carbamoyl]-1-methylethyl}carbamoyl]-3-methylbutyl]carbamoyl}-3-methylbutyl]carbamoyl}-1-methylethyl)-4-methylpentanamide.

10 In a further very preferred embodiment, said compound of formula (I) is **25041**:(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-{{[(2S)-1-(morpholin-4-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide.

15 In a further very preferred embodiment, said compound of formula (I) is **25042**:(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methyl-N-(1-methyl-1-{{[(1S)-3-methyl-1-{{[(1S)-3-methyl-1-{{1-methyl-1-[(1-methyl-1-{{2-(4-methylpiperazin-1-yl)ethyl}carbamoyl}ethyl)carbamoyl]ethyl}carbamoyl]butyl]carbamoyl}butyl]carbamoyl}ethyl)pentanamide.

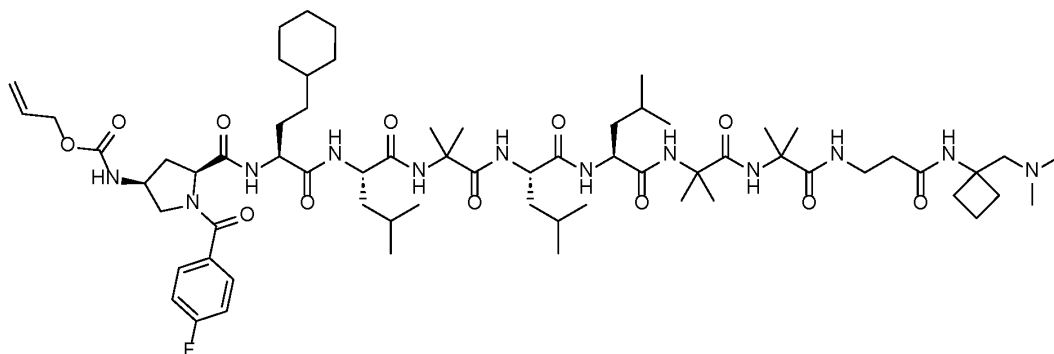
20 In a further very preferred embodiment, said compound of formula (I) is **25088**:(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-N-(1-{{[(1S)-1-{{[(1S)-1-{{1-[(1-{{2-(dimethylamino)ethyl}carbamoyl}-1-methylethyl)carbamoyl]-1-methylethyl}carbamoyl]-3-methylbutyl]carbamoyl}-3-methylbutyl]carbamoyl}-1-methylethyl)-4-methylpentanamide.

25 In a further very preferred embodiment, said compound of formula (I) is **25126**:(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-{{[(2S)-1-(piperazin-1-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide.

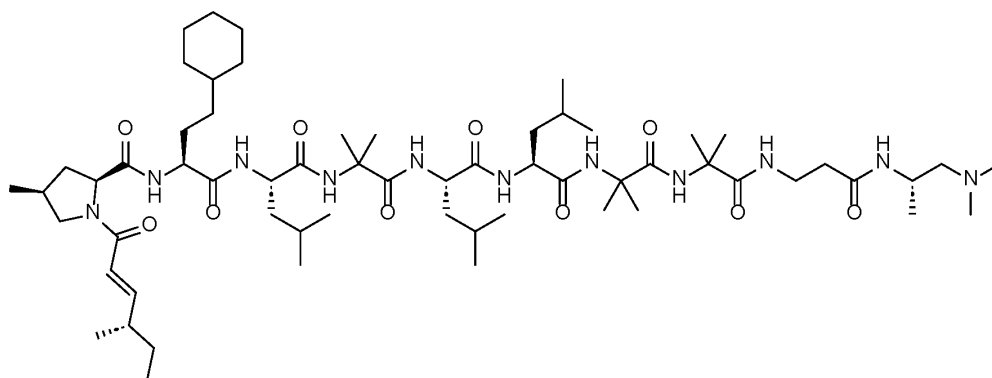
30 In a further very preferred embodiment, said compound of formula (I) is **25157**:(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-

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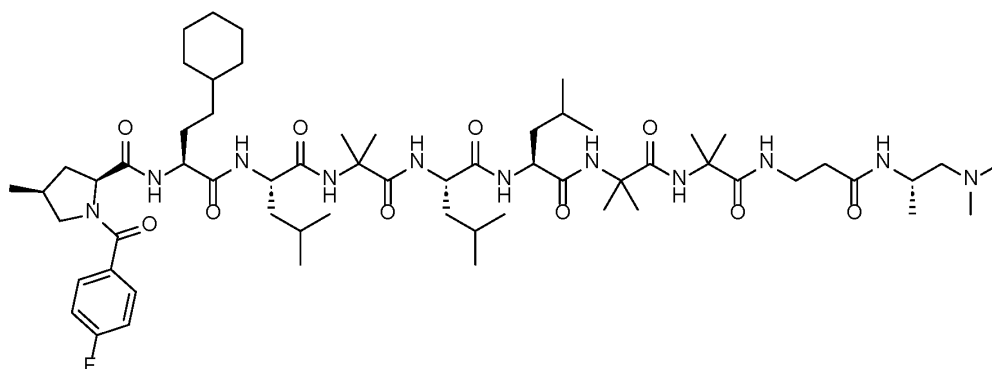
In a further very preferred embodiment, said compound of formula (I) is selected from
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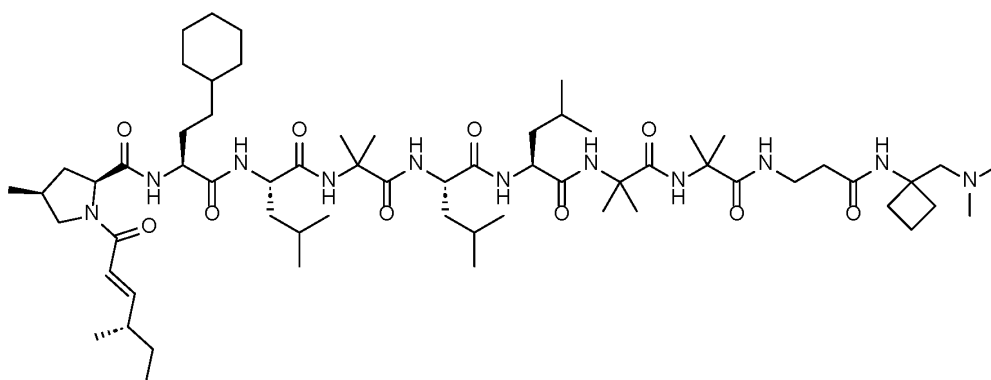
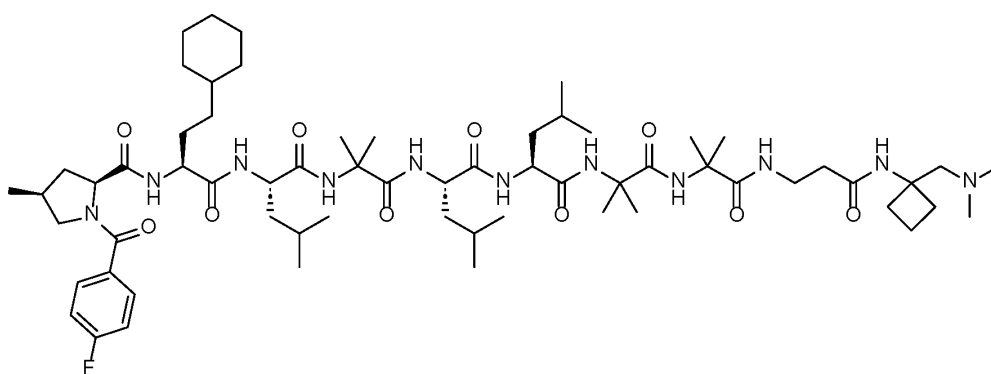
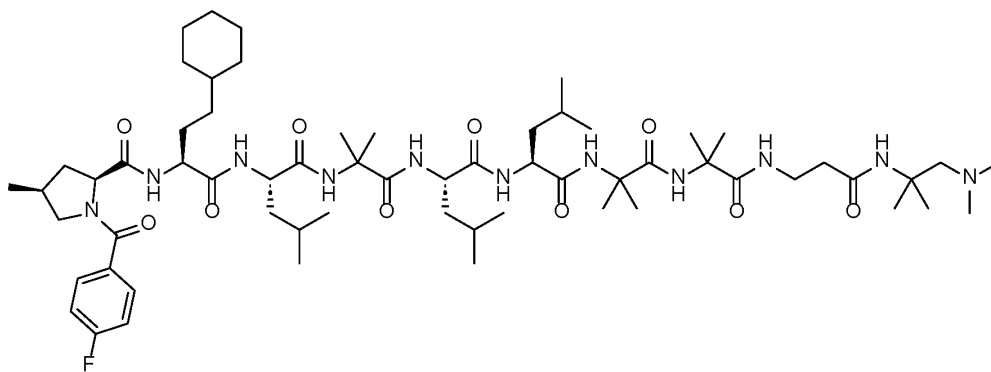
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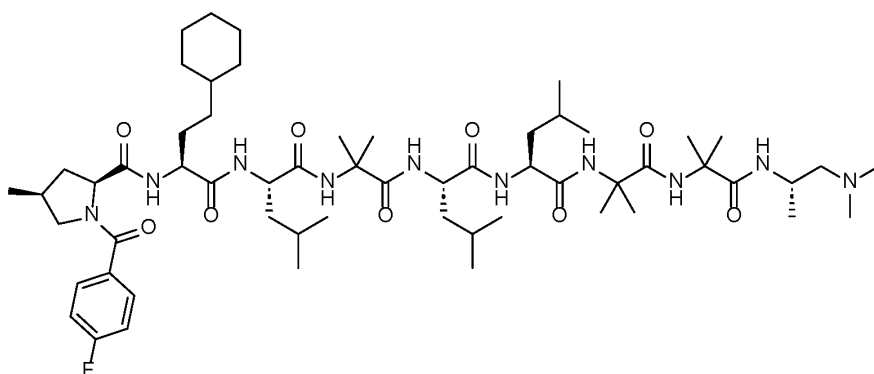


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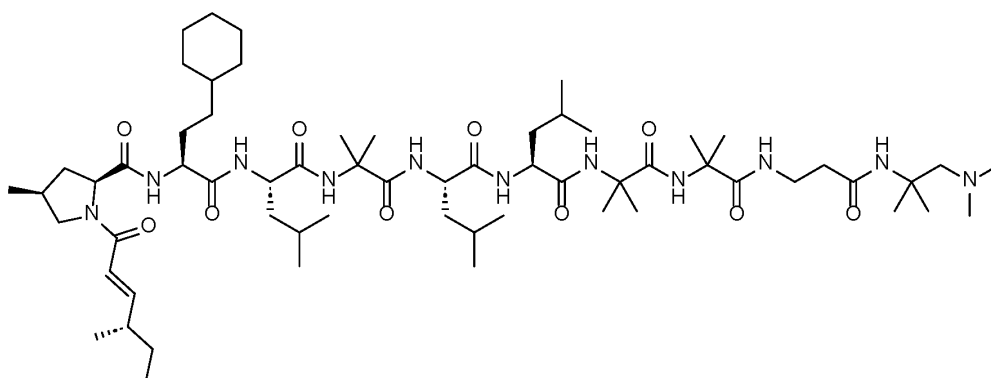


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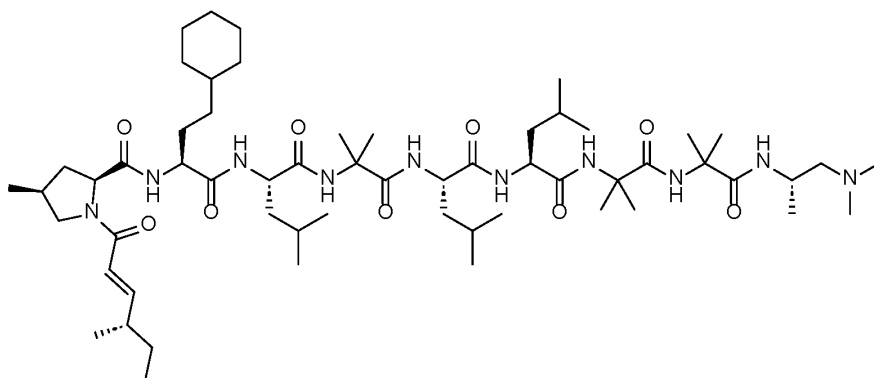
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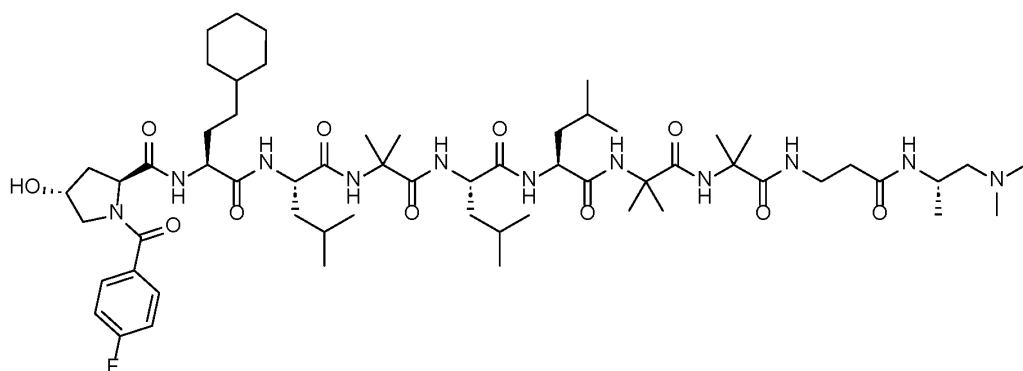
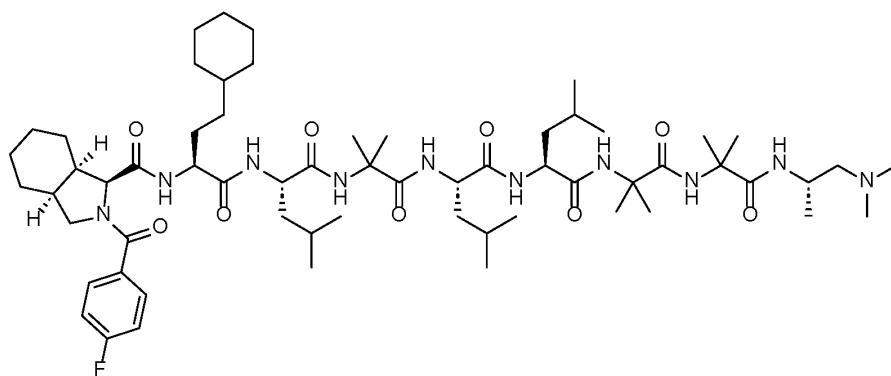
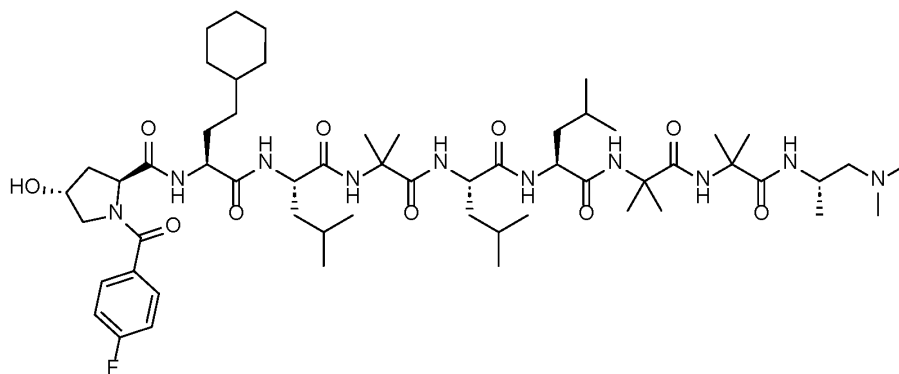
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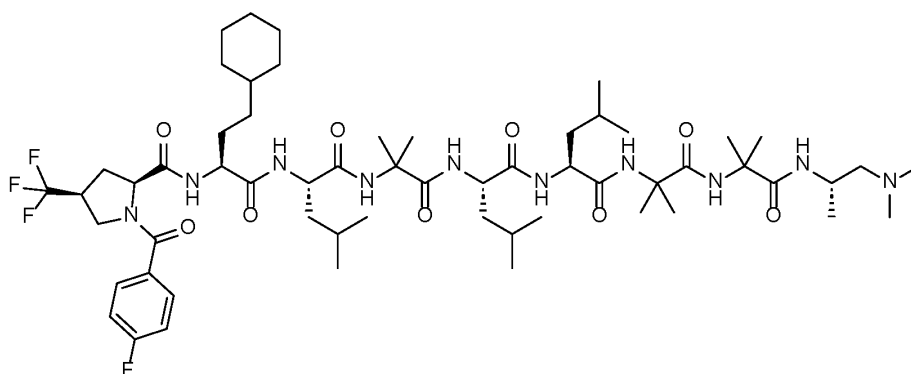


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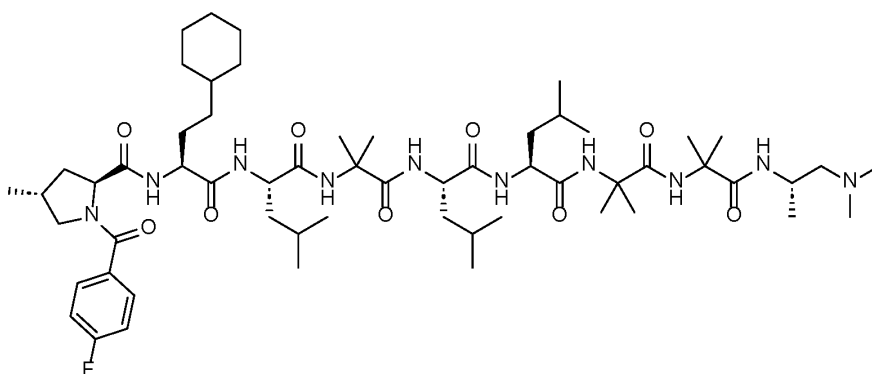


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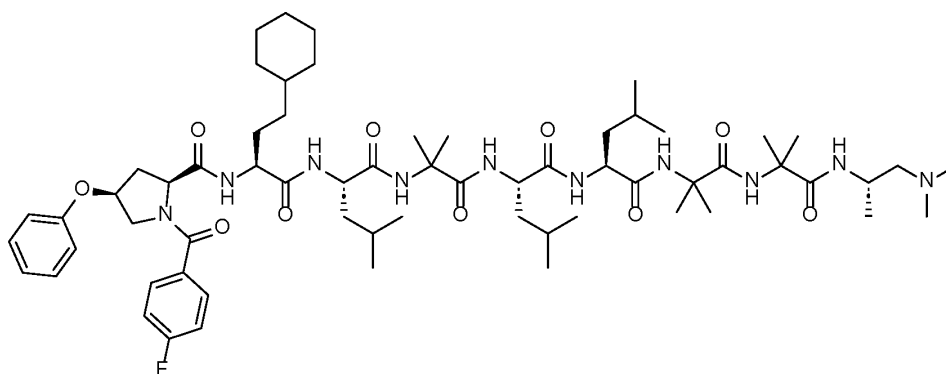
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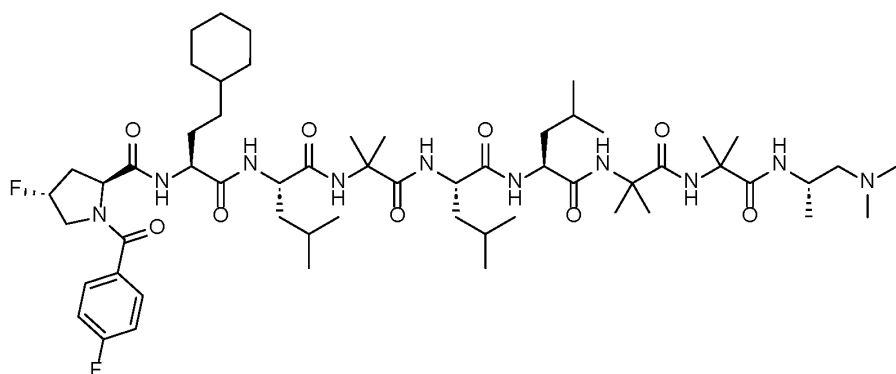
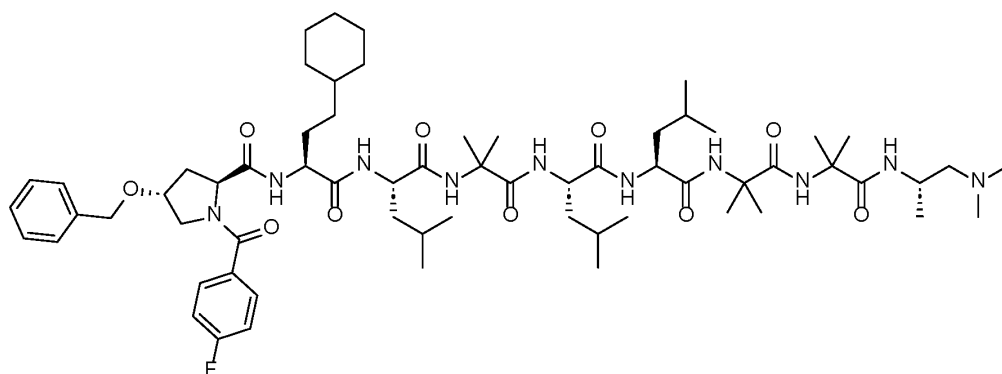
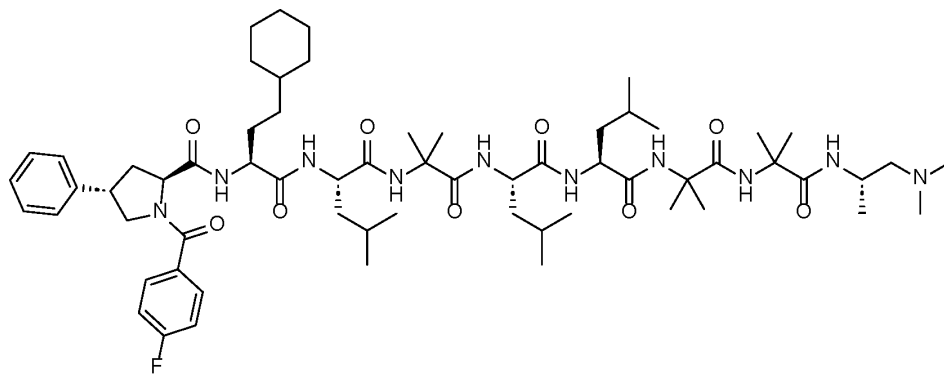
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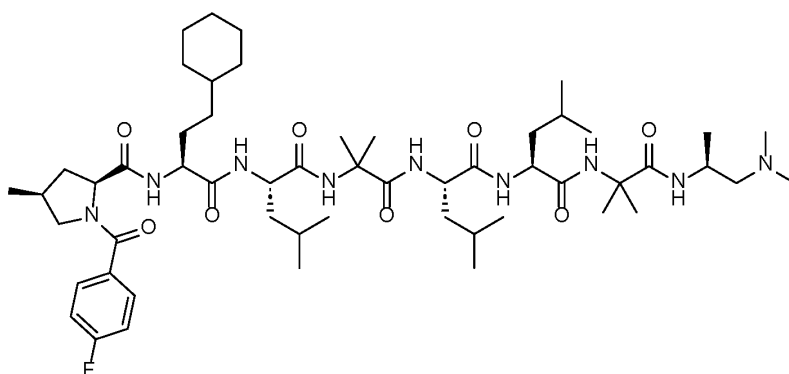


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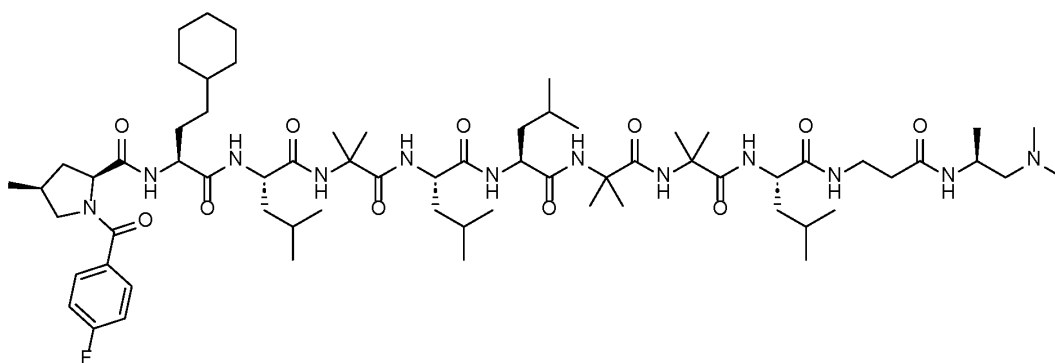


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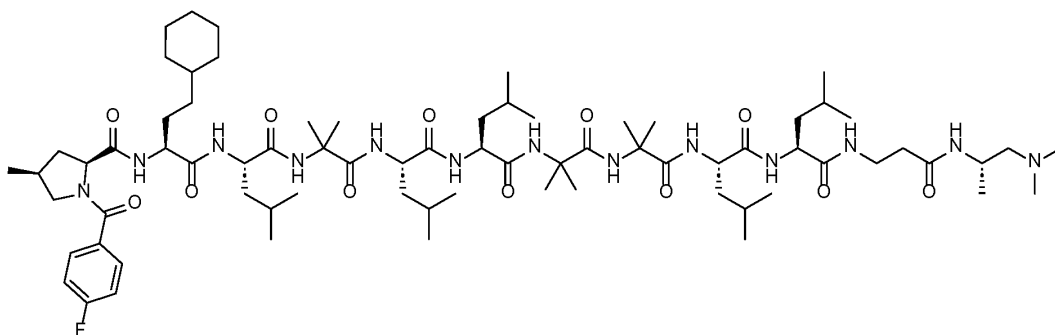
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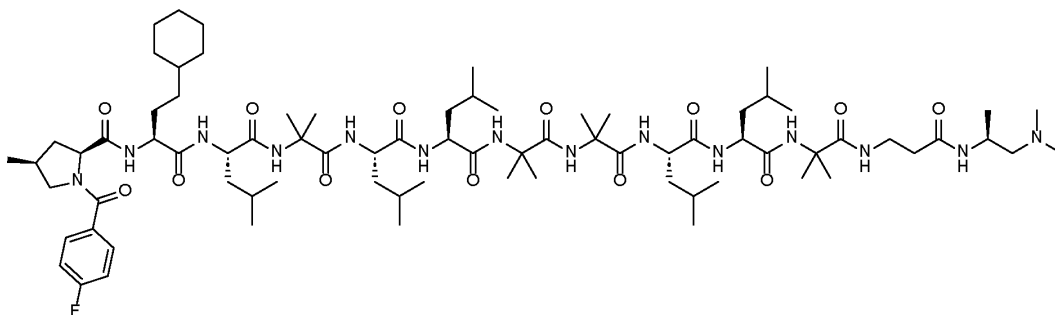


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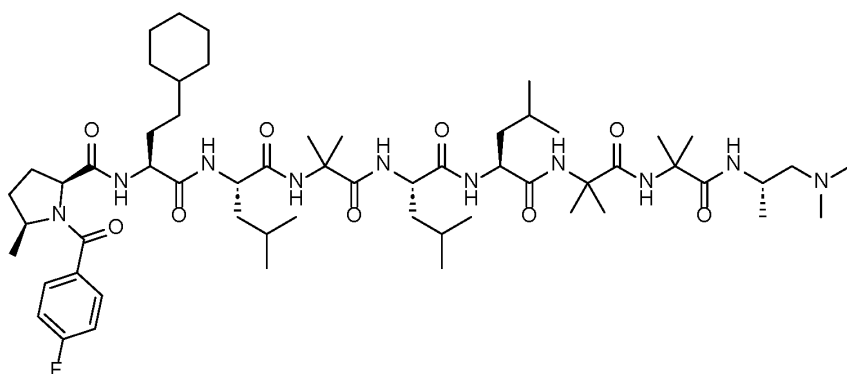
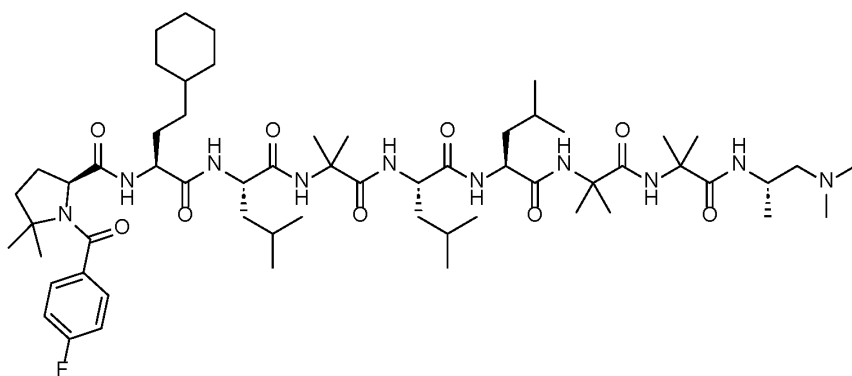
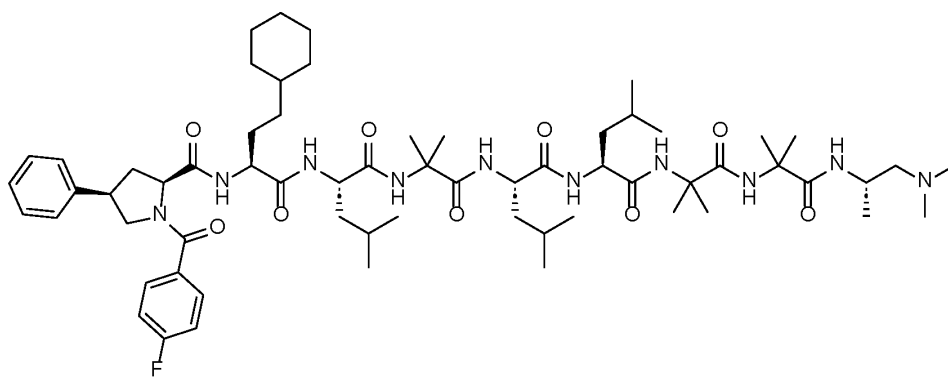


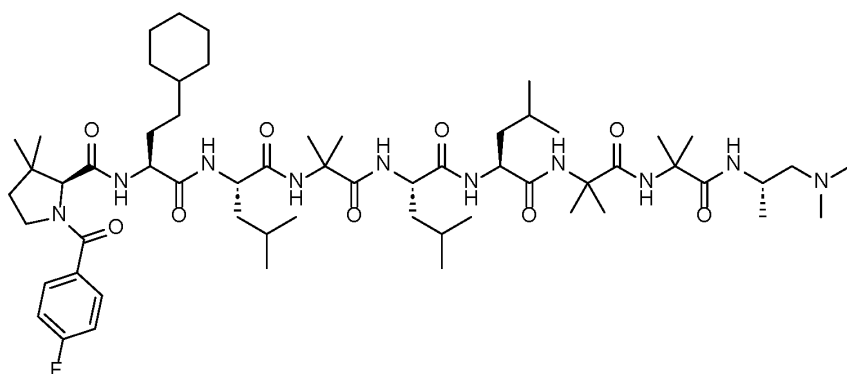
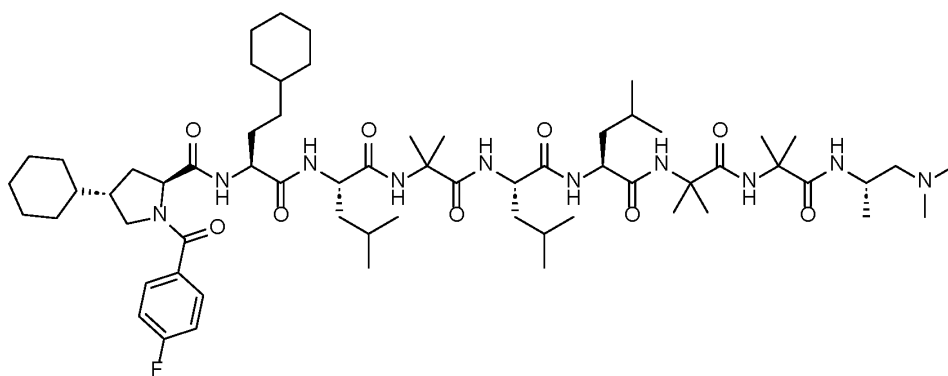
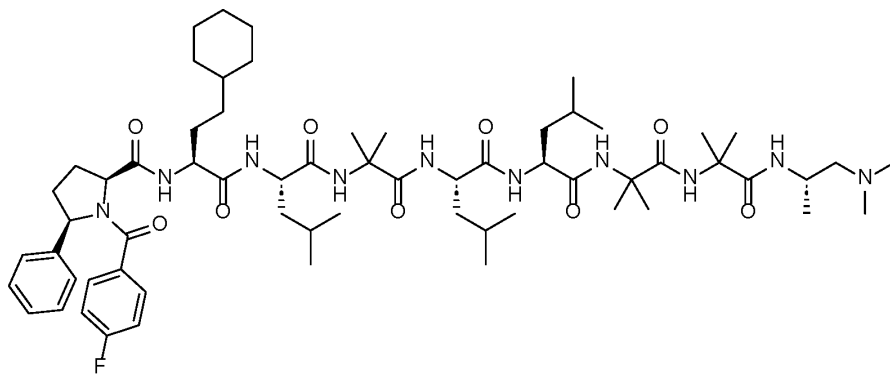
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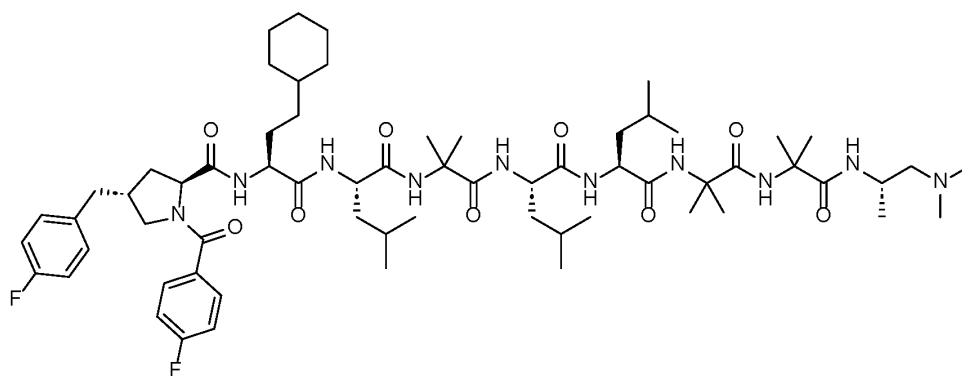
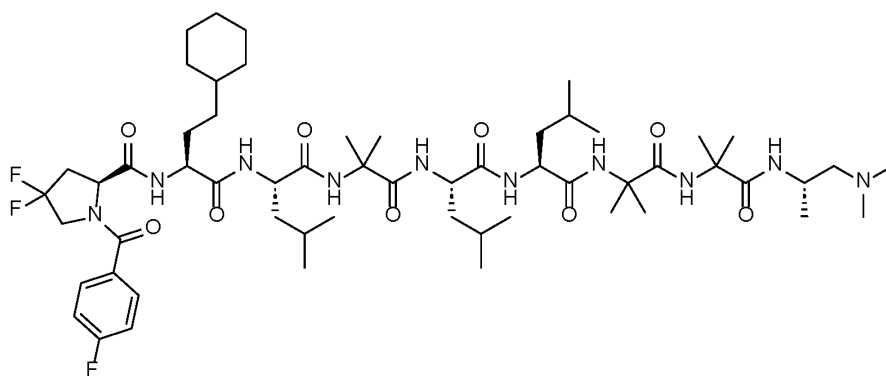
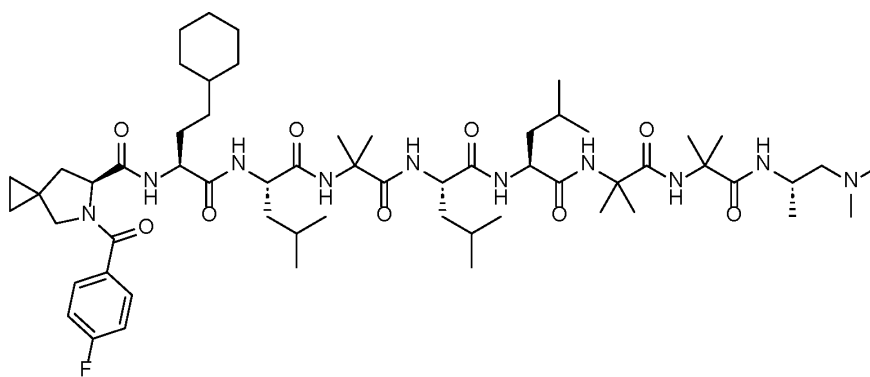
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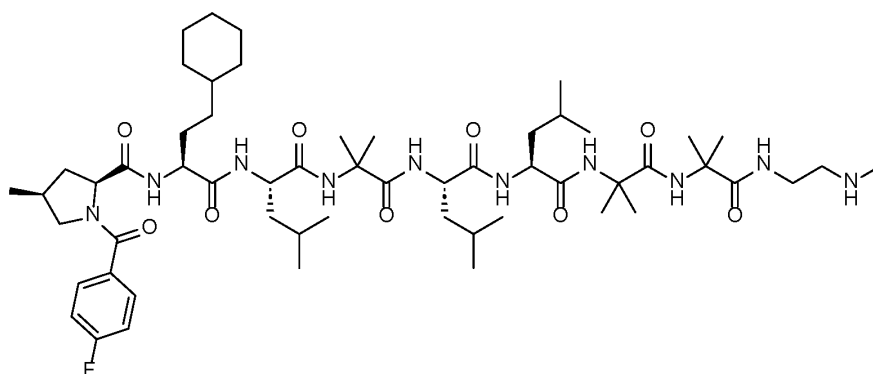
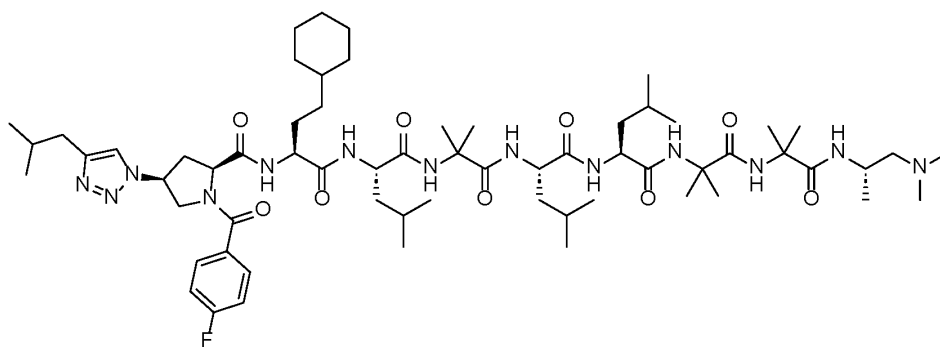
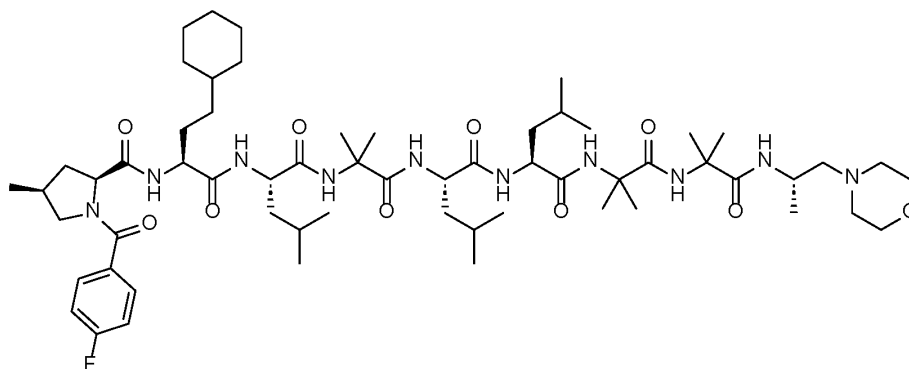


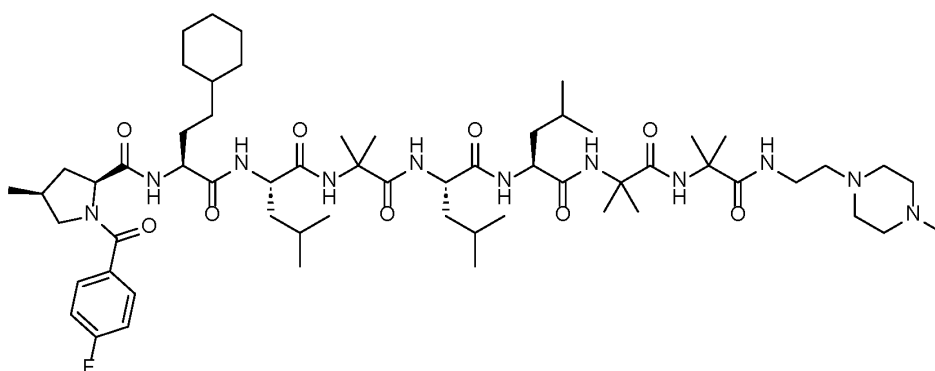
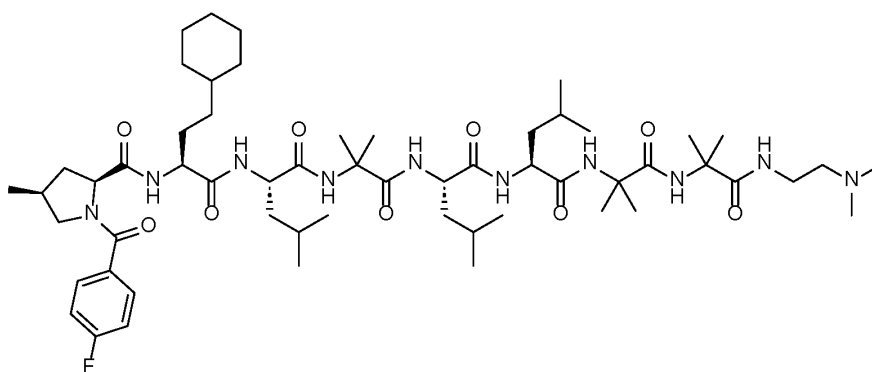
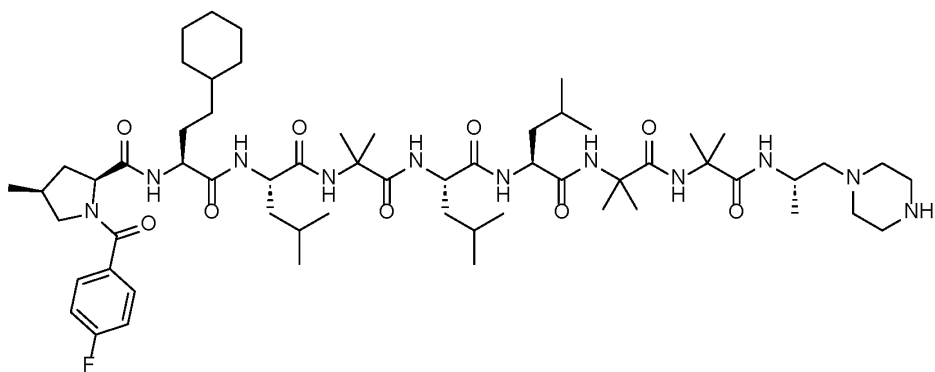
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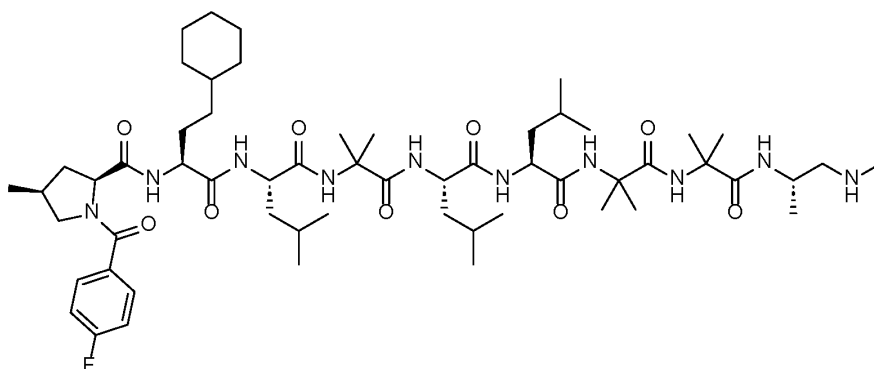
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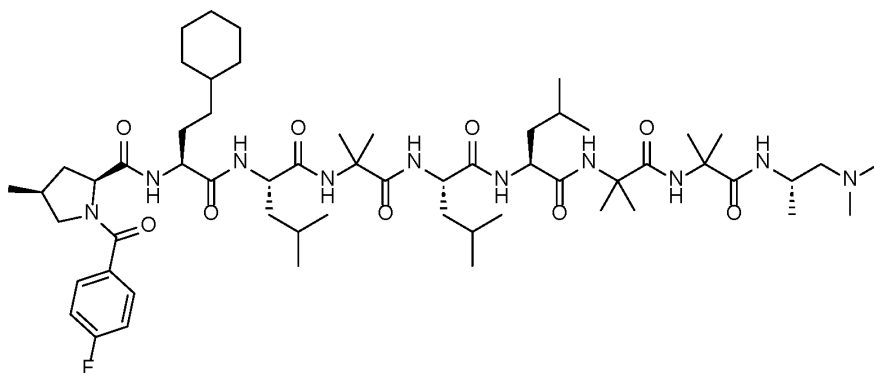
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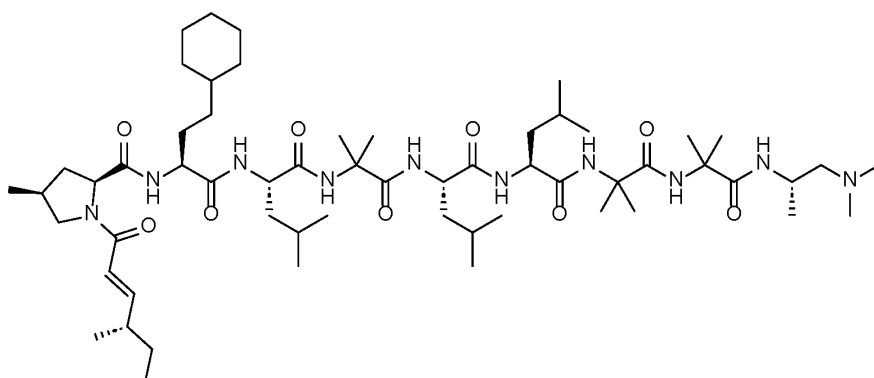
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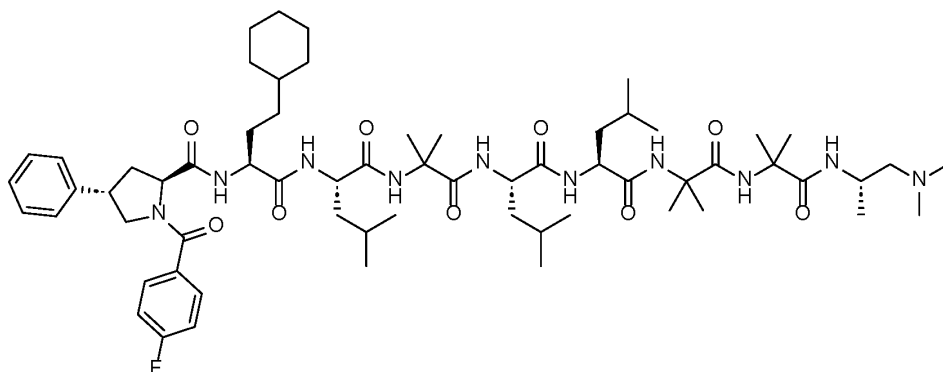
In a further very preferred embodiment, said compound of formula (I) is
23526:



5 In a further very preferred embodiment, said compound of formula (I) is
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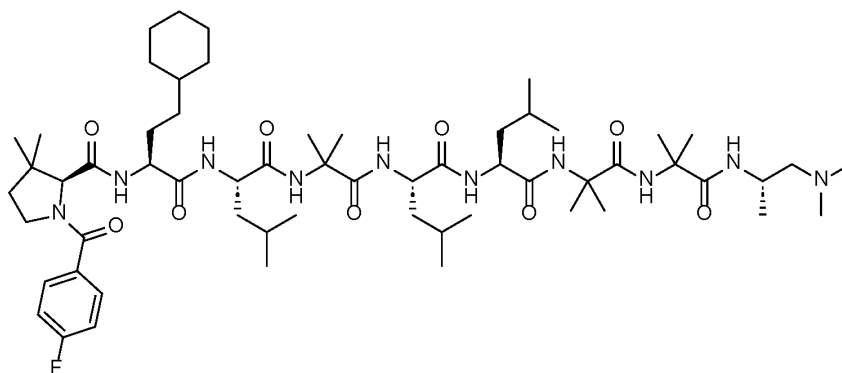


In a further very preferred embodiment, said compound of formula (I) is
23612:



In a further very preferred embodiment, said compound of formula (I) is

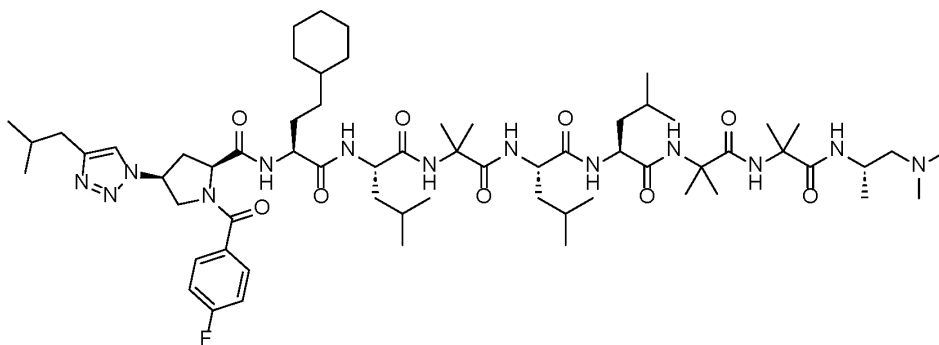
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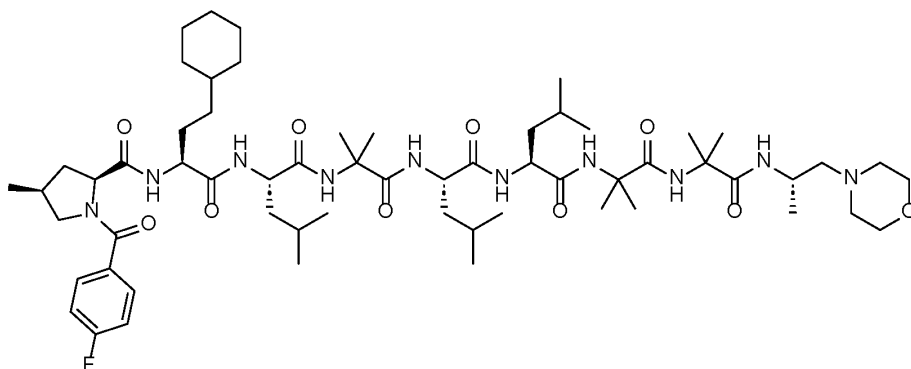
In a further very preferred embodiment, said compound of formula (I) is

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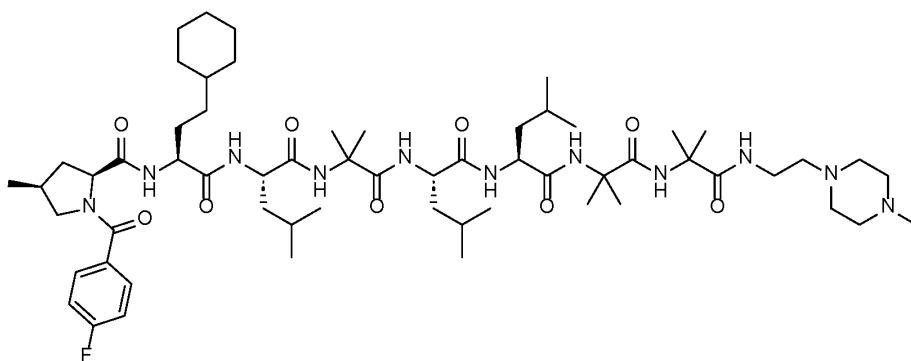
In a further very preferred embodiment, said compound of formula (I) is

25041:



In a further very preferred embodiment, said compound of formula (I) is

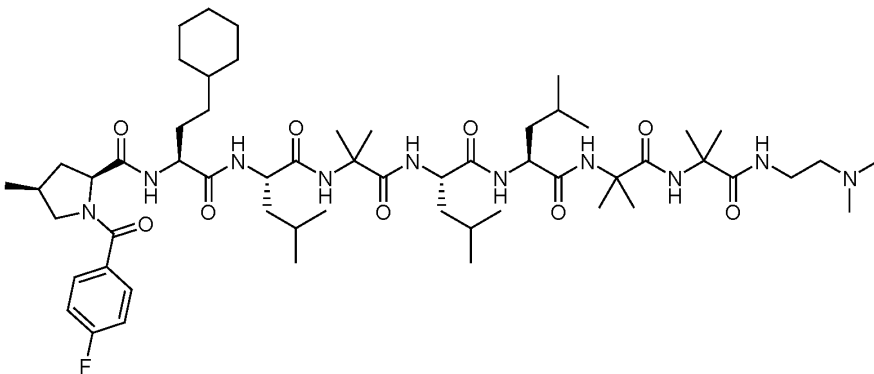
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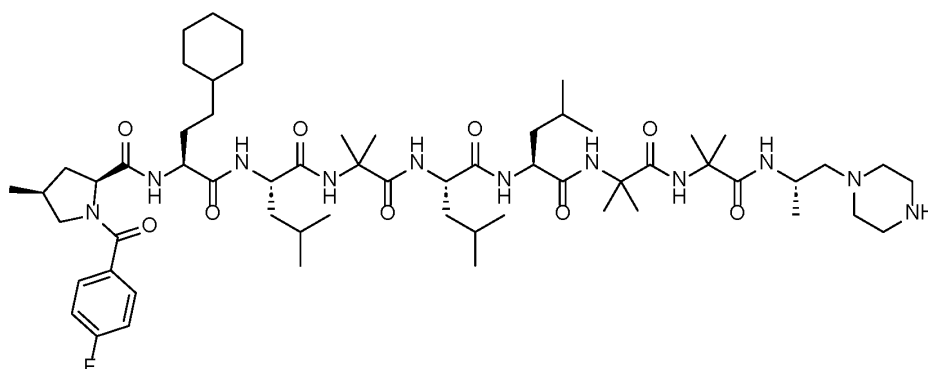
In a further very preferred embodiment, said compound of formula (I) is

25088:



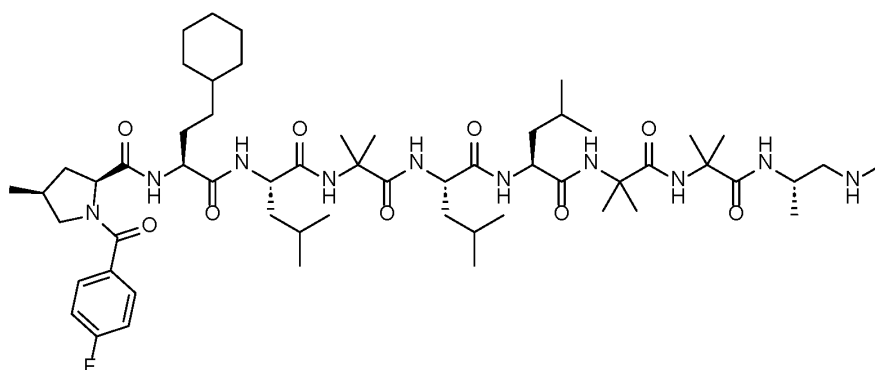
In a further very preferred embodiment, said compound of formula (I) is

25126:



In a further very preferred embodiment, said compound of formula (I) is

25157:



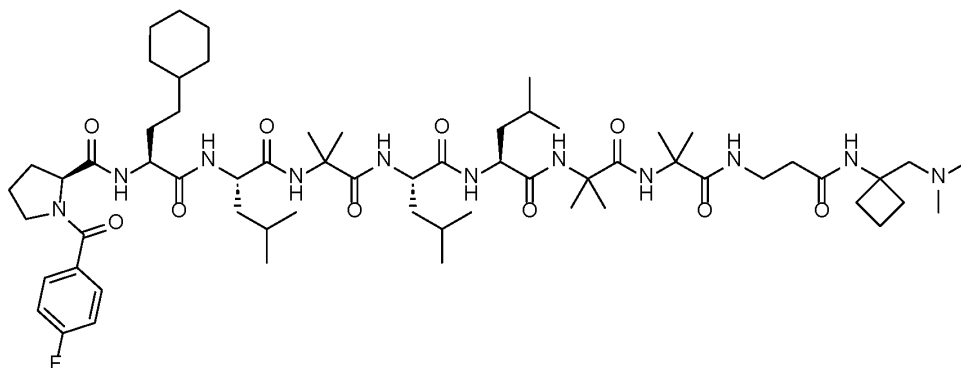
- 5 In a further aspect, the present invention provides for the use of a compound of formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound of formula (I), or said
- 10 pharmaceutically acceptable salt thereof, or said pharmaceutical composition of the invention, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound, or said pharmaceutically acceptable salt thereof, or said pharmaceutical composition, to said mammal, preferably to said human.

In a preferred embodiment, said cancer is selected from the group consisting of skin cancer, breast cancer, colorectal cancer, hematopoietic cancer, cancer of the female genitourinary (GU) system, lung cancer, head and neck cancer, pancreas cancer, prostate cancer, bladder cancer cells, CNS cancer, stomach cancer, endocrine cancer and kidney cancer.

15 In a preferred embodiment, said cancer is a solid tumor.

In a further aspect, the present invention provides the use of a compound of formula

(6027)



or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound 6027 or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound 6027, or said pharmaceutically acceptable salt thereof, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound 6027, or said pharmaceutically acceptable salt thereof, to said mammal, preferably to said human, provided that said use is not a method of topical treatment of a skin cancer of a mammal, wherein said method comprises topical administration of said compound to said mammal. In a preferred embodiment, said cancer is selected from the group consisting of skin cancer, breast cancer, colorectal cancer, hematopoietic cancer, cancer of the female genitourinary (GU) system, lung cancer, head and neck cancer, pancreas cancer, prostate cancer, bladder cancer cells, CNS cancer, stomach cancer, endocrine cancer and kidney cancer. In a preferred embodiment, said cancer is a solid tumor.

In a further aspect, the present invention provides the use of **6027:(S)-N-((12S,15S,21S,24S)-26-cyclohexyl-1-((1-((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide** or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound 6027 or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a cancer of a mammal, preferably of a human, wherein said method comprises administration of said compound 6027, or said pharmaceutically acceptable salt thereof, to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound 6027, or said pharmaceutically acceptable salt thereof, to said mammal, preferably to said human provided

that said use is not a method of topical treatment of a skin cancer of a mammal, wherein said method comprises topical administration of said compound to said mammal. In a preferred embodiment, said cancer is selected from the group consisting of skin cancer, breast cancer, colorectal cancer, hematopoietic cancer, cancer of the female genitourinary (GU) system, lung cancer, head and neck cancer, pancreas cancer, prostate cancer, bladder cancer cells, CNS
5 cancer, stomach cancer, endocrine cancer and kidney cancer. In a preferred embodiment, said cancer is a solid tumor.

The present invention provides a compound of formula (I) for use in a method of treatment of a skin cancer of a mammal, wherein said method comprises administration of an
10 effective amount of said compound, or a pharmaceutically acceptable salt thereof, to said mammal. In a preferred embodiment, said mammal is a human.

In a further preferred embodiment, said skin cancer is selected from a melanoma skin cancer, a non-melanoma skin cancer and a cutaneous lymphoma, and any pre-invasive form thereof. In a further preferred embodiment, said skin cancer is selected from a melanoma, a
15 non-melanoma skin cancer, and any pre-invasive form thereof, wherein preferably said non-melanoma skin cancer is a basal cell carcinoma, Merkel cell carcinoma or a cutaneous squamous cell carcinoma, and wherein further preferably said non-melanoma skin cancer is a basal cell carcinoma or a cutaneous squamous cell carcinoma, or any precancer form thereof. In a further preferred embodiment, said skin cancer is selected from a melanoma skin cancer, a
20 non-melanoma skin cancer and a cutaneous lymphoma, and any pre-invasive form thereof, wherein preferably said non-melanoma skin cancer is a basal cell carcinoma, Merkel cell carcinoma or a cutaneous squamous cell carcinoma, and wherein further preferably said non-melanoma skin cancer is a basal cell carcinoma or a cutaneous squamous cell carcinoma, or any pre-invasive form thereof. In a further preferred embodiment, said skin cancer is selected from
25 a melanoma, a non-melanoma skin cancer, and any pre-invasive form thereof, wherein preferably said non-melanoma skin cancer is a basal cell carcinoma, Merkel cell carcinoma or a cutaneous squamous cell carcinoma, and wherein further preferably said non-melanoma skin cancer is a basal cell carcinoma or a cutaneous squamous cell carcinoma, or any pre-invasive form thereof.

30 In a further preferred embodiment, said skin cancer is selected from a melanoma and a non-melanoma skin cancer, wherein preferably said non-melanoma skin cancer is a basal cell carcinoma or a cutaneous squamous cell carcinoma. In a further preferred embodiment, said skin cancer is a melanoma. In a further preferred embodiment, said skin cancer is a non-

melanoma skin cancer, wherein preferably said non-melanoma skin cancer is a basal cell carcinoma, Merkel cell carcinoma or a cutaneous squamous cell carcinoma, or any pre-invasive form thereof, and wherein further preferably said non-melanoma skin cancer is a basal cell carcinoma or a cutaneous squamous cell carcinoma, or any pre-invasive form thereof. In a further preferred embodiment, said skin cancer is a basal cell carcinoma. In a further preferred embodiment, said skin cancer is a cutaneous squamous cell carcinoma. In a preferred embodiment, said skin cancer is a pre-invasive form of non-melanoma skin cancer. In another preferred embodiment, said skin cancer is a non-melanoma skin cancer. In another preferred embodiment, said skin cancer is a cutaneous lymphoma.

10 In a further preferred embodiment, said cutaneous squamous cell carcinoma (cSCC) is an invasive cSCC. In a further preferred embodiment, said cutaneous squamous cell carcinoma (cSCC) is a metastatic cSCC. In a further preferred embodiment, said basal cell carcinoma is selected from the group consisting of superficial basal cell carcinoma (also known as “in situ basal cell carcinoma” or “superficial multicentric basal-cell carcinoma”), infiltrative basal cell carcinoma and nodular basal cell carcinoma. In a preferred embodiment, said basal cell carcinoma is a superficial basal cell carcinoma (also known as “in situ basal cell carcinoma” or “superficial multicentric basal-cell carcinoma”). In a further preferred embodiment, said basal cell carcinoma is an infiltrative basal cell carcinoma. In a further preferred embodiment, said basal cell carcinoma is a nodular basal cell carcinoma. In another embodiment, said basal cell carcinoma is selected from the group consisting of cystic basal cell carcinoma, cicatricial basal cell carcinoma (also known as “morpheaform basal cell carcinoma” or “morphoeic basal cell carcinoma”), micronodular basal cell carcinoma, pigmented basal cell carcinoma, rodent ulcer (also known as “Jacob’s ulcer”), fibroepithelioma of Pinkus, polypoid basal cell carcinoma, pore-like basal cell carcinoma and aberrant basal cell carcinoma.

25 In another preferred embodiment, said skin cancer is a pre-invasive form of a non-melanoma skin cancer, wherein said pre-invasive form is selected from the group consisting of cutaneous squamous cell carcinoma in situ (cSCCis, also known as “Bowen’s disease”) and precancerous actinic keratosis (AK). In another preferred embodiment, said skin cancer is a pre-invasive form of a non-melanoma skin cancer, wherein said pre-invasive form is cutaneous squamous cell carcinoma in situ (cSCCis, also known as “Bowen’s disease”). In a further preferred embodiment, said skin cancer is a pre-invasive form of a non-melanoma skin cancer, wherein said pre-invasive form is precancerous actinic keratosis (AK). In another preferred embodiment, said skin cancer is actinic keratosis (AK). In another preferred embodiment, said skin cancer is cutaneous squamous cell carcinoma in situ (cSCCis). In another preferred

embodiment, said skin cancer is a cutaneous lymphoma, wherein preferably said cutaneous lymphoma is a cutaneous T-cell lymphoma (CTCL) or a cutaneous B-cell lymphoma (CBCL). In another preferred embodiment, said skin cancer is a cutaneous lymphoma, wherein said cutaneous lymphoma is a cutaneous T-cell lymphoma (CTCL). In another preferred embodiment, said skin cancer is a cutaneous lymphoma, wherein said cutaneous lymphoma is a cutaneous B-cell lymphoma (CBCL). In another preferred embodiment, said skin cancer is a pre-invasive form of a non-melanoma skin cancer, and wherein said pre-invasive form is actinic keratosis (AK). In another preferred embodiment, said skin cancer is a pre-invasive form of a non-melanoma skin cancer, and said pre-invasive form is cSCC in situ (cSCCis).

The compounds and methods described herein are advantageously used to inhibit proliferation of skin cancer cells. Preferably, the compounds and methods provide treatment of a mammal, preferably a human, against skin cancer. The methods provides treatment against the various types of skin cancer, in particular of basal cell carcinoma, cutaneous squamous cell carcinoma or melanoma or cutaneous lymphoma. Thus, administering of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same provide treatment of a patient against skin cancer.

EXAMPLES

All reagents and solvents used in the synthesis were purchased from Sigma Aldrich, Bachem, Iris Biotech, Fluorochem, Enamine, Combi-Blocks, Merck, Alchem Pharmatech and used as received. Solvents were stored over molecular sieves 4 Å. Peptides were synthesized on a 0.25-mmol or 0.10-mmol scale on Fmoc-β-Ala Wang resin (0.72 mmol g⁻¹) or Fmoc-Aib Wang resin (0.49 mmol g⁻¹) using a Liberty Blue microwave peptide synthesizer (CEM Corp., Matthews, NC) employing Fmoc solid-phase techniques with repeated steps of coupling, deprotection, and washing, as further described in Example 1.

Mass and purity of final compounds was determined by UHPLC-MS using a Thermo Scientific UltiMate 3000 System equipped with a Accucore™ C18 column and diode array detector (254 nm). The mobile phase consisted of H₂O-Acetonitrile (solvent A, 97:3 v/v, LC-MS Ultra Chromasolv®, UHPLC grade, Sigma-Aldrich, Germany) and 0.1 % Formic acid (LC-MS grade, Sigma-Aldrich, Germany) and Acetonitrile-H₂O (solvent B, 97:3 v/v, LC-MS Ultra Chromasolv®, UHPLC grade, Sigma-Aldrich, Germany) and 0.1 % Formic acid (LC-MS grade, Sigma-Aldrich, Germany) with a 3 min run time, 1.3 ml/min flow rate, 5 µL injection volume and a gradient elution according to the following program: linear increment starting

with 100 % A to 100 % B in 1.35 min and holding 100 % B for 0.9 min before returning to the initial conditions within the next 0.75 min. MS detection of analytes was performed on a Thermo Scientific single quadrupole mass spectrometer equipped with electrospray ionization (ESI) interface (Thermo Scientific, MSQ Plus Mass Detector) in positive and negative ion mode
5 with mass range from 100-1700 m/z.

EXAMPLE 1

General procedure for the synthesis for compounds of formula (I)

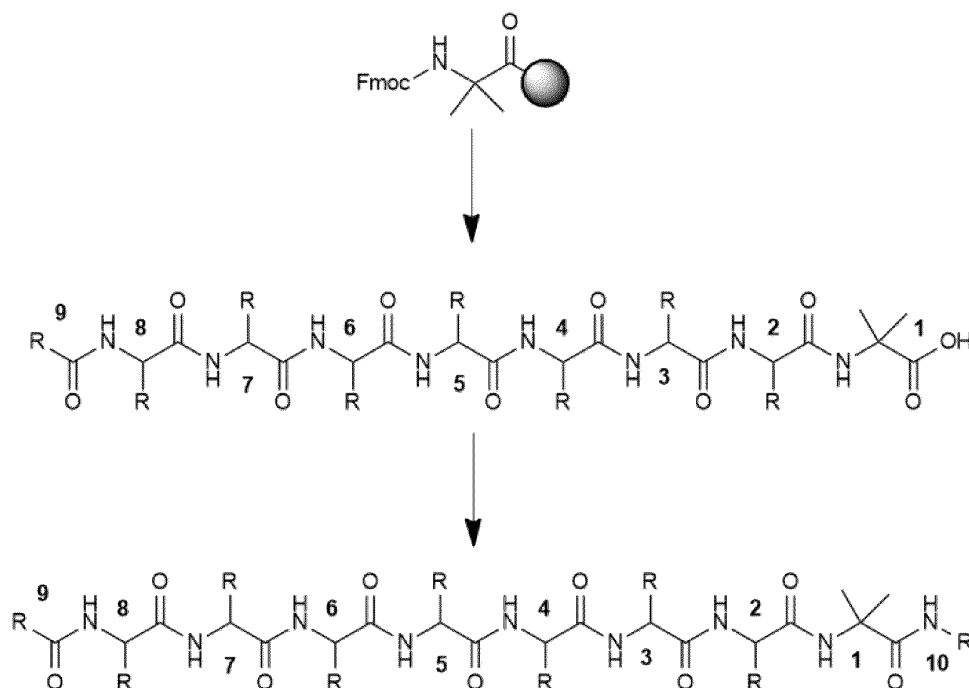
The peptides were synthesized using a Liberty Blue microwave peptide synthesizer (CEM Corp., Matthews, NC) starting from Fmoc-Aib-OH or Fmoc-beta-Ala linked to Wang resin
10 employing Fmoc solid-phase techniques with repeated steps of coupling, deprotection, and washing. Coupling was performed as follows: Fmoc-L-amino acids or the capping group (5.0 equiv., 0.2M in DMF), DIC (5.0 equiv., 0.5M in DMF), and Oxyma (5.0 equiv., 0.5M in DMF) for 4 minutes with microwave irradiation at 90°C. For the second Aib coupling, a double coupling with each 15 minutes microwave irradiation at 90°C was performed. Fmoc
15 deprotection was performed as follows: 10% piperazine in NMP/ethanol (9:1, v/v) for 1 minute with microwave irradiation at 90°C.

By employing sequentially the amino acid building blocks listed in Table 1 and free acid derivatives listed in Table 2, the different peptides were assembled on solid phase support. Said syntheses are illustrated for inventive octa- and nonapeptides in Scheme 1A and Scheme 1B,
20 wherein the numbering is depicted accordingly, namely the amino acids used in steps 1 to 8 (Scheme 1A) or in steps 1 to 9 (Scheme 1B) and the free acid derivatives used in step 9 (Scheme 1A) or in step 10 (Scheme 1B). The corresponding shorter or longer peptide chains were synthesized and numbered accordingly.

Following synthesis, the peptide was cleaved from the resin by treatment with a cleavage
25 mixture (1mL/0.1g resin) consisting of TFA/H₂O (95:5, v/v) for 90 minutes at ambient temperature. The suspended resin was removed by filtration and the filtrate was concentrated *in vacuo*. The crude peptides were dissolved in acetonitrile and were purified by ISCO chromatography system using as mobile phase H₂O/acetonitrile (95:5, v/v) and acetonitrile/H₂O (95:5, v/v), gradient ACN 10% to 100%, to give peptide acids with ≥ 90% purity. The
30 purified peptide acid (1.0 equiv.) was coupled in solution (DMF) with the respective amine (2.0 equiv.) listed in Table 3 in presence of DIPEA (3.0 equiv.) and HATU (2.0 equiv.) to give the final peptide (illustrated as step 10 in Scheme 1A and step 11 in Scheme 1B). The final peptide

was then diluted with ethyl acetate and washed with an aqueous HCl (1M) solution, followed by an aqueous NaOH (1M) solution and a saturated NaCl solution. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude peptide was purified on Gilson PLC 2020 Personal Purification System, as described above, to give final products with $\geq 90\%$ purity, typically with $\geq 95\%$ purity. In two cases the remaining protection group was removed in an HCl solution and once with Palladium on carbon under a hydrogen atmosphere.

Scheme 1A: Scheme for the synthesis of the respective inventive compounds of formula (I) comprising an octapeptide



10 Scheme 1B: Scheme for the synthesis of the respective inventive compounds of formula (I) comprising a nonapeptide

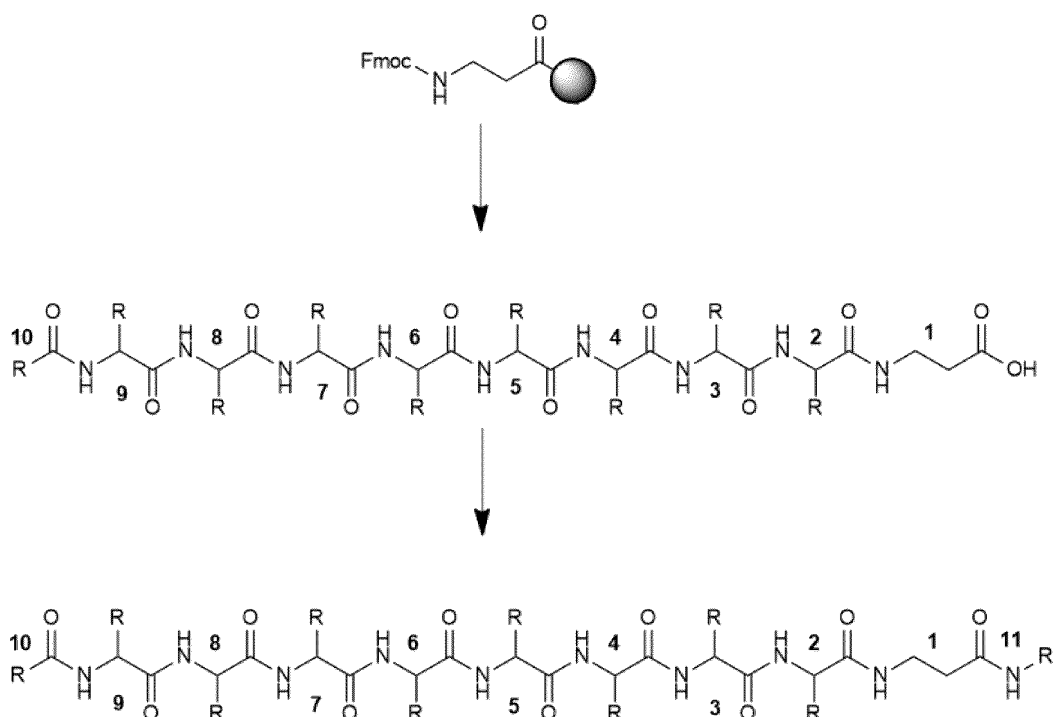
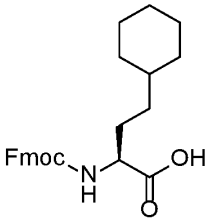
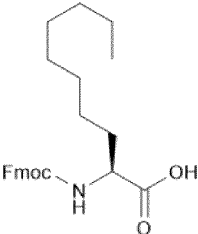
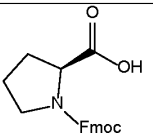
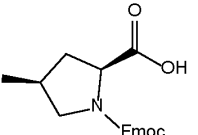
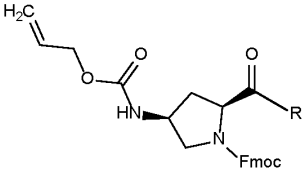
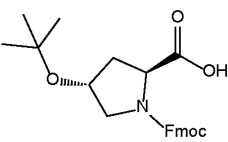
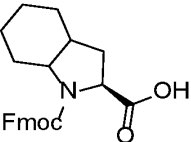
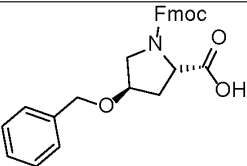
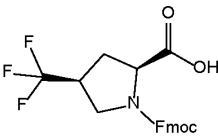
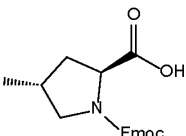
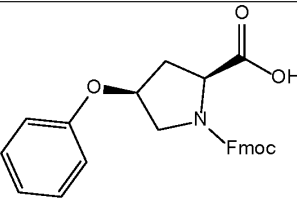
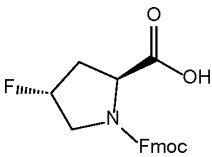
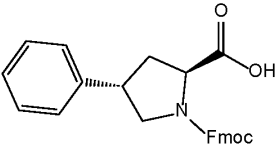
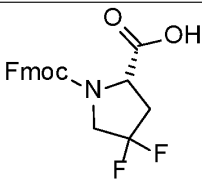
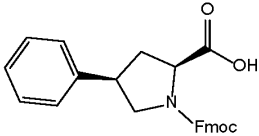
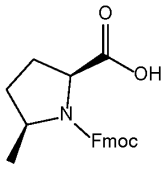
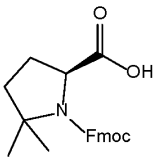
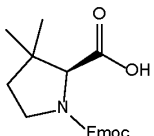
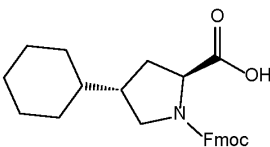
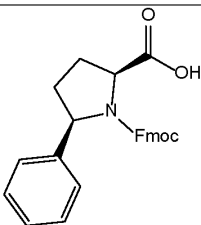
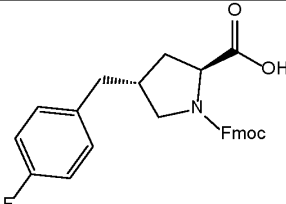
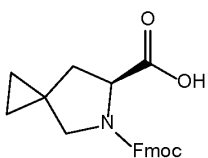
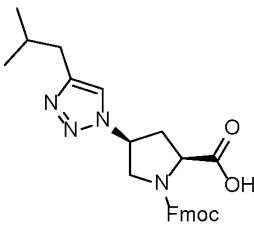


Table 1: Amino acid building blocks used for the synthesis of compounds of formula (I)

AMINO ACIDS		
Short Name	Structure	IUPAC Name
Fmoc-β-Ala-OH		3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propanoic acid
Fmoc-Aib-OH		2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methylpropanoic acid
Fmoc-Leu-OH		(((9H-fluoren-9-yl)methoxy)carbonyl)-L-leucine

Fmoc-L-homocyclohexylalanine		(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-cyclohexylbutanoic acid
(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)decanoic acid		(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)decanoic acid
Fmoc-L-Pro-OH		(((9H-fluoren-9-yl)methoxy)carbonyl)-L-proline
Fmoc-L-Pro(4S-Methyl)-OH		(2S,4S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpyrrolidine-2-carboxylic acid
Fmoc-L-Pro(4-NH-Alloc)-OH (2S, 4R)		(2S,4R)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)-4-((allyloxy)carbonyl)amino)pyrrolidine-2-carboxylic acid
Fmoc-Hyp(tBu)-OH		(2S,4R)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)-4-(tert-butoxy)pyrrolidine-2-carboxylic acid
Fmoc-L-Octahydroindole-2-carboxylic acid		(2S)-1-[[[(9H-fluoren-9-yl)methoxy]carbonyl]-octahydro-1H-indole-2-carboxylic acid
Fmoc-Hyp(Bzl)-OH		(2S,4R)-4-(benzyloxy)-1-[[[(9H-fluoren-9-yl)methoxy]carbonyl]pyrrolidine-

		2-carboxylic acid
Fmoc-L-Pro(4-CF ₃)-OH		(2S,4S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid
Fmoc-L-Pro(4R-Methyl)-OH		(2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpyrrolidine-2-carboxylic acid
(2S, 4S)-Fmoc-4-phenoxy-pyrrolidine-2-carboxylic acid		(2S,4S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-phenoxy-pyrrolidine-2-carboxylic acid
Fmoc-L-Pro(4-F)-OH (2S,4R)		(2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-fluoropyrrolidine-2-carboxylic acid
Fmoc-(2S,4S)-4-phenylpyrrolidine-2-carboxylic acid		(2S,4S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-phenylpyrrolidine-2-carboxylic acid
Fmoc-L-4,4,-difluoroproline		(2S)-1-[[[(9H-fluoren-9-yl)methoxy]carbonyl]-4,4-difluoropyrrolidine-2-carboxylic acid
Fmoc-(2S,4R)-4-phenylpyrrolidine-2-carboxylic acid		(2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-phenylpyrrolidine-2-carboxylic acid
Fmoc-L-Pro(5-Me)-OH (2S,5S)		(2S,5S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-methylpyrrolidine-2-carboxylic acid

Fmoc-5,5-dmP-OH (S)		(S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-5,5-dimethylpyrrolidine-2-carboxylic acid
Fmoc-3,3-dmP-OH (S)		(S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-3,3-dimethylpyrrolidine-2-carboxylic acid
Fmoc-L-Pro(4Chx)-OH (2S,4S)		(2S,4S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-cyclohexylpyrrolidine-2-carboxylic acid
Fmoc-L-Pro(5-Ph)-OH (2S,5R)		(2S,5R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-phenylpyrrolidine-2-carboxylic acid
Fmoc-L-Pro(4-p-F-Ph)-OH (2S,4R)		(2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid
(S)-5-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid		(S)-5-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid
(2S,4S)-1-{[(9H-fluoren-9-yl)methoxy]carbonyl}-4-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylic acid		(2S,4S)-1-{[(9H-fluoren-9-yl)methoxy]carbonyl}-4-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylic acid

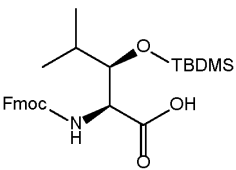
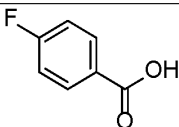
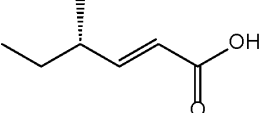
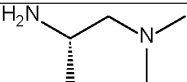
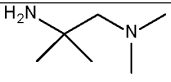
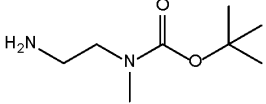
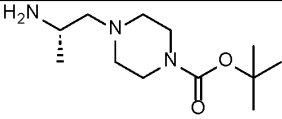
(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)-amino)-3-((tert-butyl dimethylsilyl)oxy)-4-methylpentanoic acid		(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((tert-butyl dimethylsilyl)oxy)-4-methylpentanoic acid
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Table 2: Free acids used for the synthesis of compounds of formula (I)

ACIDS		
Short Name	Structure	IUPAC Name
4-Fluorobenzoic acid		4-Fluorobenzoic acid
(S,E)-4-methylhex-2-enoic acid		(S,E)-4-methylhex-2-enoic acid

5

Table 3: Primary or secondary amines used for the synthesis of compounds of formula (I).

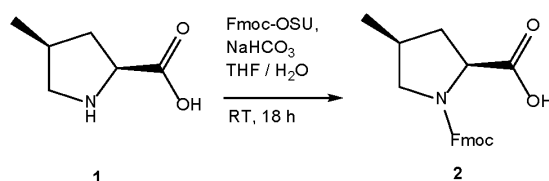
AMINES		
Short Name	Structure	IUPAC Name
1-[(dimethylamino)methyl]cyclobutan-1-amine		1-[(dimethylamino)methyl]cyclobutan-1-amine
[(2S)-2-aminopropyl]dimethylamine		(2S)-N ¹ ,N ¹ -dimethylpropane-1,2-diamine
N ¹ ,N ¹ -2-trimethylpropane-1,2-diamine		N ¹ ,N ¹ -2-trimethylpropane-1,2-diamine
tert-butyl (2-aminoethyl)-(methyl)carbamate		tert-butyl (2-aminoethyl)-(methyl)carbamate
tert-butyl 4-[(2S)-2-aminopropyl]piperazine-1-carboxylate		tert-butyl 4-[(2S)-2-aminopropyl]piperazine-1-carboxylate

(2-aminoethyl)dimethylamine		(2-aminoethyl)dimethylamine
(2S)-1-(morpholin-4-yl)propan-2-amine		(2S)-1-(morpholin-4-yl)propan-2-amine
2-(4-methylpiperazin-1-yl)ethan-1-amine		2-(4-methylpiperazin-1-yl)ethan-1-amine
benzyl N-[(2S)-2-aminopropyl]-N-methylcarbamate		benzyl N-[(2S)-2-aminopropyl]-N-methylcarbamate

EXAMPLE 2

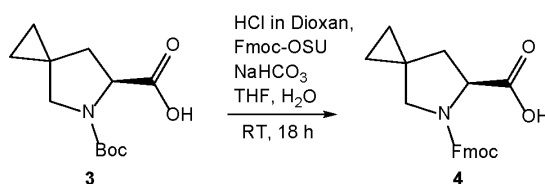
Synthesis of amino acids as building blocks for compounds of formula (I)

Some amino acids needed for the synthesis of compounds of formula (I) were not commercially available. In this case, they were synthesized. In *Scheme 2*, *Scheme 3*, *Scheme 4* and *Scheme 5* these syntheses are presented.

Scheme 2: Synthesis of not commercially available amino acid **2**.

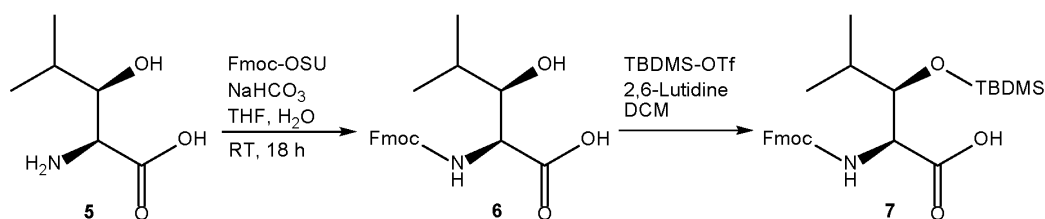
The synthesis of the amino acids **2** is depicted at *Scheme 2*. To begin with, (4S)-4Methyl-L-Proline (**1**, 7.7 mmol, 1.0 equiv.) was suspended in THF (4 ml / mmol of **1**) and water (2.5 ml / mmol of **1**). A saturated solution of NaHCO₃ in water (1.5 ml / mmol of **1**) was added. Fmoc-OSU (9.3 mmol, 1.2 equiv.) was added and the reaction was stirred at room temperature for 18 hours. The THF was removed in vacuo and the remaining mixture was diluted with an aqueous HCl (2 M, 25 ml) solution. The aqueous layer was extracted three times with ethyl acetate (3 x 50 ml). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reversed phase chromatography to obtain **2** as a white solid.

Scheme 3: Synthesis of not commercially available amino acid **4**.



The synthesis of the amino acid **4** is depicted at *Scheme 3*. To begin with, compound **3** (2.5 mmol, 1.0 equiv.) was diluted in a HCl solution (4 M, 1 ml / 0.5 mmol of **3**) in dioxane and stirred at room temperature for 3 hours. Then a saturated aqueous solution of NaHCO₃ (1 ml / 0.25 mmol of **3**) and Fmoc-OSU (3.0 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature for 18 hours. The dioxane was removed in vacuo and the remaining mixture was diluted with an aqueous HCl (2 M, 20 ml) solution. The aqueous layer was extracted three times with ethyl acetate (3 x 40 ml). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reversed phase chromatography to obtain **4** as a white solid.

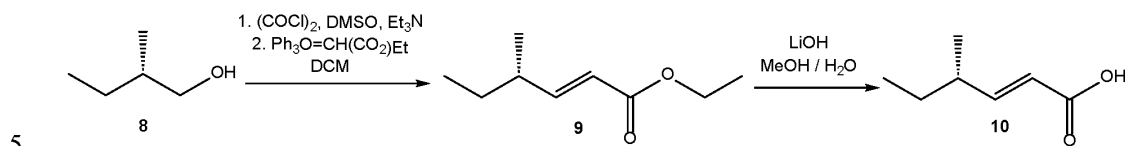
Scheme 4: Synthesis of not commercially available amino acid **7**.



The synthesis of the amino acid **7** is depicted in *Scheme 4*. To begin with, compound **5** (3.1 mmol, 1.0 equiv.) was dissolved in a mixture of THF (3 ml / mmol of **5**) and water (3 ml / mmol of **5**). A saturated aqueous NaHCO₃ solution was added until pH ~10 was reached. A solution of Fmoc-OSu (3.8 mmol, 1.2 equiv.) in THF (3 ml / mmol of **5**) was added over 30 minutes at 0°C. After the addition, the suspension was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was acidified to pH ~3 with an aqueous 10% citric acid solution. The mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography to obtain **6**. To a solution of **6** (3.1 mmol, 1.0 equiv.) in DCM (10 ml / mmol of **6**), 2,6-Lutidine (15.6 mmol, 5.0 equiv.) and TBDMS-OTf (8.8 mmol, 2.5 equiv.) were added at 0 °C. The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. The mixture was quenched with an aqueous saturated NH₄Cl solution and the two phases separated. The aqueous phase was extracted once with DCM

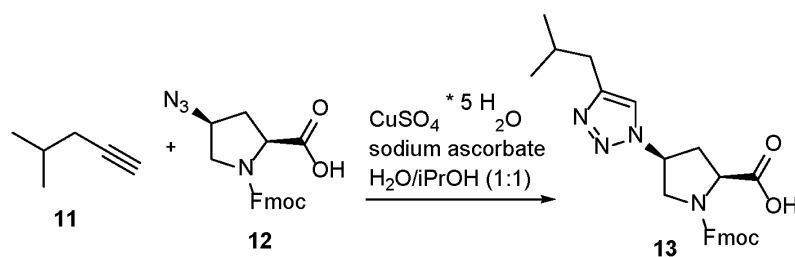
(50 ml). The combined organic layers were washed with an aqueous 1 M HCl solution, brine and then dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography to afford **7** as a solid.

Scheme 5: Synthesis of not commercially available building block **10**



The synthesis of the free acid **10** is depicted in *Scheme 5*. To begin with, a solution of dimethyl sulfoxide (34.0 mmol, 3.0 equiv.) in dichloromethane (1.5 ml / mmol of **8**) was added to a solution of oxalyl chloride (22.7 mmol, 2.0 equiv.) in dichloromethane (1.75 ml / mmol of **8**) at -78 °C. After stirring for 5 min at -78 °C, a solution of (S)-(-)-2-methyl-1-butanol (**8**, 11.3 mmol, 1.0 equiv.) in dichloromethane (2.4 ml / mmol of **8**) was added. After stirring for 1 hour at -78 °C, a solution of triethylamine (68 mmol, 6.0 equiv.) was added and the mixture was warmed to room temperature. After stirring for 1 hour at room temperature, the reaction was quenched with water (50 ml). The two layers were separated and the aqueous one was extracted twice with dichloromethane (2 x 50 ml). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The aldehyde was diluted in dichloromethane (5 ml / mmol of **8**) and (carbethoxymethylene)triphenylphosphorane (14.7 mmol, 1.3 equiv.) was added. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with hexane (50 ml) and the suspension was filtered through Celite®. The filtrate was concentrated in vacuo and the residue was purified by normal-phase column chromatography, to obtain **9** as a colorless oil. To a solution of **9** (6.8 mmol, 1.0 equiv.) in methanol and water (4:1, 3.5 ml / mmol of **9**), lithium hydroxide monohydrate (13.6 mmol, 2.0 equiv.) was added. The reaction was stirred overnight at room temperature. The reaction mixture was basified with an aqueous NaOH (2 M, 0.5 ml / mmol of **9**) solution and extracted with dichloromethane. The organic phase was discarded and the aqueous phase was acidified with an aqueous HCl (2 M, 2 ml / mmol of **9**) solution and extracted with dichloromethane. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude oil was purified by normal-phase chromatography to afford **10** as a yellowish oil.

Scheme 6: Synthesis of not commercially available amino acid **13**.



The synthesis of the free acid **13** is depicted in *Scheme 6*. To begin with, compound **12** (7 μmol , 1.0 equiv.) was dissolved in $\text{H}_2\text{O}/i\text{PrOH}$ (1:1, 1 ml/10 μmol of **12**). Compound **11** (8 μmol , 1.1 equiv.), Copper(II) sulfate pentahydrate (1 μmol , 0.1 equiv.) and sodium ascorbate (4 μmol , 0.5 equiv.) were added to the solution of **12** in $\text{H}_2\text{O}/i\text{PrOH}$ at room temperature. The reaction mixture was stirred for 48 hours at room temperature. The reaction mixture was diluted with acetonitrile and directly purified by reversed-phase chromatography to afford **13** as a white solid.

EXAMPLE 3

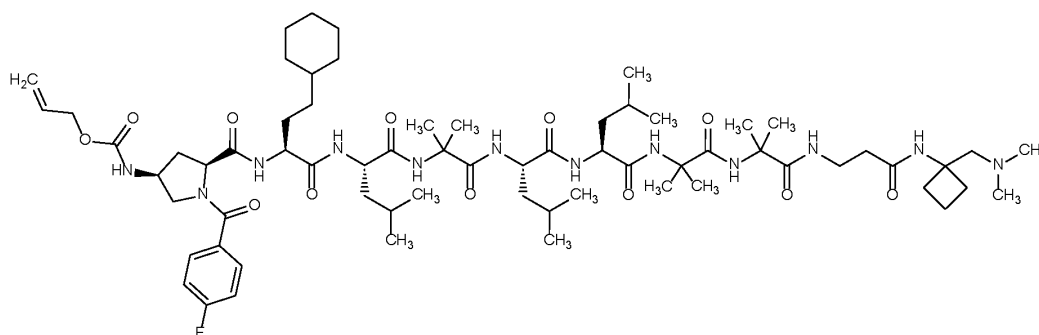
10

Synthesis of compounds of formula (I)

The compounds of formula (I) have been synthesized in accordance with the general procedures described above and as depicted in Schemes 1A and 1B for the inventive octa- and nonapeptides. Each of the synthesized compounds are identified by its compound number (4 or 5-digit number), its structural formula and its IUPAC name as generated by the ChemDraw software. Furthermore, the synthesis is described by way of the building blocks, acids and amines used as disclosed in Tables 1-3. Moreover, the experimentally measured molecular mass is provided. Finally, for each specifically identified compound of formula (I) the characterization of the substituents R_1 , R_2 , and R_3 in accordance with formula (I) is given, wherein the residue R within said definition of said substituents R_1 , R_2 , and R_3 corresponds to and indicates the respective attachment within formula (I). The synthesis of the reference compound 6027 has been described in EP3345917.

20

20762:



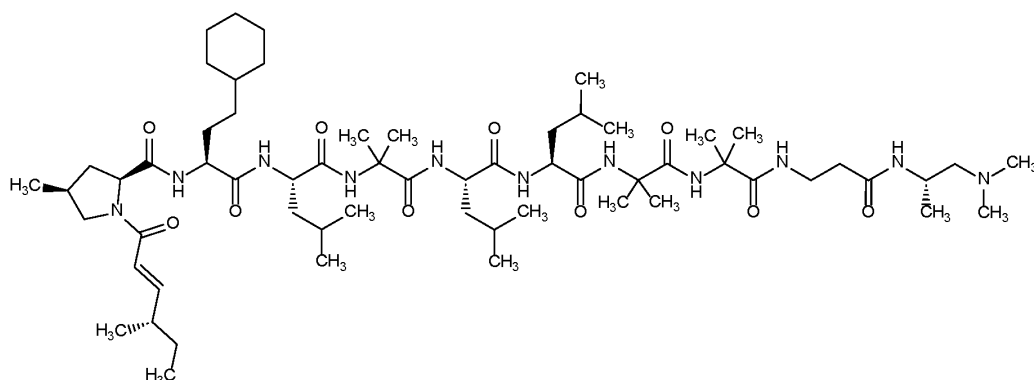
5 Allyl ((3S,5S)-5-(((12S,15S,21S,24S)-26-cyclohexyl-1-((1-((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)carbamoyl)-1-(4-fluorobenzoyl)pyrrolidin-3-yl)carbamate

Cpd	1	2	3	4	5	6
20762	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexyl-alanine	Fmoc-L-Pro(4-NH-Alloc)-OH (2S, 4R)	4-Fluorobenzoic acid	1-[(dimethylamino)methyl]cyclobutan-1-amine	

Cpd	Molecular weight	Experimentally measured mass
20762 [M+H] ⁺	1279.7	1280.2

Cpd	R1	R2	R3
20762			

22178:

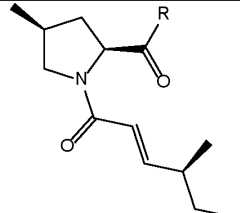
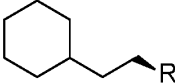
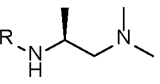


(2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide

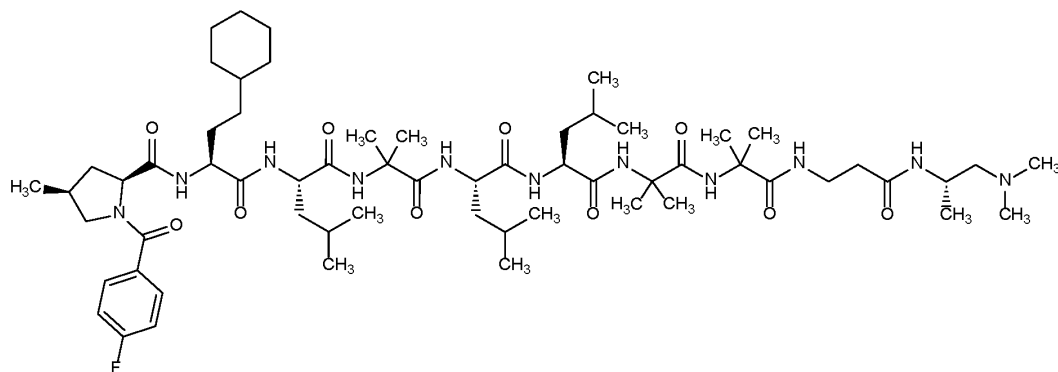
Cpd	1	2	3	4	5	6
22178	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexyl-alanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

5

Cpd	Molecular weight	Experimentally measured mass
22178 [M] ⁺	1156.6	1156.6

Cpd	R1	R2	R3
22178			

22179:

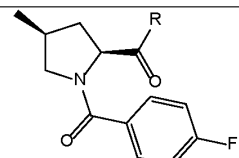
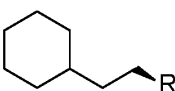
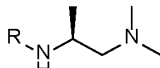


(2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

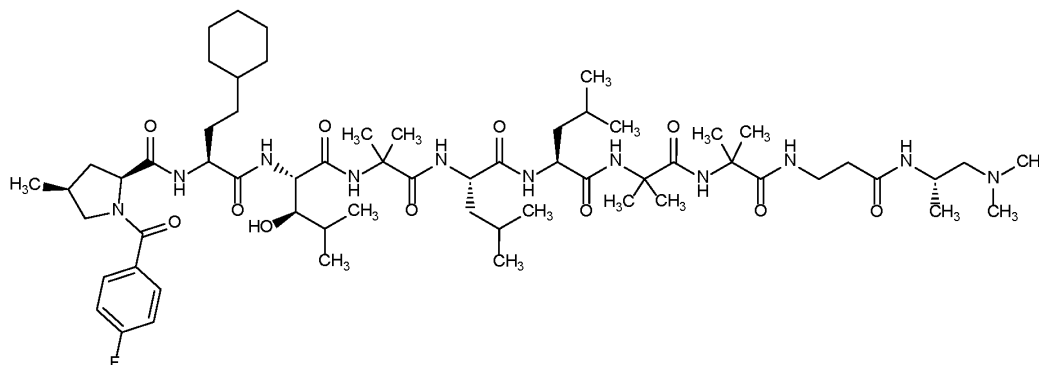
Cpd	1	2	3	4	5	6
22179	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

Cpd	Molecular mass	Experimentally measured mass
22179 [M+H] ⁺	1168.5	1169.2

5

Cpd	R1	R2	R3
22179			

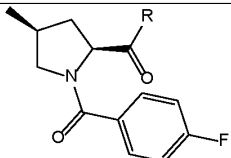
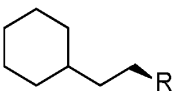
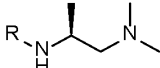
22180 (reference example):



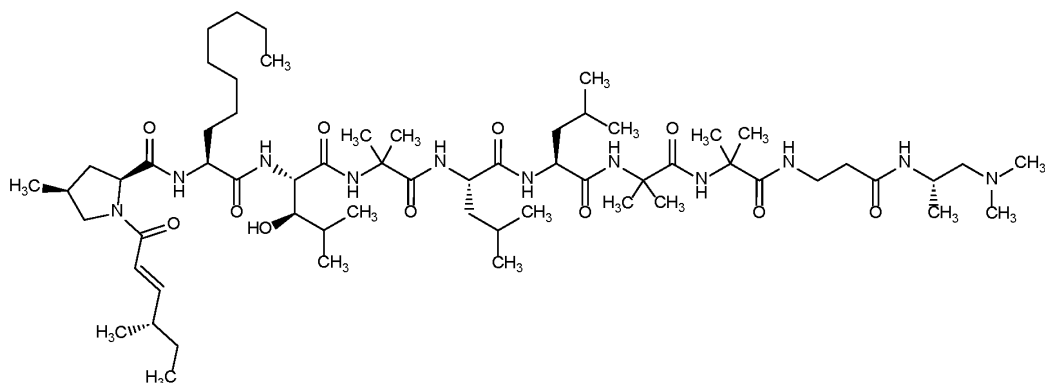
10 (2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-26-((R)-1-hydroxy-2-methylpropyl)-17,20-diisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6
22180	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

Cpd	Molecular mass		Experimentally measured mass
22180 [M+H] ⁺	1184.5		1185.1

Cpd	R1	R2	R3
22180			

22430 (reference example):



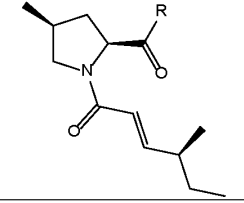
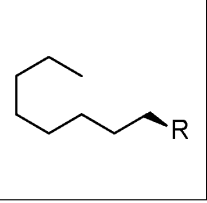
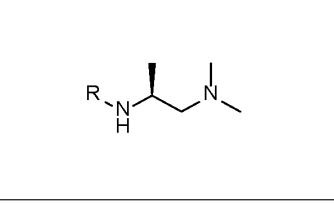
- 5 (2S,4S)-N-((4S,17S,20S,26S,29S)-26-((R)-1-hydroxy-2-methylpropyl)-17,20-diisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazaheptatriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6
22430	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7		8	9	10	11
	(2S,3R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-amino-3-((tert-butyldimethylsilyl)oxy)-4-methylpentanoic acid		(S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)decanoic acid	Fmoc-L-Pro(4S-Methyl)-OH	(S,E)-4-methylhex-2-enoic acid	[(2S)-2-aminopropyl]dimethylamine

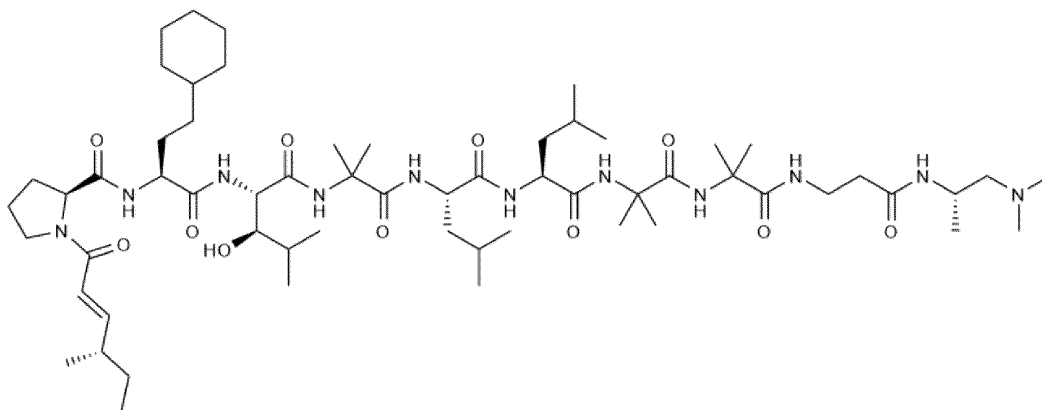
Cpd	Molecular mass		Experimentally measured mass
22430 [M+H] ⁺	1174.6		1175.7

10

Cpd	R1	R2	R3

22430			
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22432 (reference example):

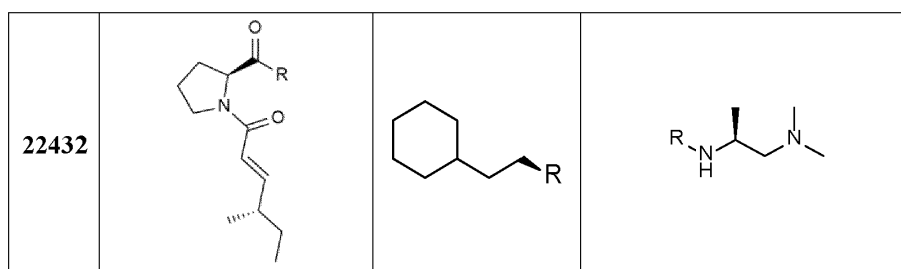


(S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-26-((R)-1-hydroxy-2-methylpropyl)-17,20-diisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octa-oxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-((S,E)-4-methylhex-2-en-2-en-1-yl)pyrrolidine-2-carboxamide

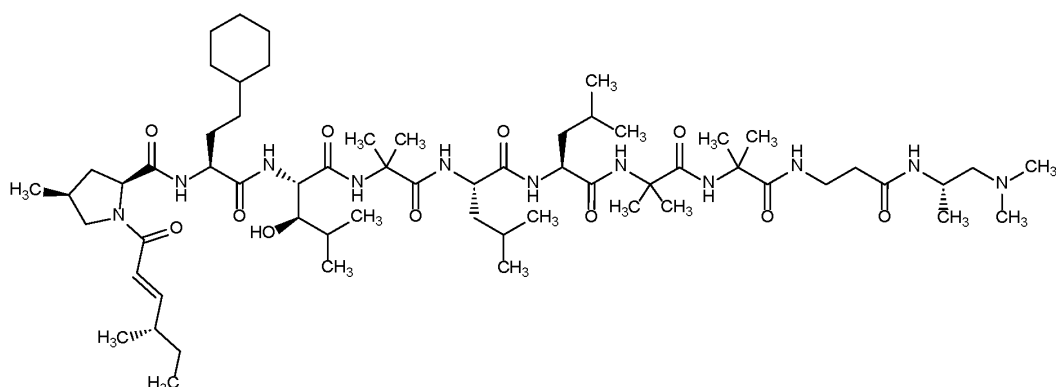
Cpd	1	2	3	4	5	6
22432	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)-amino)-3-((tert-butyl)dimethylsilyl)oxy)-4-methylpentanoic acid	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro-OH	(S,E)-4-methylhex-2-enoic acid	[(2S)-2-amino-propyl]dimethylamine	

Cpd	Molecular mass	Experimentally measured mass
22432 [M+H] ⁺	1158.6	1159.6

Cpd	R1	R2	R3
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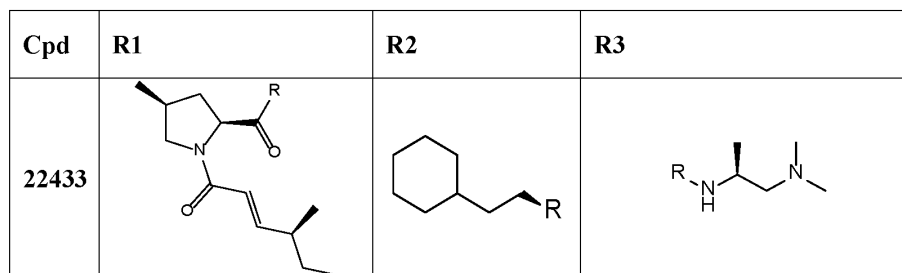
22433 (reference example):

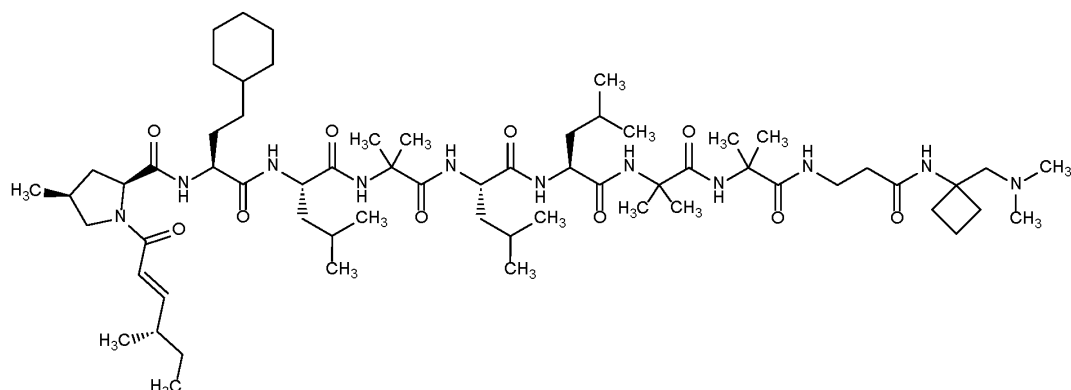


(2S,4S)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-26-((R)-1-hydroxy-2-methylpropyl)-17,20-
 5 diisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-
 2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-
 enoyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6
22433	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7		8	9	10	11
	(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)-amino)-3-((tert-butyldimethylsilyl)oxy)-4-methylpentanoic acid		Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	(S,E)-4-methylhex-2-enoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
22433 [M] ⁺	1172.6	1172.8



23103:

- (2S,4S)-N-((12S,15S,21S,24S)-26-cyclohexyl-1-((1-
 5 ((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-
 1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)-4-methyl-1-
 ((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide

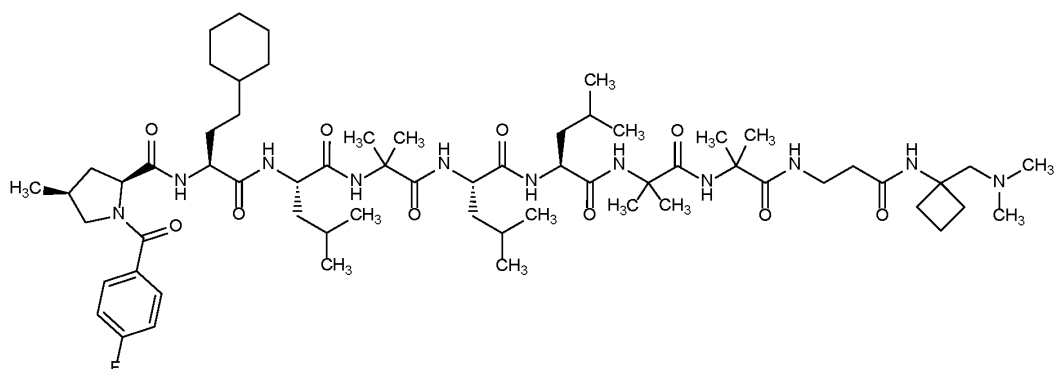
Cpd	1	2	3	4	5	6
23103	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-Pro(4S-Methyl)-OH	(S,E)-4-methylhex-2-enoic acid	1-[(dimethylamino)methyl]cyclobutan-1-amine	

Cpd	Molecular mass	Experimentally measured mass
23103 [M] ⁺	1182.6	1182.6

Cpd	R1	R2	R3
23103			

10

23491:



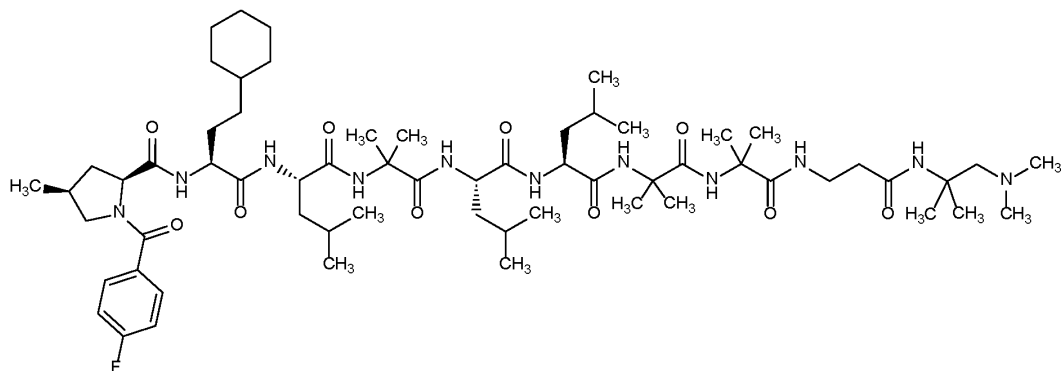
- (2S,4S)-N-((12S,15S,21S,24S)-26-cyclohexyl-1-((1-
 ((dimethylamino)methyl)cyclobutyl)amino)-12,15,21-triisobutyl-6,6,9,9,18,18-hexamethyl-
 1,5,8,11,14,17,20,23-octaoxo-4,7,10,13,16,19,22-heptaazahexacosan-24-yl)-1-(4-
 5 fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6
23491	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	1-[(dimethylamino)methyl]cyclobutan-1-amine	

Cpd	Molecular mass	Experimentally measured mass
23491 [M] ⁺	1194.6	1194.7

Cpd	R1	R2	R3
23491			

23525:



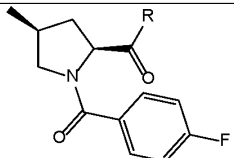
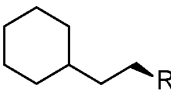
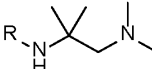
10

(2S,4S)-N-((17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,4,11,11,14,14,23,23-

nonamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

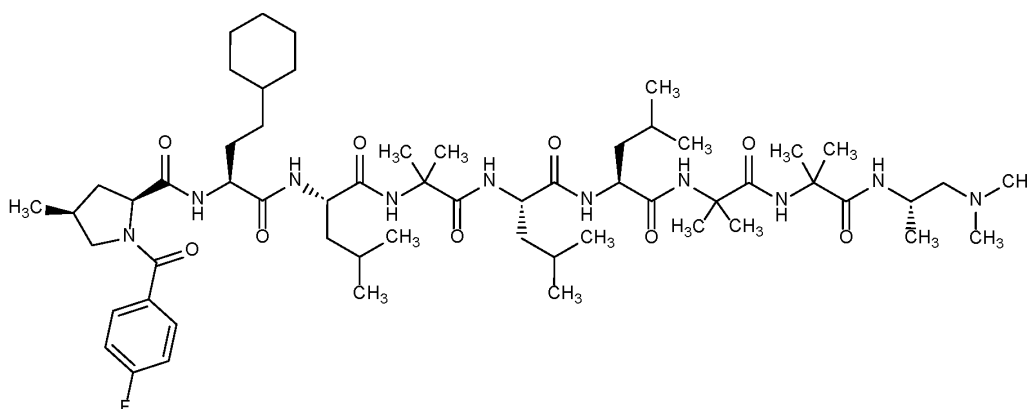
Cpd	1	2	3	4	5	6
23525	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	N ¹ ,N ¹ -2-trimethylpropane-1,2-diamine	

Cpd	Molecular mass	Experimentally measured mass
23525 [M] ⁺	1182.6	1182.7

Cpd	R1	R2	R3
23525			

5

23526:



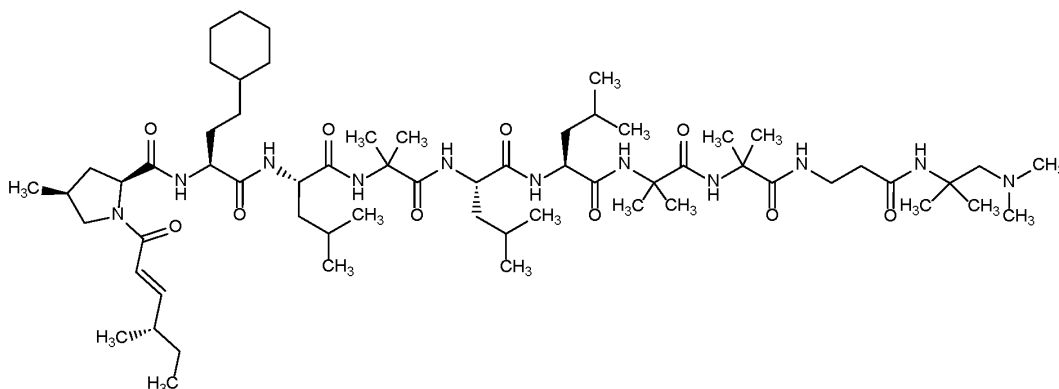
(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaoxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

10

Cpd	1	2	3	4	5
23526	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23526 [M] ⁺	1097.5	1097.6

Cpd	R1	R2	R3
23526			

23538:

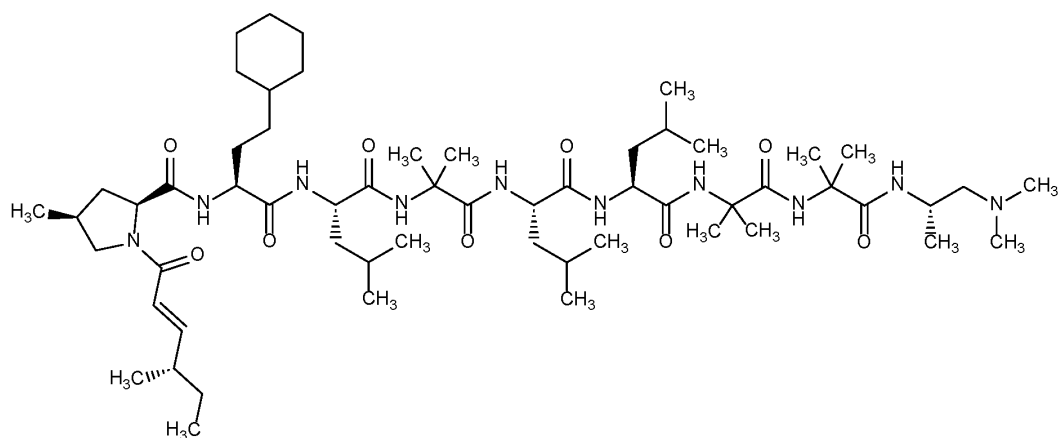
(2S,4S)-N-((17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,4,11,11,14,14,23,23-nonamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6
23538	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-Pro(4S-Methyl)-OH	(S,E)-4-methylhex-2-enoic acid	N ¹ ,N ¹ -2-trimethylpropane-1,2-diamine	

Cpd	Molecular mass	Experimentally measured mass
23538 [M] ⁺	1170.6	1170.7

Cpd	R1	R2	R3
23538			

10 **23542:**



(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-4-methyl-1-((S,E)-4-methylhex-2-enoyl)pyrrolidine-2-carboxamide

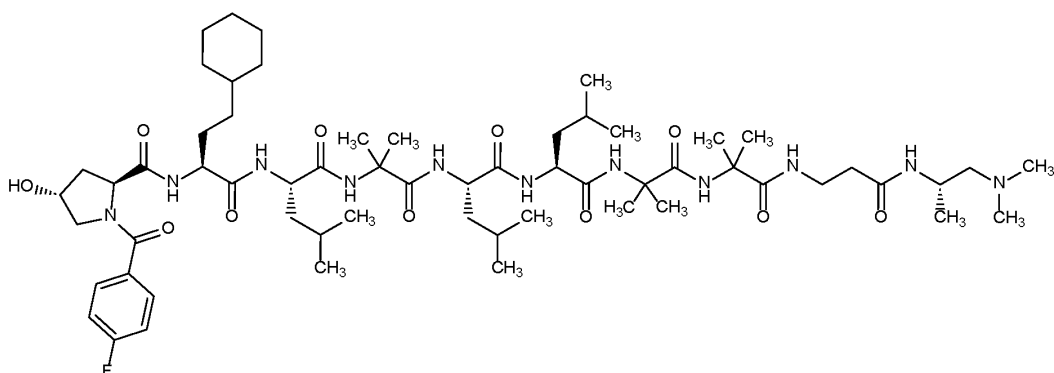
Cpd	1	2	3	4	5
23542	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	(S,E)-4-methylhex-2-enoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23542 [M] ⁺	1085.5	1085.7

Cpd	R1	R2	R3
23542			

23549:



(2S,4R)-N-((4S,17S,20S,26S,29S)-31-cyclohexyl-17,20,26-triisobutyl-2,4,11,11,14,14,23,23-octamethyl-6,10,13,16,19,22,25,28-octaoxo-2,5,9,12,15,18,21,24,27-nonaazahentriacontan-29-yl)-1-(4-fluorobenzoyl)-4-hydroxypyrrolidine-2-carboxamide

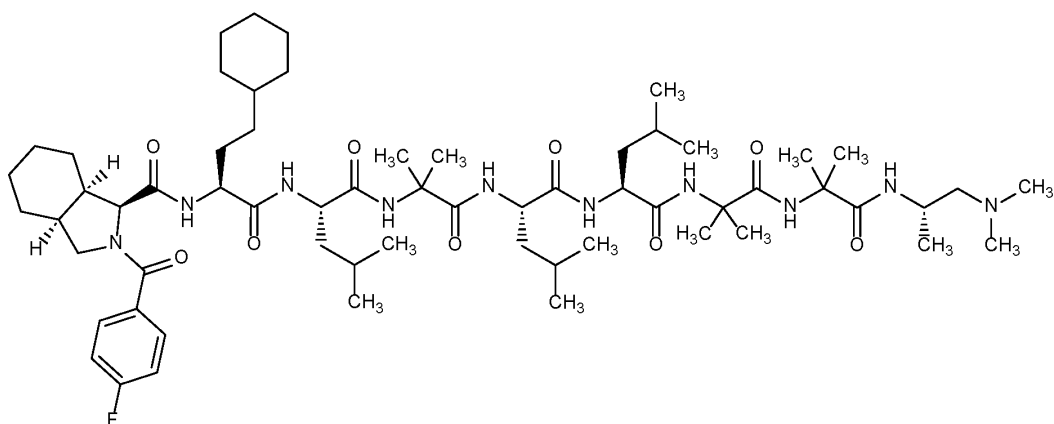
Cpd	1	2	3	4	5	6
23549	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	7	8	9	10	11	
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-Hyp(tBu)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

5

Cpd	Molecular mass	Experimentally measured mass
23549 [M] ⁺	1170.5	1170.7

Cpd	R1	R2	R3
23549			

23552:

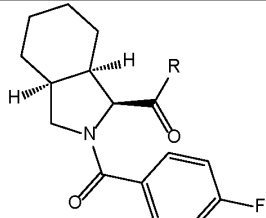
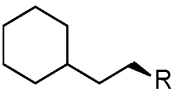
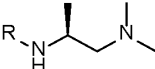


(1S,3aS,7aR)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-2-(4-fluorobenzoyl)octahydro-1H-isoindole-1-carboxamide

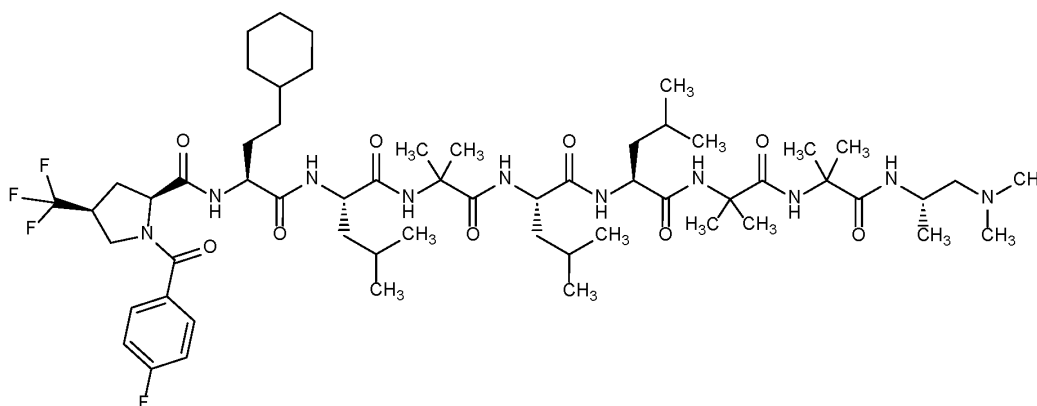
Cpd	1	2	3	4	5
23552	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Octahydroindole-2-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23552 [M+H] ⁺	1137.5	1138.6

5

Cpd	R1	R2	R3
23552			

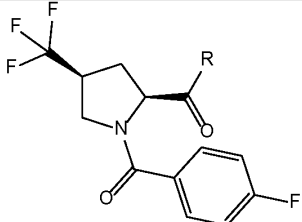
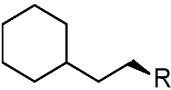
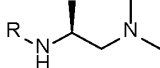
23585:

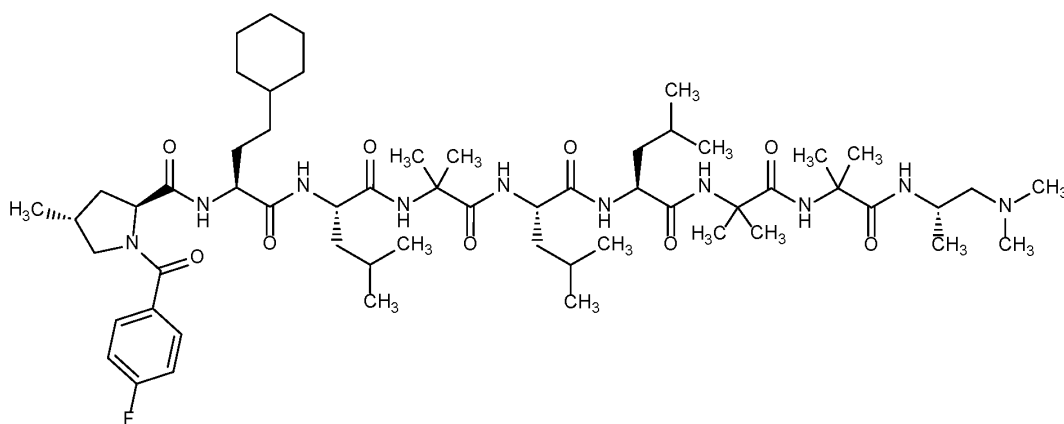


10 (2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23585	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4-CF ₃)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23585 [M] ⁺	1151.4	1151.6

Cpd	R1	R2	R3
23585			

23586:

5

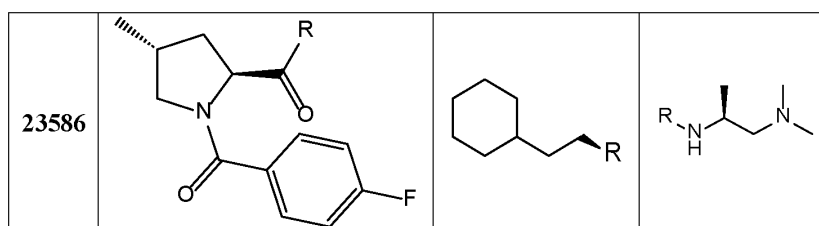
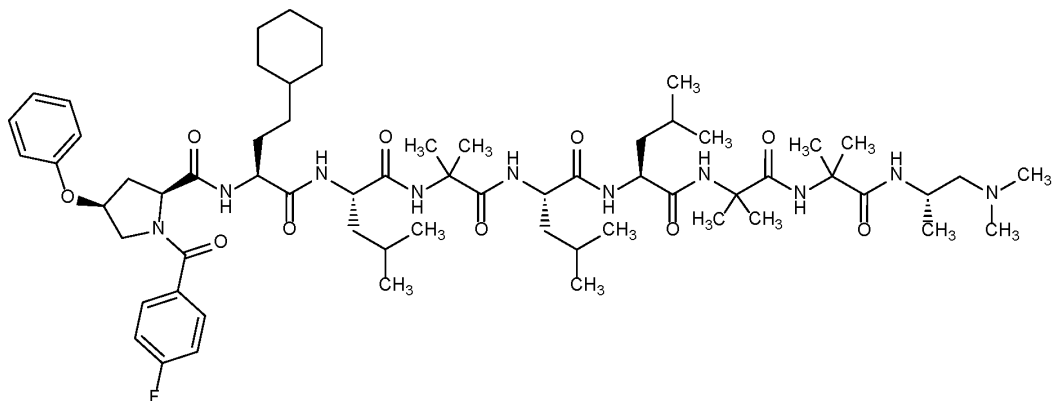
(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaooxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23586	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
6	7	8	9	10	
Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4R-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

Cpd	Molecular mass	Experimentally measured mass
23586 [M] ⁺	1097.5	1097.6

10

Cpd	R1	R2	R3
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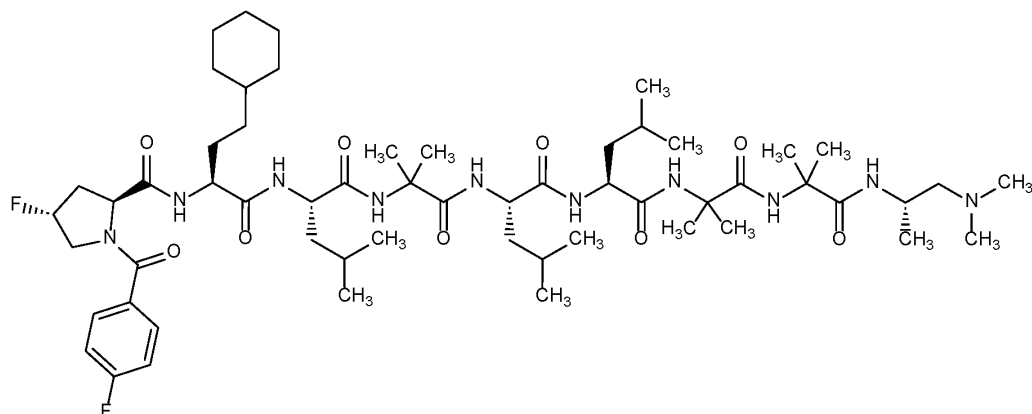
**23594:**

(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaooxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenoxypyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23594	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	(2S, 4S)-Fmoc-4-phenoxy-pyrrolidine-2-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23594 [M] ⁺	1175.5	1175.7

Cpd	R1	R2	R3
23594			

23595:

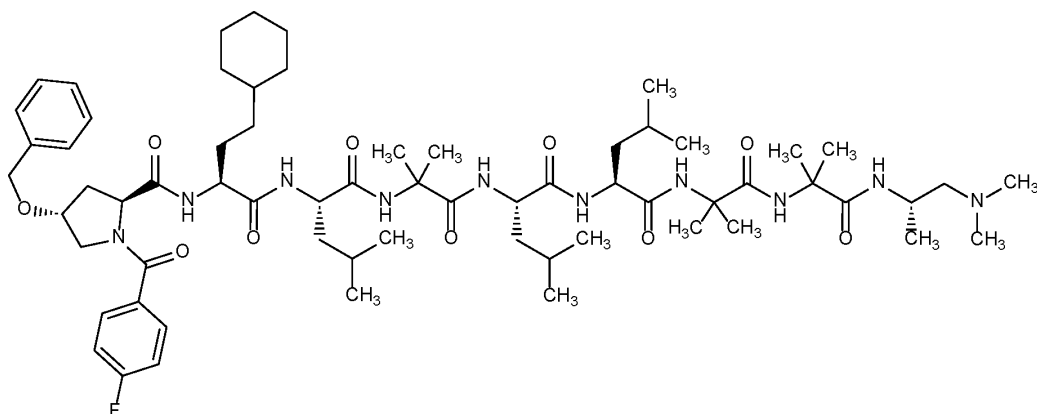
(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-trisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-4-fluoro-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23595	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4-F)-OH (2S,4R)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23595 [M] ⁺	1101.4	1101.6

Cpd	R1	R2	R3
23595			

23596:



(2S,4R)-4-(benzyloxy)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaooxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide

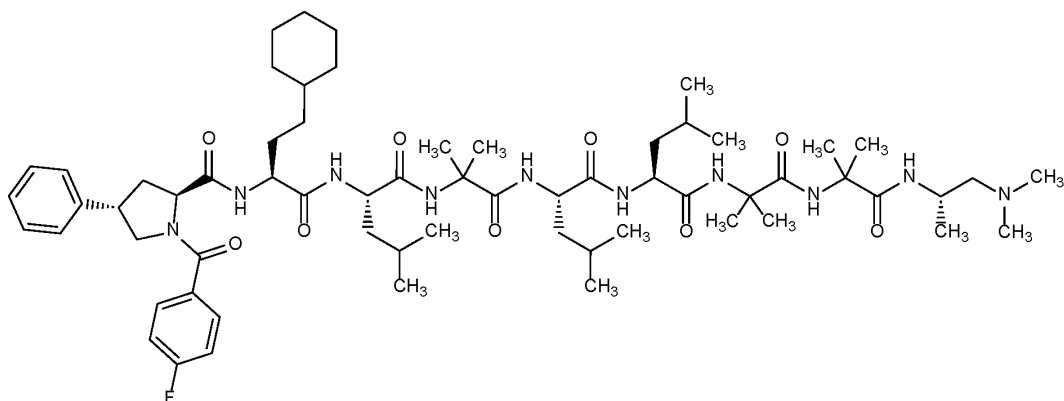
Cpd	1	2	3	4	5
23596	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-Hyp(Bzl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23596 [M] ⁺	1189.6	1189.7

Cpd	R1	R2	R3
23596			

23612:



(2S,4S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide

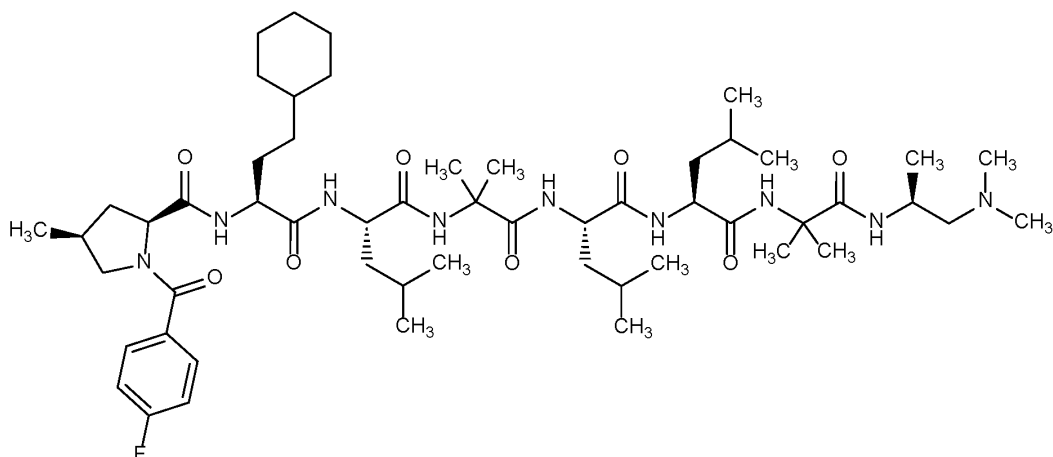
5

Cpd	1	2	3	4	5
23612	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-(2S,4S)-4-phenylpyrrolidine-2-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23612 [M] ⁺	1159.5	1159.7

Cpd	R1	R2	R3
23612			

23687:



(2S,4S)-N-((4S,10S,13S,19S,22S)-24-cyclohexyl-10,13,19-triisobutyl-2,4,7,7,16,16-hexamethyl-6,9,12,15,18,21-hexaoxo-2,5,8,11,14,17,20-heptaazatetracosan-22-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

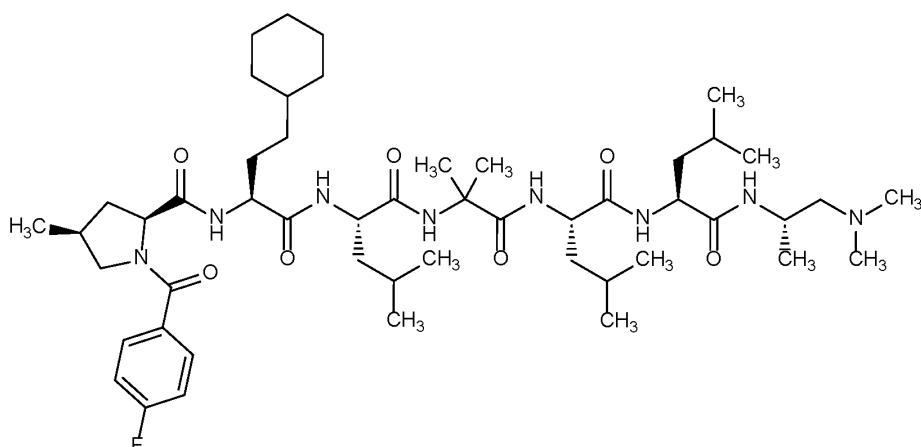
Cpd	1	2	3	4	5
23687	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Leu-OH
	6	7	8	9	
	Fmoc-L-homocyclohexyl alanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	-

5

Cpd	Molecular mass	Experimentally measured mass
23687 [M] ⁺	1012.4	1012.6

Cpd	R1	R2	R3
23687			

23688 (reference example):



(2S,4S)-N-((4S,7S,10S,16S,19S)-21-cyclohexyl-7,10,16-trisobutyl-2,4,13,13-tetramethyl-6,9,12,15,18-pentaoxo-2,5,8,11,14,17-hexaazahenicosan-19-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

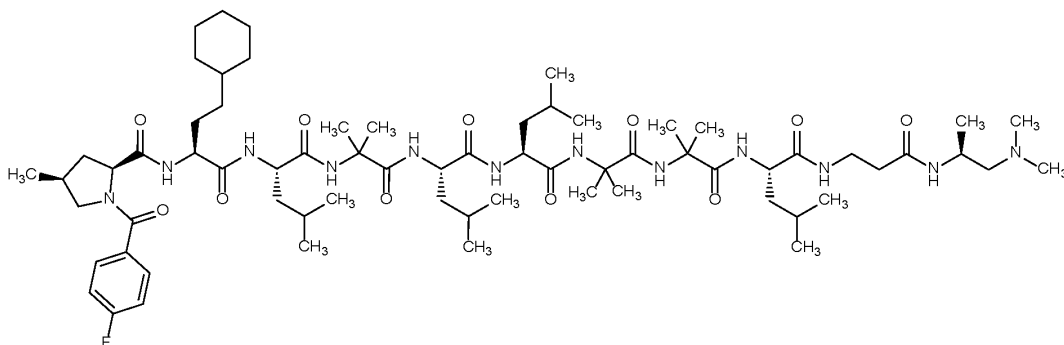
Cpd	1	2	3	4	5
23688	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexyl-alanine
	6	7	8		
	Fmoc-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	-	-

5

Cpd	Molecular mass	Experimentally measured mass
23688 [M] ⁺	927.2	927.6

Cpd	R1	R2	R3
23688			

23692:

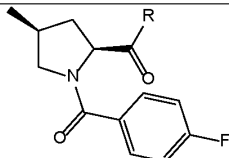
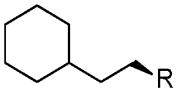
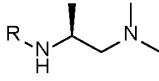


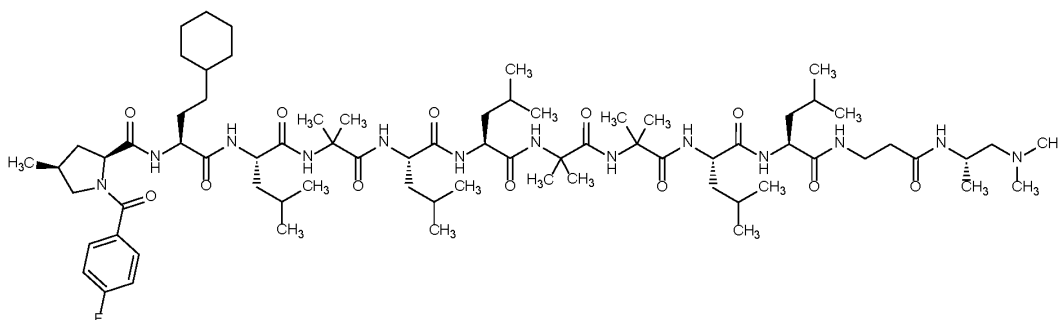
(2S,4S)-N-((4S,11S,20S,23S,29S,32S)-34-cyclohexyl-11,20,23,29-tetraisobutyl-2,4,14,14,17,17,26,26-octamethyl-6,10,13,16,19,22,25,28,31-nonaoxo-2,5,9,12,15,18,21,24,27,30-decaazatetracontan-32-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

5

Cpd	1	2	3	4	5	6
23692	Fmoc-β-Ala-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH
	7	8	9	10	11	12
	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23692[M] ⁺	1281.7	1281.8

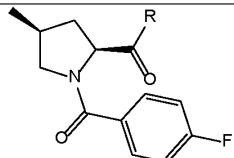
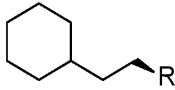
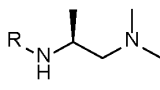
Cpd	R1	R2	R3
23692			

23693:

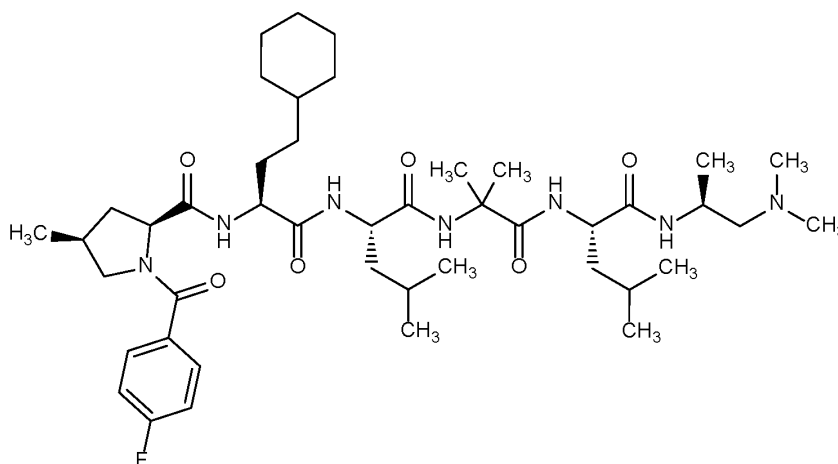
10 (2S,4S)-N-((4S,11S,14S,23S,26S,32S,35S)-37-cyclohexyl-11,14,23,26,32-pentaisobutyl-2,4,17,17,20,20,29,29-octamethyl-6,10,13,16,19,22,25,28,31,34-decaoxo-2,5,9,12,15,18,21,24,27,30,33-undecaazaheptatriacontan-35-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6	7
23693	Fmoc-β-Ala-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH
	8	9	10	11	12	13	
	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

Cpd	Molecular mass	Experimentally measured mass
23693 [M] ⁺	1394.9	1394.9

Cpd	R1	R2	R3
23693			

5 **23704** (reference example):



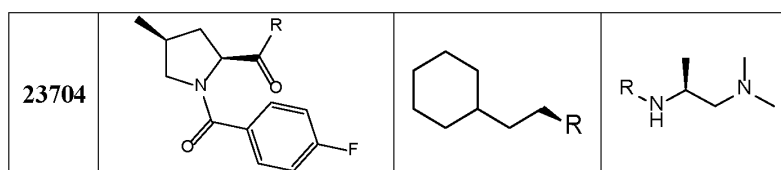
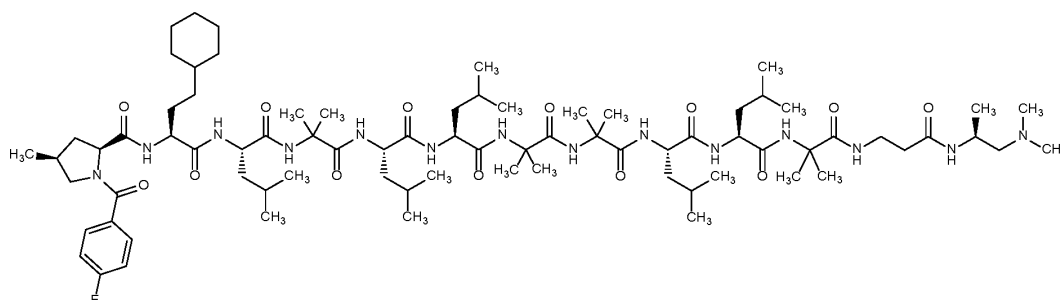
(2S,4S)-N-((4S,7S,13S,16S)-18-cyclohexyl-7,13-diisobutyl-2,4,10,10-tetramethyl-6,9,12,15-tetraoxo-2,5,8,11,14-pentaazaoctadecan-16-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4
23704	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine
	5	6	7	
	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine	

10

Cpd	Molecular mass	Experimentally measured mass
23704 [M] ⁺	814.1	814.3

Cpd	R1	R2	R3
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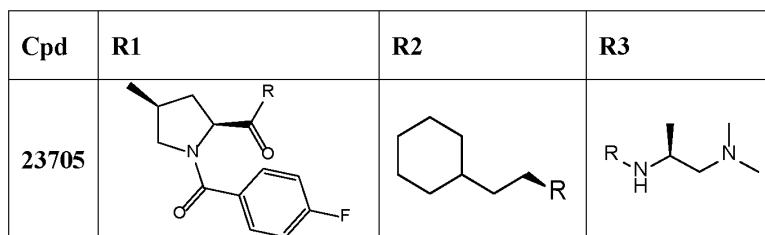
**23705:**

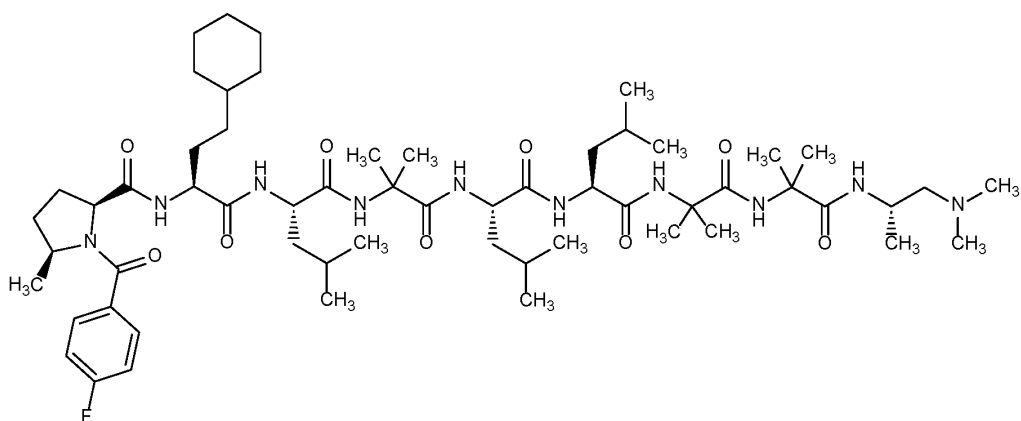
- (2S,4S)-N-((4S,14S,17S,26S,29S,35S,38S)-40-cyclohexyl-14,17,26,29,35-pentaisobutyl-
 5 2,4,11,11,20,20,23,23,32,32-decamethyl-6,10,13,16,19,22,25,28,31,34,37-undeca-oxo-
 2,5,9,12,15,18,21,24,27,30,33,36-dodecaazatetracontan-38-yl)-1-(4-fluorobenzoyl)-4-
 methylpyrrolidine-2-carboxamide

Cpd	1	2	3	4	5	6	7
23705	Fmoc-β-Ala-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH
	8	9	10	11	12	13	14
	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

10

Cpd	Molecular mass	Experimentally measured mass
23705 [M] ⁺	1480.0	1479.9

**23717:**



(2S,5S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5-methylpyrrolidine-2-carboxamide

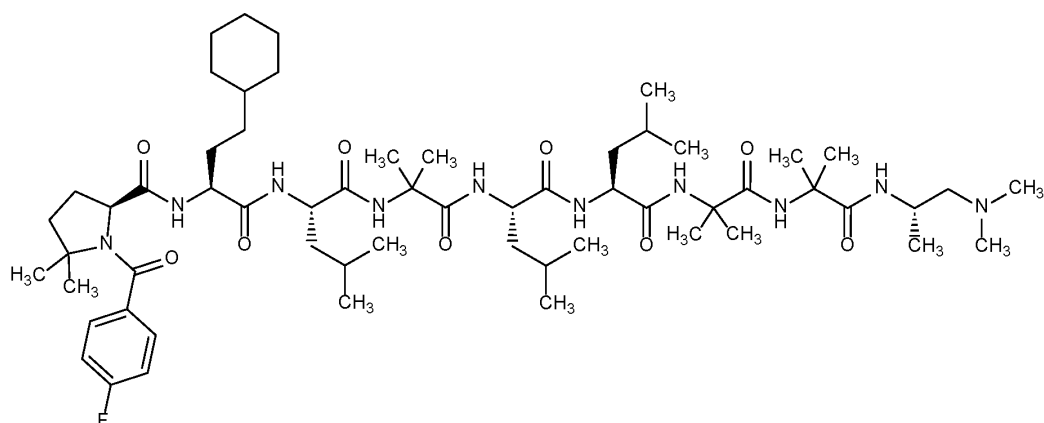
Cpd	1	2	3	4	5
23717	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocysteine	Fmoc-L-Pro(5-Me)-OH (2S,5S)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23717 [M] ⁺	1097.5	1097.5

Cpd	R1	R2	R3
23717			

23718:



(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5,5-dimethylpyrrolidine-2-carboxamide

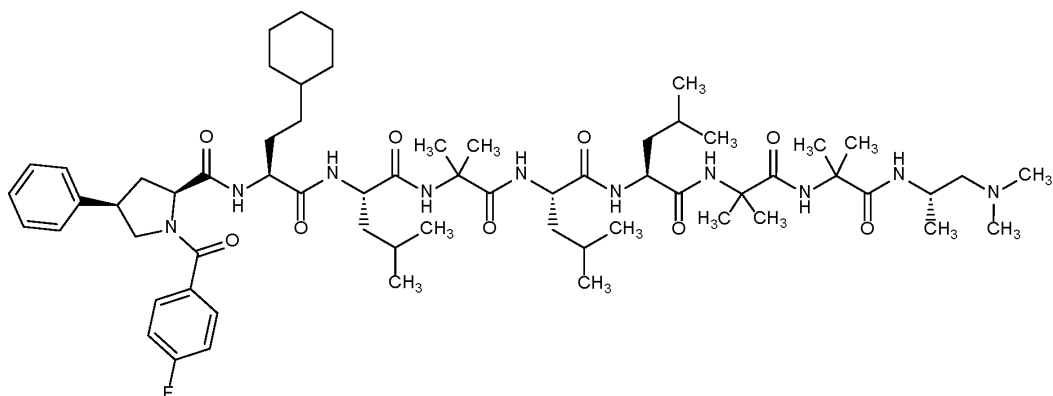
Cpd	1	2	3	4	5
23718	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-5,5-dmP-OH (S)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23718 [M] ⁺	1111.5	1111.6

Cpd	R1	R2	R3
23718			

23720:



(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide

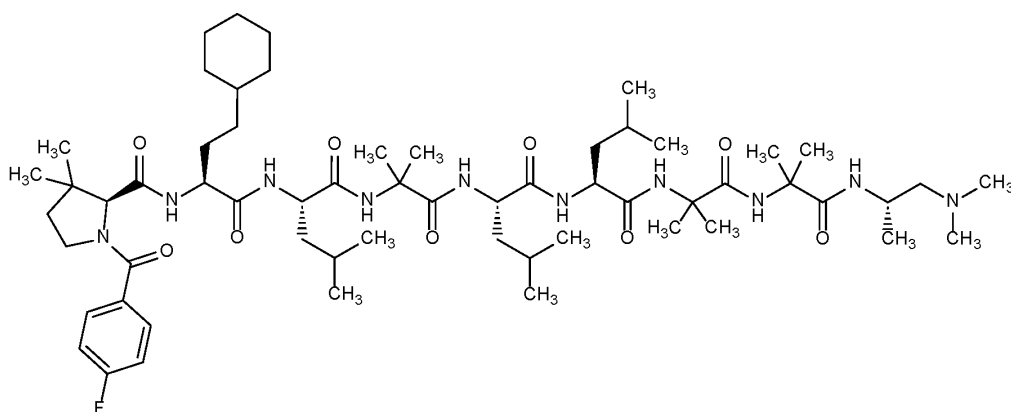
Cpd	1	2	3	4	5
23720	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-(2S,4R)-4-phenylpyrrolidine-2-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23720 [M] ⁺	1159.5	1159.7

Cpd	R1	R2	R3
23720			

23736:



(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-3,3-dimethylpyrrolidine-2-carboxamide

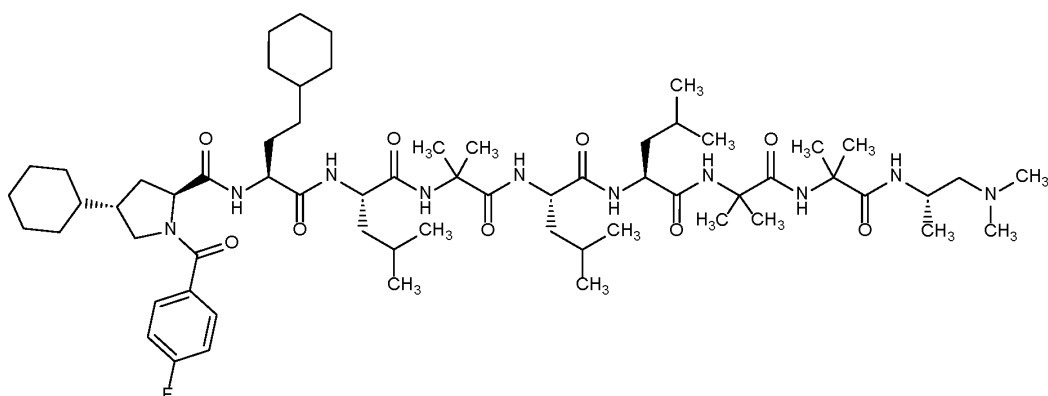
Cpd	1	2	3	4	5
23736	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-3,3-dmP-OH (S)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23736 [M] ⁺	1111.5	1111.6

Cpd	R1	R2	R3
23736			

23738:



(2S,4S)-4-cyclohexyl-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide

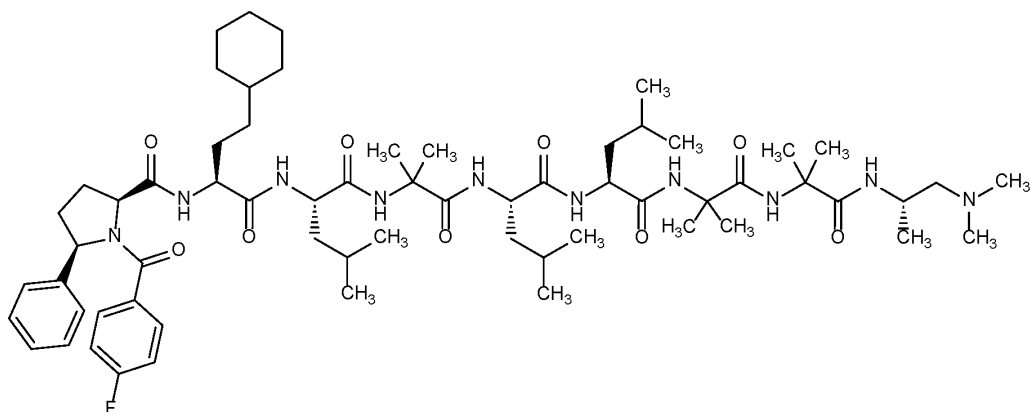
Cpd	1	2	3	4	5
23738	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4Chx)-OH (2S,4S)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23738 [M] ⁺	1165.6	1165.6

Cpd	R1	R2	R3
23738			

23739:



(2S,5R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaooxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-5-phenylpyrrolidine-2-carboxamide

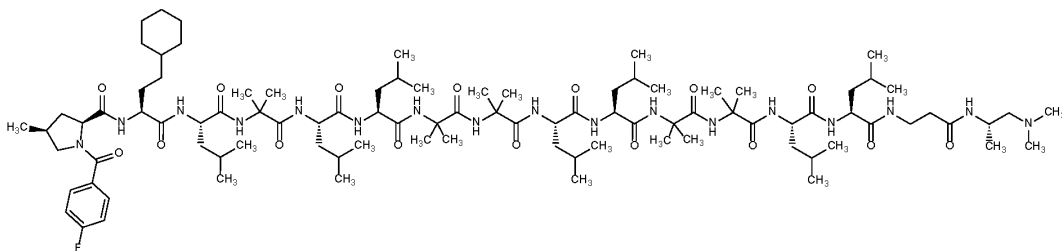
Cpd	1	2	3	4	5
23739	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(5-Ph)-OH (2S,5R)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]d-imethylamine

5

Cpd	Molecular mass	Experimentally measured mass
23739 [M] ⁺	1159.5	1159.6

Cpd	R1	R2	R3
23739			

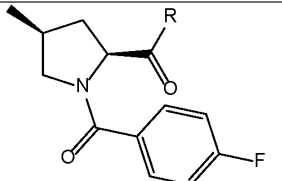
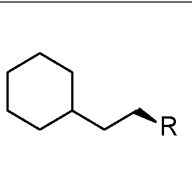
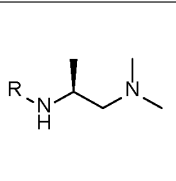
23741 (reference example):

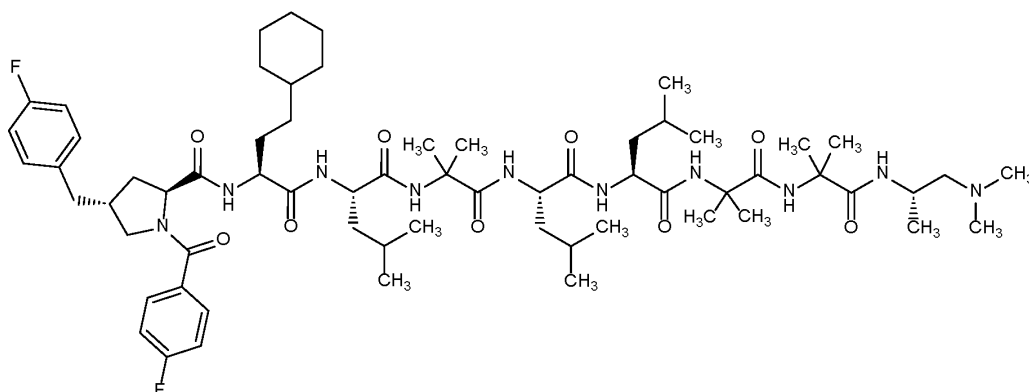


Cpd	1	2	3	4	5	6	7	8	9
23741	Fmoc-β-Ala-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Aib-OH
	10	11	12	13	14	15	16	17	

	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine
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Cpd	Molecular mass	Experimentally measured mass
23741 ($[M+2H]^{2+}$)/2	1791.4	896.6 ($[M+2H]^{2+}$)/2

Cpd	R1	R2	R3
23741			

23742:

5

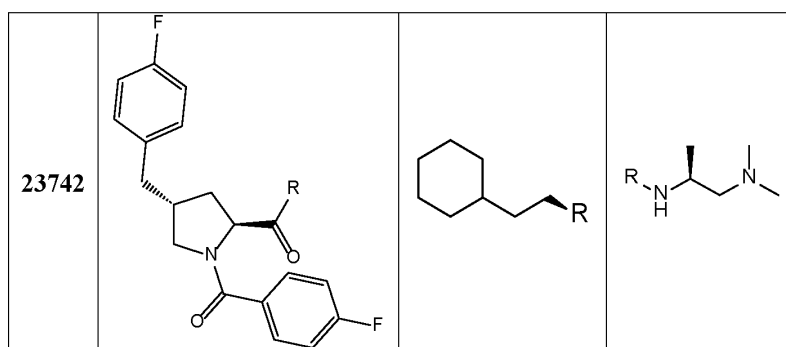
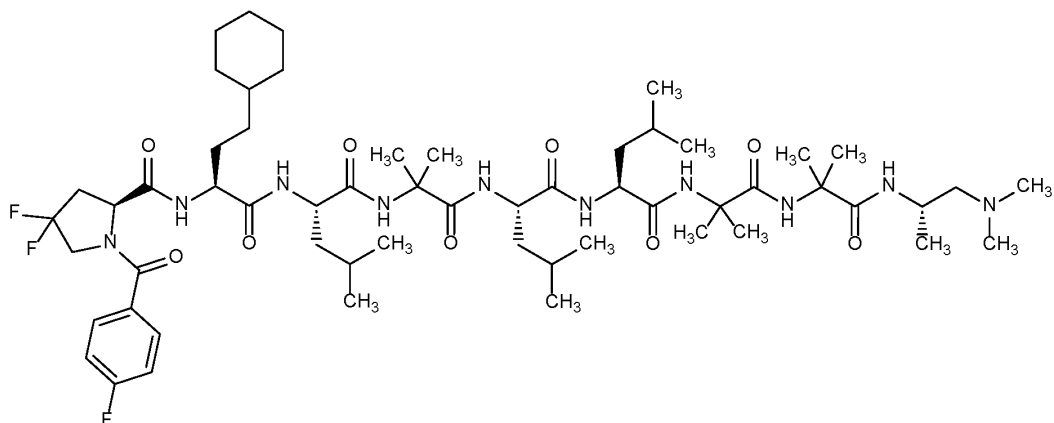
(2S,4R)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaaxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-(4-fluorobenzyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23742	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4-p-F-Ph)-OH (2S,4R)	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23742 $[M]^+$	1191.4	1191.6

10

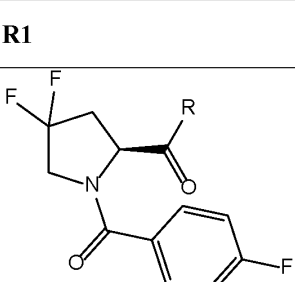
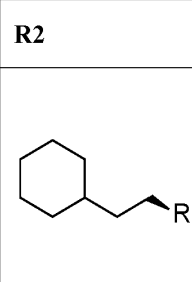
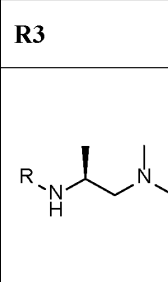
Cpd	R1	R2	R3
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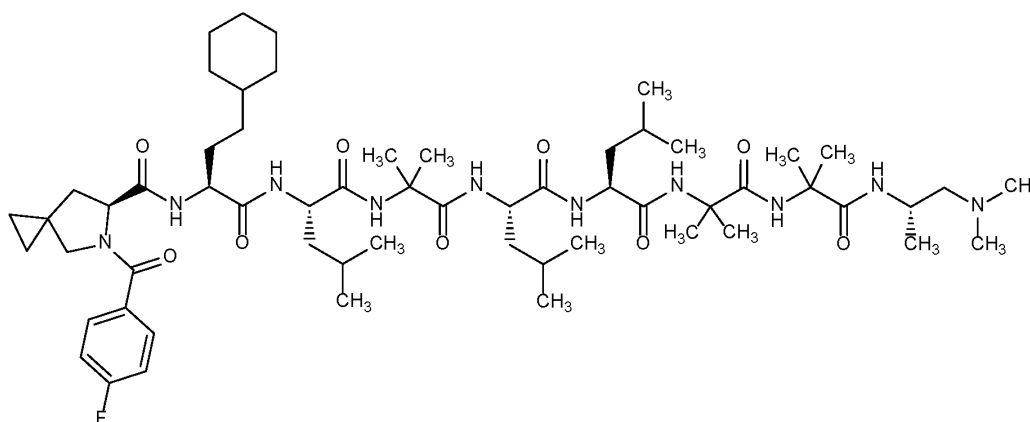
**23794:**

- (S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-heptaazaoctacosan-25-yl)-4,4-difluoro-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide

Cpd	1	2	3	4	5
23794	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-4,4-difluoroproline	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23794 [M] ⁺	1119.41	1119.17

Cpd	R1	R2	R3
23794			

23795:

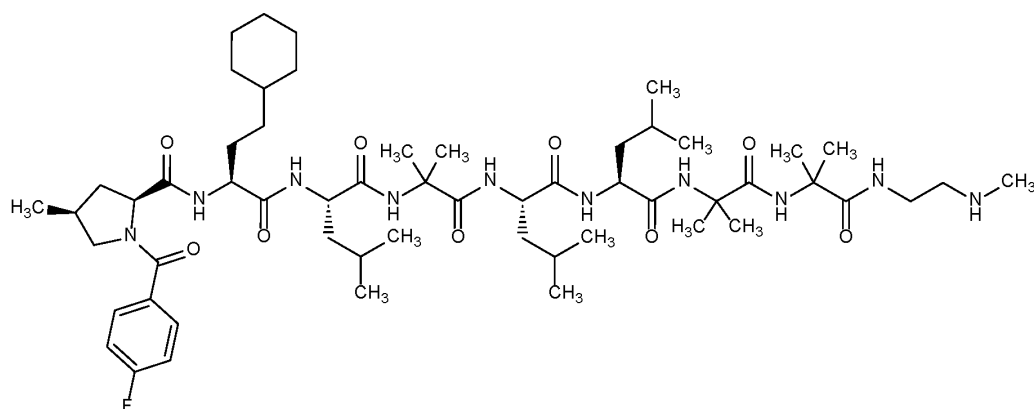
(S)-N-((4S,13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-2,4,7,7,10,10,19,19-octamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-5-(4-fluorobenzoyl)-5-azaspiro[2.4]heptane-6-carboxamide

Cpd	1	2	3	4	5
23795	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	(S)-5-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

Cpd	Molecular mass	Experimentally measured mass
23795 [M] ⁺	1109.46	1109.17

Cpd	R1	R2	R3
23795			

10 **23826:**



(2S,4S)-N-((13S,16S,22S,25S)-27-cyclohexyl-13,16,22-triisobutyl-7,7,10,10,19,19-hexamethyl-6,9,12,15,18,21,24-hepta-oxo-2,5,8,11,14,17,20,23-octaazaheptacosan-25-yl)-1-(4-fluorobenzoyl)-4-methylpyrrolidine-2-carboxamide

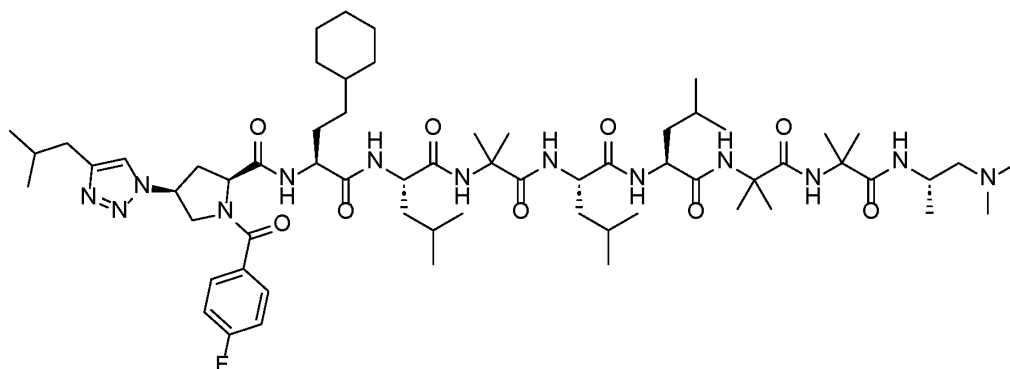
Cpd	1	2	3	4	5
23826	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	tert-butyl (2-aminoethyl)-(methyl)carbamate

5

Cpd	Molecular mass	Experimentally measured mass
23826 [M] ⁺	1069.40	1069.17

Cpd	R1	R2	R3
23826			

24879:



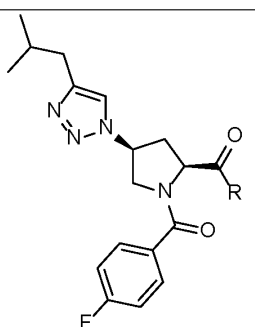
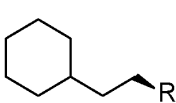
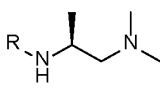
10 (2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)-4-[4-(2-methylpropyl)-1H-1,2,3-

triazol-1-yl]pyrrolidin-2-yl]formamido}butanamido]-N-(1-{{[(1S)-1-{{[(1S)-1-{{[(1-{{[(2S)-1-(dimethylamino)propan-2-yl]carbamoyl}-1-methylethyl]carbamoyl]-1-methylethyl]carbamoyl}-3-methylbutyl]carbamoyl}-3-methylbutyl]carbamoyl}-1-methylethyl]-4-methylpentanamide

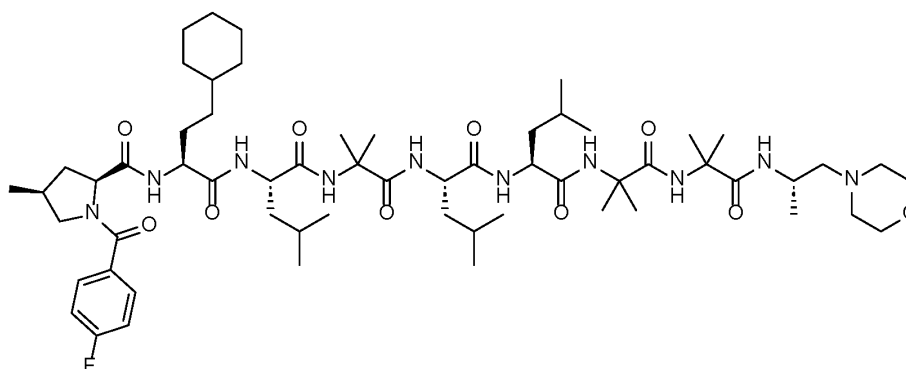
Cpd	1	2	3	4	5
24879	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	(2S,4S)-1-{{[(9H-fluoren-9-yl)methoxy]carbonyl}-4-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylic acid	4-Fluorobenzoic acid	[(2S)-2-aminopropyl]dimethylamine

5

Cpd	Molecular mass	Experimentally measured mass
24879 [M] ⁺	1206.58	1206.95

Cpd	R1	R2	R3
24879			

25041:



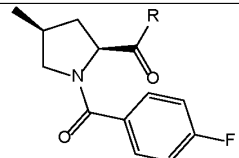
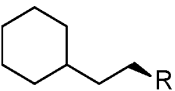
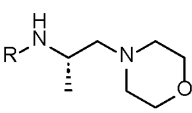
(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-

10

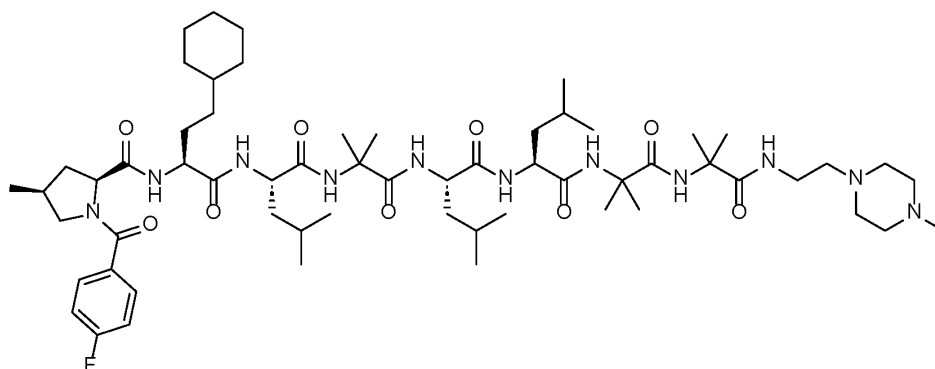
methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(2S)-1-(morpholin-4-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl} pentanamide

Cpd	1	2	3	4	5
25041	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	(2S)-1-(morpholin-4-yl)propan-2-amine

Cpd	Molecular mass	Experimentally measured mass
25041 [M+H] ⁺	1139.49	1140.23

Cpd	R1	R2	R3
25041			

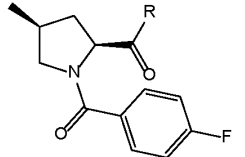
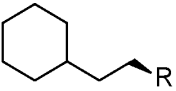
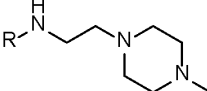
5 25042:

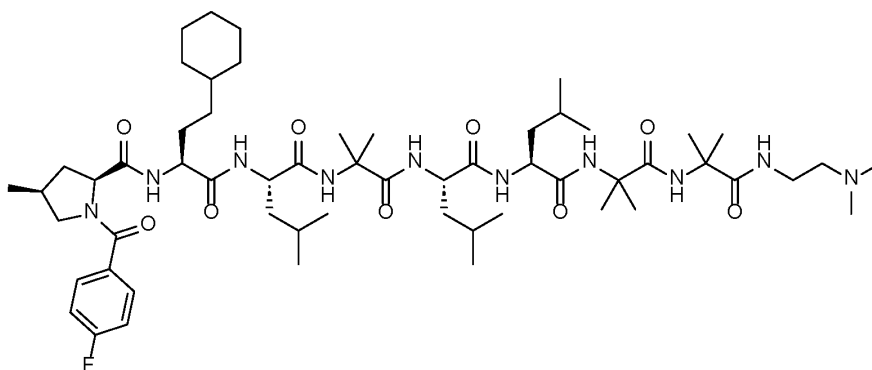


(2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido} butanamido]-4-methyl-N-(1-methyl-1-[[[(1S)-3-methyl-1-[[[(1S)-3-methyl-1-([1-methyl-1-[(1-methyl-1-[2-(4-methylpiperazin-1-yl)ethyl]carbamoyl}ethyl)carbamoyl]ethyl} carbamoyl)butyl]carbamoyl} butyl]carbamoyl} ethyl)pentanamide

Cpd	1	2	3	4	5
25042	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	2-(4-methylpiperazin-1-yl)ethan-1-amine

Cpd	Molecular mass	Experimentally measured mass
25042 [M+H] ⁺	1138.51	1139.13

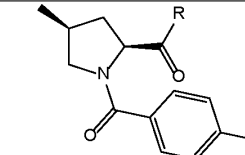
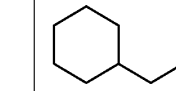
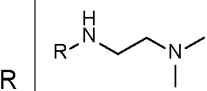
Cpd	R1	R2	R3
25042			

25088:

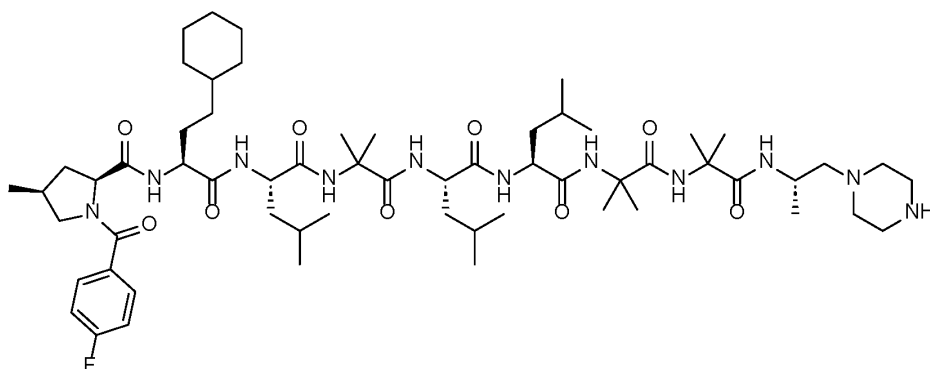
(2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido]butanamido]-N-(1-{[(1S)-1-{[(1S)-1-{1-[(1-{[2-(dimethylamino)ethyl]carbamoyl}-1-methylethyl]carbamoyl]-1-methylethyl]carbamoyl]-3-methylbutyl]carbamoyl}-3-methylbutyl]carbamoyl]-1-methylethyl)-4-methylpentanamide

Cpd	1	2	3	4	5
25088	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	(2-aminoethyl)dimethylamine

Cpd	Molecular mass	Experimentally measured mass
25088 [M+H] ⁺	1083.43	1084.08

Cpd	R1	R2	R3
25088			

25126:



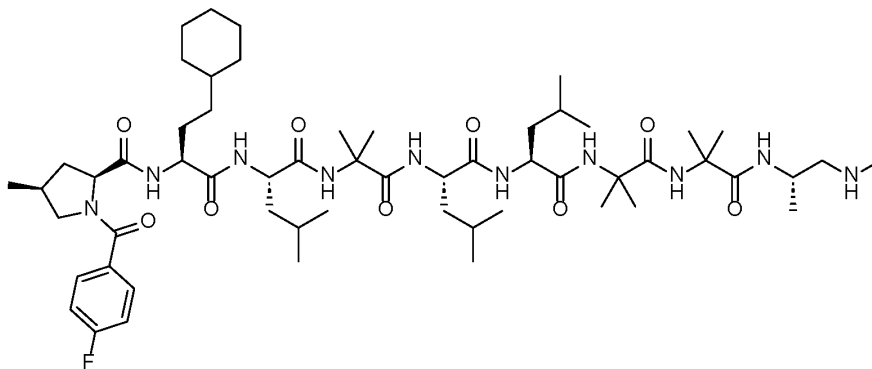
- (2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-[[[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(1-methyl-1-[(2S)-1-(piperazin-1-yl)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide

Cpd	1	2	3	4	5
25126	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	tert-butyl 4-[(2S)-2-aminopropyl]-piperazine-1-carboxylate

Cpd	Molecular mass	Experimentally measured mass
25126 [M+H] ⁺	1138.51	1139.29

Cpd	R1	R2	R3
25126			

25157:

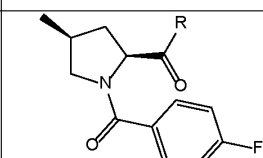
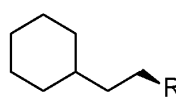
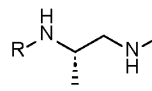


(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-4-cyclohexyl-2-[(2S,4S)-1-(4-fluorobenzoyl)-4-methylpyrrolidin-2-yl]formamido}butanamido]-4-methylpentanamido]-2-methylpropanamido}-4-methylpentanamido]-4-methyl-N-{1-methyl-1-[(1-methyl-1-[(2S)-1-(methylamino)propan-2-yl]carbamoyl}ethyl)carbamoyl]ethyl}pentanamide vanadium

Cpd	1	2	3	4	5
25157	Fmoc-Aib-OH	Fmoc-Aib-OH	Fmoc-Leu-OH	Fmoc-Leu-OH	Fmoc-Aib-OH
	6	7	8	9	10
	Fmoc-Leu-OH	Fmoc-L-homocyclohexylalanine	Fmoc-L-Pro(4S-Methyl)-OH	4-Fluorobenzoic acid	benzyl N-[(2S)-2-aminopropyl]-N-methylcarbamate

5

Cpd	Molecular mass	Experimentally measured mass
25157 [M+H] ⁺	1138.51	1139.29

Cpd	R1	R2	R3
25157			

EXAMPLE 4

***In vitro* anti-proliferative effects of the inventive compounds against cutaneous squamous carcinoma cells and keratinocytes**

10 Cutaneous squamous cell carcinoma of the skin is a common form of skin cancer that develops in the squamous cells that make up the middle and outer layers of the skin. Cutaneous squamous cell carcinoma of the skin is usually not life-threatening, though it can be aggressive. Untreated, squamous cell carcinoma of the skin can grow large or spread to other parts of your body, causing serious complications. Most squamous cell carcinomas of the skin result from
15 prolonged exposure to ultraviolet (UV) radiation, either from sunlight or from tanning beds or lamps. Avoiding UV light helps reduce your risk of squamous cell carcinoma of the skin and other forms of skin cancer. Squamous cells are found in many places in the body, and squamous cell carcinoma can occur anywhere squamous cells are found. Squamous cell carcinoma of the skin, and cutaneous squamous cell carcinoma (cSCC), respectively, refers to cancer that forms
20 in the squamous cells found in the skin. Cutaneous squamous cell carcinoma is a malignant neoplasm formed from keratinocytes found in the squamous cell layer of the skin.

The *in vitro* anti-proliferative effects of inventive compounds against cutaneous squamous carcinoma cells as well as keratinocytes have been tested. In particular, the *in vitro*

anti-proliferative effects of inventive compounds against the cutaneous squamous cell carcinoma cell lines SCC13 and A431_SCC as well as CCD-1102 KERTr cell culture (KERTr) have been tested.

1. Representative and preferred inventive compounds have been tested and showed activities against cutaneous squamous cell carcinoma cell line SCC13 *in vitro* as depicted in Table 4. cSCC cell culture SCC13 has a TP53 as well as a NF2 mutation and is derived from an advanced stage female 56 years old patient.

Methodology. The cutaneous squamous cell carcinoma cell culture SCC13 was cultivated in Dulbecco's Modified Eagle Medium (DMEM, Cat#11966025, Gibco) supplemented with 10% heat-inactivated fetal bovine serum (Cat# S006420H01, BioWest). For the library screening, cells were distributed to 96-well plates in a cell density of 1,500 cells in 90µl/well and let to adhere over night at 37°C and 5% CO₂ in a cell culture incubator. Serial dilution of compounds in DMSO to 1000x was performed (10 mM, 5 mM, 1 mM, 500 µM, 250 µM, 100 µM, 10 µM, 1 µM). 2 µl of these dilutions were further diluted in 198 µl Dulbecco's Modified Eagle Medium with supplements, mixed well and 10 µl were further dispensed in triplicates to the 96-well plates containing SCC cells in 90 µl. These dilutions resulted in a final compound concentration of 10 µM, 5 µM, 1µM, 500 nM, 250 nM, 100 nM, 10 nM, 1 nM on cells. Plates were incubated for additional 72 hours and cell culture medium was replaced to medium containing 0.1% of Resazurin-sodium salt stock solution (stock: 0.015mg/ml, in PBS, Cat# R7017, Sigma-Aldrich). Cell culture plates were incubated for 2-3 hours in cell culture incubator at 37°C and 5% CO₂. With a fluorescence-based plate reader (Infinite M200 Pro, Tecan, Switzerland) using excitations between 530-560nm and emissions at 590nm the cell-culture plates were readout. The calculations and graphs are performed with GraphPad Prism program. Vehicle treated wells were set to 100% viability.

- 25 Table 4: Half maximal inhibitory concentrations (IC₅₀) of inventive compounds in cutaneous squamous cell carcinoma cell line SCC13.

<u>Compound</u>	<u>IC₅₀ (nM)</u>
6027 (reference example)	191.0
20762	54.5
22178	68.4
22179	57.6
22180 (reference example)	134.5
23103	30.1

23491	43.9
23525	46.2
23526	18.0
23538	46.4
23542	12.9
23549	179.0
23552	27.9
23585	48.4
23586	48.5
23594	65.3
23595	52.5
23596	46.3
23612	10.1
23687	48.3
23688 (reference example)	286.9
23692	25.7
23693	45.3
23704 (reference example)	6341.6
23705	46.1
23717	46.4
23718	61.2
23720	36.7
23736	20.9
23738	40.1
23739	55.6
23741 (reference example)	NA
23742	45.2
23794	46.9
23795	29.6
23826	74.3

Results. The inventive compounds showed significant activities and IC₅₀ values in the double digit nM range against cutaneous squamous cell carcinoma SCC13 *in vitro* confirming its use as drugs for the treatment of skin cancers in particular cutaneous squamous skin cancer.

5 In particular, the inventive compounds showed significant increased activities as compared to

the reference compound 6027. The reduction to an amino acid chain length of a total of five (23704) or six (23688), or the increase to an amino acid chain length of a total of fifteen (23741) led to a significant decrease and/or of any measurable effectiveness (23741).

Surprisingly, the reduction of the amino acid chain length of a total of eight, in particular
5 as represented by formula (III) is considered to not only reduce costs of goods of such compounds and drugs, respectively, but further led to an additional increase in efficacy. Very preferred examples thereof are 23526, 23542, 23612 and 23736.

The further provided reference example 22180 also shows reasonable efficacy. However, as described in the following Example 5, it has been found that the presence of 3-Hydroxy-
10 Leucin within the amino acid chain, as it is the case in Leucinostatin A, led to a substantial not acceptable increase in toxicity.

2. The significant activity of the inventive compounds against cSCC has been confirmed in another *in vitro* anti-proliferative assay, wherein preferred inventive compounds have been tested in a further cutaneous squamous cell carcinoma cell line, namely A431_SCC. A431_SCC
15 is a cSCC cell culture with a TP53 mutation derived from an advanced stage female 85 years old patient. The results are depicted in Table 5.

Methodology. The cutaneous squamous cell carcinoma cell culture A431_SCC was cultivated in Dulbecco's Modified Eagle Medium (DMEM, Cat#11966025, Gibco) supplemented with 10% heat-inactivated fetal bovine serum (Cat# S006420H01, BioWest). For
20 the library screening, cells were distributed to 96-well plates in a cell density of 1,500 cells in 90µl/well and let to adhere over night at 37°C and 5% CO₂ in a cell culture incubator. Serial dilution of compounds in DMSO to 1000x was performed (10 mM, 5 mM, 1 mM, 500 µM, 250 µM, 100 µM, 10 µM, 1 µM). 2 µl of these dilutions were further diluted in 198 µl keratinocyte growth medium with supplements, mixed well and 10 µl were further dispensed in triplicates
25 to the 96-well plates containing SCC cells in 90 µl. These dilutions resulted in a final compound concentration of 10 µM, 5 µM, 1µM, 500 nM, 250 nM, 100 nM, 10 nM, 1 nM on cells. Plates were incubated for additional 72 hours and cell culture medium was replaced to medium containing 0.1% of Resazurin-sodium salt stock solution (stock: 0.015mg/ml, in PBS, Cat# R7017, Sigma-Aldrich). Cell culture plates were incubated for 2-3 hours in cell culture
30 incubator at 37°C and 5% CO₂. With a fluorescence-based plate reader (Infinite M200 Pro, Tecan, Switzerland) using excitations between 530-560nm and emissions at 590nm the cell-culture plates were readout. The calculations and graphs are performed with GraphPad Prism program. Vehicle treated wells were set to 100% viability.

Table 5: Half maximal inhibitory concentrations (IC₅₀) of inventive compounds in cutaneous squamous cell carcinoma cell line A431_SCC.

<u>Compound</u>	<u>IC₅₀ (nM)</u>
6027 (reference example)	70.0
23526	15.0
23542	11.9
23585	47.8
23586	36.1
23594	53.1
23595	49.1
23596	28.1
23612	10.3
23688 (reference example)	328.1
23692	17.2
23693	32.5
23704 (reference example)	4700.7
23705	45.3
23717	45.0
23720	20.1
23736	9.9
23738	19.1
23739	50.3
23741 (reference example)	NA
23742	40.8
23794	42.6
23826	46.9

3. The significant activities of the inventive compounds against cutaneous squamous cell carcinoma cell lines cSCC and A431_SCC, as reported above, has additionally been confirmed in another in vitro anti-proliferative assay, wherein preferred inventive compounds were tested in CCD-1102 KERTr cell culture (KERTr), which is commonly used to study actinic keratosis due to its ability to mimic the characteristic of this precancerous skin condition effectively. It is an immortalized keratinocyte cell culture and as cSCC is a keratinocyte based disorder as well, we used this cell culture to proof general efficacy of inventive compounds in keratinocyte based cancerous cell disorders. The results are depicted in Table 6.

Methodology. The immortalized keratinocyte cell culture CCD-1102 KERTr was cultivated in keratinocyte-SFM media (KSFM, Cat# 17005042, Gibco) supplemented with human recombinant epidermal growth factor 1-53 (EGF 1-53) and bovine pituitary extract (BFE). For the library screening, cells were distributed to 96-well plates in a cell density of 3000 cells in 90µl/well and let to adhere over night at 37°C and 5% CO₂ in a cell culture incubator. Serial dilution of compounds in DMSO to 1000x was performed (10 mM, 5 mM, 1 mM, 500 µM, 250 µM, 100 µM, 10 µM, 1 µM). 2 µl of these dilutions were further diluted in 198 µl keratinocyte growth medium with supplements, mixed well and 10 µl were further dispensed in triplicates to the 96-well plates containing SCC cells in 90 µl. These dilutions resulted in a final compound concentration of 10 µM, 5 µM, 1µM, 500 nM, 250 nM, 100 nM, 10 nM, 1 nM on cells. Plates were incubated for additional 72 hours and cell culture medium was replaced to medium containing 0.1% of Resazurin-sodium salt stock solution (stock: 0.015mg/ml, in PBS, Cat# R7017, Sigma-Aldrich). Cell culture plates were incubated for 2-3 hours in cell culture incubator at 37°C and 5% CO₂. With a fluorescence-based plate reader (Infinite M200 Pro, Tecan, Switzerland) using excitations between 530-560nM and emissions at 590nM the cell-culture plates were readout. The calculations and graphs are performed with GraphPad Prism program. Vehicle treated wells were set to 100% viability.

Table 6: Half maximal inhibitory concentrations (IC₅₀) in nM of inventive compounds in immortalized keratinocyte cell culture (CCD-1102 KERTr (KERTr)).

<u>Compound</u>	KERTr
6027 (reference example)	82.3
23526	35.1
23704 (reference example)	7813.0
23720	70.3
23736	56.4
23738	44.6
23741 (reference example)	NA
23742	47.1
23794	56.8
23795	41.8
23826	43.5

EXAMPLE 5

***In vitro* anti-proliferative effects of the inventive compounds against lung cancer and breast cancer cells**

The *in vitro* anti-proliferative effects of the inventive compounds against mouse lung carcinoma cells (LLC) as well as human mammary gland carcinoma cells (Du4475) have been tested in a resazurin-based viability assay.

The resazurin-based viability assay is a homogeneous, fluorometric assay that uses resazurin indicator dye to measure the metabolic capability of cells. Viable cells are able to convert non-fluorescent resazurin to its fluorescent product, resorufin. Nonviable cells are unable to reduce resazurin and thus do not display a fluorescent signal. Reduction of resazurin to resorufin also involves a shift of the absorbance maximum from 605 nm to 573 nm, so viability may also be estimated using absorbance. However, fluorescence measurement is usually preferred, as it is more sensitive and requires fewer calculations

The LL/2 (LLC1) CRL-1642 lewis lung carcinoma is a cell line established from the lung of a C57BL mouse bearing a tumor resulting from an implantation of primary Lewis lung carcinoma. This cell line is widely used as a model for metastasis and studying the mechanisms of cancer chemotherapeutic agents.

The Du4475 (HTB-123) cell line is a ductal adenocarcinoma breast cancer cell line, which was isolated from a 70-year-old female.

Methodology: Before plating, the cells were first washed with DPBS and then trypsinized with trypsin solution in DPBS. The appropriate volume of culture medium was placed in a flask to stop trypsinization. Cells were centrifuged, resuspended, stained with Trypan Blue and counted using a counting chamber. The appropriate volume of the cell suspension was placed in the falcon tube containing plating medium RPMI 1640 with 1% FBS, 2 mM L-glutamine, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells at 125000 cells/ml density were seeded in sterile 384-well plates (Greiner Bio-One, Cat# 781091) in 40 µl/well (5000 cells/well) and covered with sterile transparent seals. Plates were left overnight in a humidified atmosphere at 37°C and 5% CO₂ for adaptation.

Cytotoxicity for the test compounds was assessed at the final concentrations ranging from 0.005 µM to 100.0 µM (10 points, 3-fold serial dilutions). Incubation was performed for 48 hours in a humidified atmosphere at 37°C and 5% CO₂. The final concentration of DMSO in the assay was 0.5 %.

Then resazurin (50 µM final concentration) was added and incubated for 3 hours in a

humidified atmosphere at 37°C and 5% CO₂. The presence of resorufin was quantified by measuring fluorescence Ex – 555 nm, Em – 585 nm, cut-off 570, bottom read.

Results: The inventive compounds showed significant activities and IC₅₀ values in the double to low triple digit nM range against mouse lung carcinoma cells (LLC) as well as human mammary gland carcinoma cells (Du4475) *in vitro*, confirming its use as drugs for the treatment of different types of cancer, such as lung and skin cancer.

The change of the amine moiety shows good tolerance in the activity. Surprisingly most amine groups show a strong increase in activity in both cell lines. Especially the use of a morpholine moiety as exemplified in 25041, as well as a secondary amine as exemplified in 25157 showed an up to 10-fold increase in activity compared to 6027 in both cell lines.

Table 7: Half maximal inhibitory concentrations (IC₅₀) in nM of inventive compounds in mouse lung carcinoma cell line (LLC) and human mammary gland carcinoma cell line (Du4475)

<u>Compound</u>	LLC	Du4475
6027 (reference sample)	391	223
24879	63	122
25041	32	32
25042	187	85
25088	99	27
25126	165	30
25157	56	21

EXAMPLE 6

Toxicity Studies

Toxicity studies with mice were effected to test for systemic toxicity upon i.v. injection, as well as to test for skin irritation upon topical applications, wherein inventive compounds or corresponding reference compounds having a 3-Hydroxy-Leucin within the amino acid chain as it is the case for the natural product Leucinostatin A have been applied.

Methodology:

For the topical application to test for skin irritation, C57BI/6 female mice bearing no tumor were treated once daily for a duration of seven (7) days (7 applications in total) with 20µl of a 0.5% (w/v) solution in a suitable carrier comprising either inventive compounds or

corresponding reference compounds having a 3-Hydroxy-Leucin within the amino acid chain as it is the case for the natural product Leucinostatin A. The compounds were each time applied on the shaved neck region of the mice and the application site was monitored.

For the injection to test for systemic toxicity, groups of each three C57BI/6N female mice of 11-13 weeks of age bearing no tumor were treated once daily by i.v. injection at a dose of 3mg/kg in a single dose with a solution (5ml/kg) in a suitable carrier (DMSO:KolliphorHS15:Saline=5:10:85) comprising either inventive compounds or corresponding reference compounds having a 3-Hydroxy-Leucin within the amino acid chain as it is the case for the natural product Leucinostatin A. After injection the animals were monitored for clinical signs of toxicity and the observation is reported after 72 hours.

Results.

During the skin irritation, the inventive compounds were tolerated and no skin irritations could be observed neither within nor after the entire treatment, while the application of the reference compounds having a 3-Hydroxy-Leucin within the amino acid chain developed and led to very bad skin irritations even after 3-4 days of treatment which caused the halt of the treatment. The results are summarized in Table 8. This finding was further confirmed by applying an even ten times higher concentrated solution of an inventive compound (5% of 22178) which again was well tolerated and did not lead to any skin irritations, while even a 0.2% of Leucinostatin A led to said very bad skin irritations and the halt of the treatment.

During the systemic toxicity testing the animals were monitored for clinical signs of toxicity and the observation 72 hours after injection reported. The results are summarized in Table 8. The animals treated with inventive compounds all showed good appearance and had no clinical symptoms, while the treatment with the reference compounds having a 3-Hydroxy-Leucin within the amino acid chain as it is the case for the natural product Leucinostatin A led to the death (---) or moribund (####) of the animals.

Table 8: Toxicity study of inventive and reference compounds with C57BI/6 female mice.

<u>Compound</u>	<u>Presence of 3-Hydroxy-Leucin</u>	<u>Skin irritation [at 0,5 % in mice]</u>	<u>Systemic Toxicity [at 3mg/kg in mice]</u>
6027	no	none	none
22178	no	none	none
22179	no	none	none
22717	no	none	none
23526	no	none	none
Leucinostatin A	yes	bad	---

22430	yes	bad	---
22432	yes	bad	###
22433	yes	bad	---

EXAMPLE 7

***In vitro* anti-proliferative effect against various melanoma cells**

In vitro anti-proliferative effects by the inventive compounds against further various skin cancer cells have been tested. Hereby, significant activities against cutaneous melanoma cell cultures (M150672, M010817 and B16-F10) as well as acral lentiginous melanoma cell cultures (ALM) (ALM_M150207, ALM_M100513) have been observed as depicted in Tables 9-10. Cell cultures M150672 and M010817 are both human derived cutaneous melanoma cell cultures derived from a subcutaneous metastasis, while cell culture B16-F10 is a mouse derived cutaneous melanoma cell culture. Cell cultures M150672 and B16-F10 have BRAF(V600E) mutations, while cell culture M010817 is NRAS(Q61R) mutated. With the above mentioned cell cultures used the most frequent occurring mutations in cutaneous melanoma are covered. Cell culture M150672 and B16-F10 are MAPK pathway inhibition resistant, while cell culture M010817 is MAPK pathway inhibition sensitive. The acral lentiginous melanoma cell cultures ALM_M150207 and ALM_M100513 are cKIT (K642E) mutated.

Methodology. For the library screening cells were distributed to 96-well plates (cell densities (cells/well): M150672 (2000), M010817 (2000) and B16-F10 (1500) in 90µl/well and let to adhere over night at 37°C and 5% CO₂ in a cell culture incubator.

For the maintenance of cutaneous and acral lentiginous melanoma cell cultures RPMI-1640 (Cat#R0883, Gibco) supplemented with L-glutamine (Cat# 25030-081, Gibco), 1mM sodium pyruvate (Cat# S8636, Sigma-Aldrich), 10% heat-inactivated fetal bovine serum (Cat# S006420H01, BioWest) and 1% Penicillin-Streptomycin (Cat#15140122, Gibco) was used.

To determine the half maximal inhibitory concentrations (IC₅₀'s) serial dilution of compounds in DMSO to 1000x was performed (10 mM, 5 mM, 1 mM, 500 µM, 250 µM, 100 µM, 10 µM, 1 µM). 2 µl of these dilutions were further diluted in 198 µl growth medium with supplements, mixed well and 10 µl were further dispensed in triplicates to the 96-well plates containing cells in 90 µl. These dilutions resulted in a final compound concentration of 10 µM, 5 µM, 1µM, 500 nM, 250 nM, 100 nM, 10 nM, 1 nM.

For each drug condition and cell culture (for each row of the triplicate) a well with only RPMI-1640 complete and one with media and DMSO were made as controls. DMSO was never

at a higher concentration than 0.2% v/v. Triplicates were seeded for each condition. On the day of the assay, the medium was exchanged with cell culture media containing 0.1% of Resazurin-sodium salt stock solution (stock: 0.015mg/ml, in PBS, Cat# R7017, Sigma-Aldrich). Cell culture plates were incubated for 2-3 hours in cell culture incubator at 37°C and 5% CO₂. With a fluorescence-based plate reader (Infinite M200 Pro, Tecan, Switzerland) using excitations between 530-560nm and emissions at 590nm the cell-culture plates were readout. The calculations and graphs are performed with GraphPad Prism program. Vehicle treated wells were set to 100% viability.

Cytotoxic potency of inventive compounds shown as IC₅₀ values in nM tested in cutaneous melanoma cell cultures (M150672, M010817 and B16-F10) are shown in Table 9. The corresponding cytotoxicity potencies of compounds in acral lentiginous melanoma cell cultures (ALM_M150207, ALM_M100513) are shown in Table 10.

Table 9: Half maximal inhibitory concentrations (IC₅₀) in nM of inventive compounds in various cutaneous melanoma cell cultures (M150672, M010817, B16-F10).

<u>Compound</u>	M150672	M010817	B16-F10
6027 (reference example)	122.0	60.0	215.9
23526	37.6	21.1	44.6
23542	50.0		56.1
23585	45.3	42.3	121.4
23586	49.4	38.3	120.3
23594	51.2	45.5	185.0
23595	44.2		184.6
23596	31.2		199.9
23612	30.2	21.2	45.3
23687	173.9	45.8	119.1
23688 (reference example)	438.1	430.9	412.3
23692	21.2	21.8	52.4
23693	36.2	348.8	62.9
23704 (reference example)	NA	NA	NA
23717	62.8	43.9	59.7
23720	34.0	27.9	80.5
23736	9.1	50.0	147.7
23738	33.5	39.2	101.7
23739	56.1	67.5	164.5

23741 (reference example)	NA	NA	NA
23794	49.4	42.8	79.6
23795	24.3	22.2	45.9

Table 10: Half maximal inhibitory concentrations (IC₅₀) in nM of inventive compounds in various acral lentiginous melanoma (ALM) cell lines (ALM_M150207, ALM_M100513).

<u>Compound</u>	<u>ALM_M150207</u>	<u>ALM_M100513</u>
23526	33.8	48.3
23585	42.3	44.1
23586	40.3	
23594	45.5	98.5
23595		60.7
23596		45.7
23612	21.2	42.9
23687	44.8	59.6
23688 (reference example)	426.9	661.8
23692	20.5	
23693	349.0	

Results. The results obtained for the preferred inventive compounds, as shown in Tables 5 9-10, demonstrate significant efficacy in the tested cell lines. These results confirm the data obtained from the assays conducted on cutaneous squamous cell carcinoma cell lines and keratinocytes, as described in Example 4.

Figures 1A-1C and FIG. 2A-C show the statistically significant increase in efficacy of the very preferred compound 23526 as compared to reference compound 6027 for the tested 10 cutaneous squamous cell carcinoma cell lines, keratinocytes as well as for various melanoma cells as reported in Example 4 and within this Example 6.

EXAMPLE 8

***In vitro* anti-proliferative effects of inventive compounds in a plurality of cancerous tissue cell panels**

15 Tumors are traditionally classified in primarily by tissue and organ type. One of the inventive compounds (23526) was tested in *in vitro* cellular models representing the most common and relevant tumor types in human disease according to this classification (types by

tissue) using cell lines that are well accepted in cancer research and representative for each tumor type. Whenever possible models from the NCI-60 cancer cell line panel used by the National Cancer Institute (NCI) for the screening of compounds to detect potential anticancer activity were used.

- 5 Broad *in vitro* anti-proliferative effects of the very preferred inventive compound **23526** were assessed in a series of specific cancer tissues and the proliferation response of those cancer cell lines to drug treatments were measured through bioluminescence. The tested cell lines are commercially available from depositories.

Methodology. Cells were grown in RPMI 1640, 10% FBS, 2 mM L-alanyl-L-glutamine,
10 1 mM Na pyruvate, or a special medium. Cells were seeded into 384-well plates (96- well plate for 6027) and incubated in a humidified atmosphere of 5% CO₂ at 37°C. Compounds were added the day following cell seeding. At the same time, a time zero untreated cell plate was generated. After a 3-day incubation period, cells were lysed with cell viability detection reagent CellTiter-Glo® (Promega). Compounds tested were serially diluted in half-log steps (3 fold
15 dilutions for 6027) from the highest test concentration of 3µM in DMSO (10µM in DMSO for 6027) and assayed over 10 concentrations with a maximum assay concentration of 0.1% DMSO (0.5% for 6027). Bioluminescence was read by a PerkinElmer Envision® microplate reader.

Cell viability was measured by the bioluminescence signal generated by the production of ATP in viable cells. The output is referred to as the relative cell count, where measured
20 bioluminescence intensity was transformed to percent of control (POC). Cell count EC50 is the test compound concentration at the curve inflection point or half the effective response. Curve-fitting, calculations, and report generation was performed using a custom data reduction engine and MathIQ based software (AIM).

1. Potency of **23526** in breast cancer.

- 25 MCF-7 is a breast cancer cell line isolated in 1970 from a 69-year-old White woman. This cell line retained several characteristics of differentiated mammary epithelium, including the ability to process estradiol via cytoplasmic estrogen receptors and the capability of forming domes.

MDA-MB-468 is a cell line that was isolated from a black 51-year-old female human
30 with metastatic adenocarcinoma of the breast in 1977, and were extracted from a pleural effusion of mammary gland and breast tissues, and have proven useful for the study of metastasis, migration, and breast cancer proliferation.

Both cell lines are widely used to test chemical breast cancer treatments and are

considered representative for the disease and are part of the NCI reference panel of cell lines for cancer testing.

Results.

Table 11: Efficacy of the preferred inventive compound 23526 in breast cancer cells given as EC₅₀ in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
MCF7	Breast	9.2	40.5	71.0
MDA MB 468	Breast	10.8	23.9	30.0

The inventive compound 23526 shows a strong anti-cancer response in the representative breast cancer cell lines of 9.2 nM against MCF7 and 10.8 nM against MDA MB 468 cells. This is multiple times stronger than the reference compound 6027 (71.0 nM against MCF7 and 30.0 nM against MDA MB 468 cells) and also multiple times more potent than Staurosporine (40.5 nM against MCF7 and 23.9 nM against MDA MB 468 cells) which serves as a suitable and very potent comparator for those skilled in the art.

2. Potency of 23526 in colorectal cancer

HT-29 is a human colon cancer cell line used extensively in biological and cancer research. Initially derived in 1964 from a 44-year-old Caucasian female, HT-29 cells form a tight monolayer while exhibiting similarity to enterocytes from the small intestine. HT-29 cells have been studied for their ability to differentiate and thus simulate real colon tissue *in vitro*, a characteristic that has made HT-29 useful for epithelial cell research.

The COLO 205 cell line is made up of epithelial cells isolated in 1975 from ascitic fluid derived from a 70-year-old, Caucasian, male with colon cancer. These cells exhibit epithelial cell morphology and come from a Dukes' type D tumor. The patient had been treated with 5-fluorouracil for approximately five weeks before removal of the specimen.

Both cell lines are widely used to test chemical colorectal cancer treatments and are considered representative for the disease and are part of the NCI reference panel of cell lines for cancer testing.

Results.

Table 12: Efficacy of the preferred inventive compound 23526 in colorectal cancer cells given as EC₅₀ in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
HT-29	Colorectal	6.2	13.7	50.0

Colo 205	Colorectal	11.9	6.9	43.0
----------	------------	------	-----	------

The inventive compound 23526 shows a strong anti-cancer response in the representative colorectal cancer cell lines of 6.2 nM against HT-29 and 11.9 nM against Colo 205 cells. This is multiple times stronger than the reference compound 6027 (50.0 nM against HT-29 and 43.0 nM against Colo 205 cells) and in the same range of potency as Staurosporine (13.7 nM against HT-29 and 6.9 nM against Colo 205 cells) which serves as a very potent and suitable comparator for those skilled in the art.

3. Potency of 23526 in hematopoietic cancer

Tumors of the hematopoietic and lymphoid tissues are tumors that affect the blood, bone marrow, lymph, and lymphatic system. Because these tissues are all intimately connected through both the circulatory system and the immune system, a disease affecting one will often affect the others as well, making aplasia, myeloproliferation and lymphoproliferation (and thus the leukemias and the lymphomas) closely related and often overlapping problems.

Hematological malignancies may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells; the lymphoid cell line produces B, T, NK and plasma cells. Lymphomas, lymphocytic leukemias, and myeloma are from the lymphoid line, while acute and chronic myelogenous leukemia, myelodysplastic syndromes and myeloproliferative diseases are myeloid in origin.

SR cells were established from the pleural effusion of an 11-year-old boy with CD30+ (Ki-1) large T cell lymphoma in 1983.

K-562 are lymphoblast cells isolated from the bone marrow of a 53-year-old chronic myelogenous leukemia patient.

MOLT-4 cells are T cell leukemia established from the peripheral blood of a 19-year-old man with acute lymphoblastic leukemia (ALL) in relapse in 1971.

CCRF-CEM are human T lymphoblasts isolated from the peripheral blood of a female, Caucasian 4-year-old with acute lymphoblastic leukemia (ALL).

All cell lines are widely used to test chemical treatments of hematopoietic cancers and are considered representative for the disease and are part of the NCI reference panel of cell lines for cancer testing.

To capture the variability within the group of hematopoietic cancers the following cell lines were used:

Table 13: Hematopoietic cancer cell lines

CELL LINE	SPECIFIC TISSUE/TUMOR SUB-TYPE	TUMOR TYPE	TISSUE SUBTYPE
SR	Large cell immunoblastic lymphoma, pleural effusion	Lymphoma	Lymphoblast
K562	Chronic myelogenous leukemia	Leukemia	Lymphoblast
MOLT-4	Acute lymphoblastic leukemia	Leukemia	T-lymphoblast
CCRFCEM	Acute lymphoblastic leukemia	Leukemia	T-lymphoblast

Results.

Table 14: Efficacy of the preferred inventive compound 23526 in hematopoietic cancer cells given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
SR	Hematopoietic	2.7	9.8	30.0
K562	Hematopoietic	7.1	63.7	29.0
MOLT-4	Hematopoietic	9.2	13.8	46.0
CCRFCEM	Hematopoietic	14.2	36.4	73.0

5

The inventive compound 23526 shows a strong anti-cancer response in the representative hematopoietic cancer cell lines of 2.7 nM against SR and 7.1 nM against K562 cells and 9.2 nM against MOLT-4 cells and 14.2 nM against CCRFCEM cells. This is multiple times stronger than the reference compound 6027 (30.0 nM against SR and 29.0 nM against K562 cells and 46.0 nM against MOLT-4 cells and 73.0 nM against CCRFCEM cells) and also multiple times more potent than Staurosporine (9.8 nM against SR and 63.7 nM against K562 cells and 13.8 nM against MOLT-4 cells and 36.4 nM against CCRFCEM cells) which serves as a very potent and suitable comparator for those skilled in the art.

10

4. Potency of 23526 in cancers of the female genitourinary (GU) system

15

OVCAR3 are epithelial cells that were isolated in 1982 from the malignant ascites of a patient with progressive adenocarcinoma of the ovary. Cells are used to study drug resistance in ovarian cancer.

C-33 A are epithelial cells isolated from the cervix of a 66-year-old, white, uterine cancer patient.

20

SiHa is a cell line isolated from fragments of a primary uterine tissue sample from a 55-year-old, female, Japanese patient with squamous cell carcinoma.

All cell lines are widely used to test chemical treatments of cancers of the female

genitourinary (*GU*) system and are considered representative for the disease. OVCAR3 is also part of the NCI reference panel of cell lines for cancer testing.

Table 15: Cancer cell lines of the female genitourinary (*GU*) system

CELL LINE	TISSUE SUBTYPE	TUMOR TYPE	TUMOR SUB-TYPE OR STAGE
OVCAR3	Ovary	Adenocarcinoma	
C-33A	Cervix	Carcinoma	Retinoblastoma
SiHa	Cervix	Squamous cell carcinoma	Grade II

Results.

5 Table 16: Efficacy of the preferred inventive compound 23526 female genitourinary (*GU*) system cells given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
OVCAR3	Female GU	3.5	12.7	14.0
C-33A	Female GU	22.4	82.3	33.0
SiHa	Female GU	58.1	71.4	67.0

The inventive compound 23526 shows a strong anti-cancer response in the representative cancer cell lines of the female genitourinary (*GU*) system of 3.5 nM against OVCAR3 and 22.4 nM against C-33A cells and 58.1 nM against SiHa cells. This is much stronger potency than the reference compound 6027 (14.0 nM against OVCAR3 and 33.0 nM against C-33A cells and 67.0 nM against SiHa cells) and Staurosporine (12.7 nM against OVCAR3 and 82.3 nM against C-33A cells and 71.4 nM against SiHa cells) which serves as a very potent and suitable comparator for those skilled in the art.

15 5. Potency of 23526 in lung cancer

Calu-6 is a cell line exhibiting epithelial morphology that was derived from a 61-year-old, white female patient with anaplastic carcinoma.

A549 cells were isolated from the lung tissue of a white, 58-year-old male with lung cancer.

20 DMS 114 is a cell line that was isolated from the lung of a white, 68-year-old, male patient with carcinoma.

NCI-H460 cells were isolated in 1982 from the pleural fluid of a male patient with large cell lung cancer.

All cell lines are widely used to test chemical treatments of lung cancers, immuno-

oncology, and toxicology research and are considered representative for the disease. A549 and NCI-460 and DMS114 are also part of the NCI reference panel of cell lines for cancer testing.

Results.

Table 17: Efficacy of the preferred inventive compound 23526 in lung cancer cells given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
Calu6	Lung	6.2	8.4	n.d.
A549	Lung	9.0	2.3	44.0
DMS114	Lung	10.9	44.6	n.d.
NCI-H460	Lung	16.8	15.0	51.0

The inventive compound 23526 shows a strong anti-cancer response in the representative lung cancer cell lines of 6.2 nM against Calu6 and 9.0 nM against A549 cells and 10.9 nM against DMS114 cells and 16.8 nM against NCI-H460 cell lines. For A549 and NCI-H460 (Calu6 and DMS114 not determined (n.d.) for this compound) this is multiple times stronger anti-cancer activity when compared to the reference compound 6027 (44.0 nM against A549 cells and 51.0 nM against NCI-H450) and also a higher potency than the reference Staurosporine against the Calu6 and DMS114 cell lines, which serves as a very potent and suitable comparator for those skilled in the art.

6. Potency of 23526 in cancers of the head and neck

FaDu is a cell line with epithelial morphology that was established in 1968 from a punch biopsy of a hypopharyngeal tumor removed from a 56-year-old, white, male patient with squamous cell carcinoma (pharynx).

A-253 cell line was isolated from tissue of a submandibular gland squamous cell carcinoma of the salivary glands.

OE21 was established in 1993 from a squamous carcinoma of mid oesophagus of a 74 year-old male patient. The tumor was identified as pathological stage IIA(UICC) and showed moderate differentiation.

All cell lines are widely used to test chemical treatments of cancers of the head and neck and are considered representative for the disease.

Results.

Table 18: Efficacy of the preferred inventive compound 23526 in head and neck cancer

cells given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
FaDu	Head and Neck	10.6	17.2	n.d.
A-253	Head and Neck	10.8	120.0	n.d.
OE21	Head and Neck	23.8	1.9	110.0

The inventive compound 23526 shows a strong anti-cancer response in the representative cell lines of cancer of the head and neck of 10.6 nM against FaDu cells and 10.8 nM against A-253 cells and 23.8 nM against OE21 cells. In case of OE21 cells, This efficacy represents a multiple times stronger anti-cancer activity when compared to the reference compound 6027 (110.0 nM against OE21; FaDu and A-253 not determined (n.d.) for 6027) and also a much higher potency (with the exception of OE21) than the reference Staurosporine (17.2 nM against FaDu cells and 120.0 nM against A-253 cells and 1.9 nM against OE21 cells) which serves as a very potent and suitable comparator for those skilled in the art.

7. Potency of 23526 in pancreatic cancer

MIA PaCa-2 is an epithelial cell line that was derived from tumor tissue of the pancreas obtained from a 65-year-old, white male.

Capan-2 is a cell line with polygonal morphology that was isolated in 1975 from the pancreas of a 56-year-old, white, male patient with pancreatic adenocarcinoma.

PANC-1 is a cell line exhibiting epithelial morphology that was isolated from the pancreatic duct of a 56-year-old, white, male with epithelioid carcinoma.

All cell lines are widely used to test chemical treatments of pancreatic cancers and are considered representative for the disease.

Results.

Table 19: Efficacy of the preferred inventive compound 23526 in pancreatic cancer cell lines given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine
Mia PaCa-2	Pancreas	11.3	17.1
Capan-2	Pancreas	38.2	42.9
PANC-1	Pancreas	38.3	83.0

The inventive compound 23526 shows a strong anti-cancer response in the representative

cell lines of pancreatic cancer of 11.3 nM against Mia PaCa-2 cells and 38.2 nM against Capan-cells and 38.3 nM against PANC-1 cells with a much higher potency than the reference Staurosporine (17.1 nM against Mia PaCa-2 cells and 42.9 nM against Capan-cells and 83.0 nM against PANC-1 cells) which serves as a very potent and suitable comparator for those skilled in the art.

8. Potency of 23526 in prostate cancer

22Rv1 is a human prostate carcinoma epithelial cell line that was derived from a human prostate carcinoma xenograft (CWR22R) that was serially propagated in nude mice after castration.

10 DU 145 is a cell line with epithelial morphology that was isolated from a metastatic central nervous system lesion in the brain of a 69-year-old, white, male with prostate cancer. established in 1975

15 PC-3 is a cell line derived from a bone marrow metastasis isolated post-mortem from a 62-year-old, white, male with grade IV prostate cancer (poorly differentiated adenocarcinoma) after androgen suppression therap

All cell lines are widely used to test chemical treatments of prostate cancers and are considered representative for the disease. DU145 and PC-3 are also part of the NCI reference panel of cell lines for cancer testing.

Results.

20 Table 20: Efficacy of the preferred inventive compound 23526 in lung cancer cell lines given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine	6027 (Reference)
22Rv1	Prostate	6.7	35.6	n.d.
DU145	Prostate	10.7	1.9	48.0
PC-3	Prostate	21.5	2.2	74.0

25 The inventive compound 23526 shows a strong anti-cancer response in the representative prostate cancer cell lines of 6.7 nM against 22Rv1 and 10.7 nM against DU145 cells and 21.5 nM against PC-3 cells. For DU145 and PC-3 (22Rv1 not determined (n.d.) for this compound) this is multiple times stronger anti-cancer activity when compared to the reference compound 6027 (48.0 nM against DU145 cells and 74.0 nM against PC-3 cells) and also a much higher potency than the reference Staurosporine for 22Rv1 (35.6 nM) which serves as a very potent

and suitable comparator for those skilled in the art. Staurosporine exhibits a higher degree of anti-cancer activity against DU145 (1.9 nM) and PC-3 (2.2 nM) than 23526.

9. Potency of 23526 in bladder cancer

5637 is a cell line exhibiting epithelial morphology that was isolated from the urinary bladder of a 68-year-old, white male patient with grade II carcinoma.

HT-1197 is a cell isolated from the urinary bladder of a white, 44-year-old, male with carcinoma.

All cell lines are widely used to test chemical treatments of bladder cancers and are considered representative for the disease.

Results.

Table 21: Efficacy of the preferred inventive compound 23526 in bladder cancer cell lines given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine
5637	Bladder	8.3	16.2
HT-1197	Bladder	11.4	94.0

The inventive compound 23526 shows a strong anti-cancer response in the representative bladder cancer cell lines of 8.3 nM against 5637 and 11.4 nM against HT-1197 cells. This is multiple times stronger anti-cancer activity when compared to Staurosporine (16.2 nM against 5637 and 94.0 nM against HT-1197 cells) which serves as a very potent and suitable comparator for those skilled in the art.

10. Potency of 23526 in CNS cancer

PFSK-1 is a cell line exhibiting fibroblast morphology that was isolated from the cerebral hemisphere of a 22-month-old, white male patient with malignant primitive neuroectodermal tumor.

U-87 MG is a cell line with epithelial morphology that was isolated from malignant gliomas from a male patient, likely with Glioblastoma.

All cell lines are widely used to test chemical treatments of CNS cancers – particularly cancers of the brain - and are considered representative for the disease.

Results.

Table 22: Efficacy of the preferred inventive compound 23526 in CNS cancer cell lines

given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine
PFSK-1	CNS	9.6	19.3
U-87 MG	CNS	18.5	91.4

The inventive compound 23526 shows a strong anti-cancer response in the representative CNS cancer cell lines of 9.6 nM against PFSK-1 and 18.5 nM against U-87MG cells. This is a multiple times stronger anti-cancer activity when compared to Staurosporine (19.3 nM against PFSK-1 and 91.4 nM against U-87MG cells) which serves as a very potent and suitable comparator for those skilled in the art.

11. Potency of 23526 in stomach cancer

SNU-16 is a cell line exhibiting epithelial morphology that was isolated in 1987 from ascites derived from a 33-year-old, female, asian, stomach cancer patient prior to chemotherapy.

The Hs746T epithelial cell line was isolated from a 74-year-old caucasian male patient with gastric carcinoma.

All cell lines are widely used to test chemical treatments of stomach cancers and are considered representative for the disease.

Results.

Table 23: Efficacy of the preferred inventive compound 23526 in stomach cancer cell lines given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine
SNU-16	Stomach	6.0	6.7
Hs 746T	Stomach	6.8	31.7

The inventive compound 23526 shows a strong anti-cancer response in the representative stomach cancer cell lines of 6.0 nM against SNU-16 and 6.8 nM against HS746T cells. This is a much stronger anti-cancer activity when compared to Staurosporine (6.7 nM against SNU-16 and 31.7 nM against HS746T cells) which serves as a very potent and suitable comparator for those skilled in the art.

12. Potency of 23526 in further cancer types

HuTu 80 is a cell line exhibiting epithelial morphology that was isolated from the small

intestine (duodenum) of a 53-year-old, white male patient with adenocarcinoma

TT is a cell line exhibiting epithelial-like morphology that was isolated from the medulla of a white, 77-year-old, female patient with carcinoma.

SK-HEP-1 are endothelial cells that were isolated from the liver of a 52-year-old, white male patient with adenocarcinoma.

Rhabdomyosarcoma (RD) cells are large, multinucleated, spindle-shaped cells isolated from muscle tissue.

All cell lines are widely used to test chemical treatments in cancers and are considered representative for the disease.

10 Results.

Table 24: Efficacy of the preferred inventive compound 23526 in other cancer cell lines given as EC50 in nM.

Cell line	Tissue Group	23526	Staurosporine
HuTu 80	Duodenum	3.1	3.1
TT	Endocrine	15.1	28.5
SK-HEP-1	Kidney	23.2	48.0
RD	Soft Tissue & Bone	8.1	11.9

The inventive compound 23526 shows a strong anti-cancer response in the representative cancer cell lines of 3.1 nM against HuTu 80 and 15.1 nM against TT cells and 23.2 nM against SK-HEP-1 cells and 8.1 nM against RD cells showing a similar (HuTu 80) or stronger anti-cancer activity when compared to Staurosporine (28.5 nM against TT cells and 48.0 nM against SK-HEP-1 cells and 11.9 nM against RD cells) which serves as a very potent and suitable comparator for those skilled in the art.

20 Summary Results

The inventive compound 23526 demonstrated strong anti-cancer activity in a broad range of cancer cell lines derived from human tissue types representative for many cancer types. The anti-cancer effect of 23526 was always multiple times stronger towards the cancer than the reference compound 6027 and typically also much stronger than Staurosporine, a very potent comparator used in the art.

In comparison, the half inhibitory concentration in the response to treatment in healthy tissue fibroblasts were 795 nM for 23526 and 489.5 nM for 6027 showing that the inventive

compound 23526 was better tolerated in healthy tissue cell lines than in the tumor cell lines, and even better than the reference compound 6027. In connection hereto and with respect to the above described effective concentration against healthy cell fibroblasts, the calculated target selectivity for the inventive compound 23526 (calculated as effective concentration in healthy cells divided by the effective concentration in the target cancer cells) is significantly high and typically multiple times higher than for the reference compound 6027 demonstrating the potential of the inventive compounds for the treatment of cancer as human disease. By way of example: For Molt-4 (Hemopoietic, Acute lymphoblastic leukemia; see Table 14) selectivity for 23526 is 86.4 and the absolute anti-cancer activity is 9.2 nM while for the reference compound 6027 the selectivity is 10.6 and the absolute anti-cancer activity is 46.0 nM.

EXAMPLE 9

Efficacy of 23526 on *ex vivo* patient-derived cutaneous Squamous Cell Carcinoma (cSCC) of the patient's capillitium

The efficacy of inventive compound 23526 was confirmed in an experiment using fresh *ex vivo* infiltrative cSCC patient material. Patient material was taken from a cSCC lesion on the capillitium of a 87 year's old male patient.

Fresh tumour material of said patient was cut into similar sized pieces, put on cell culture inserts (0.4µM, Millicell cell culture; Millipore, Cat# PICM03050) and incubated with 1ml of co-culture media (3 parts DMEM (Gibco, Cat. # 41966052), 1 part Ham's F-12 Nutrient Mix (Gibco, Cat.# 11765054), 10% Fetal Bovine serum heat inactivated (Gibco, Cat.# 1050), 0.1 mg/ml of NormocinTM (Invivogen, Cat.# ant-nr-1), 21.8 µg/mL of Adenin (Sigma-Aldrich, Cat.# A2786), 5.45 µg/mL of Apotransferrin (Sigma-Aldrich, Cat.# T1147), 2.18 nM of Triiodothyronine (Sigma-Aldrich, Cat.# T6397), 0.44 µg/mL of Hydrocortisone (Sigma-Aldrich, Cat.# H0888), 0.11 nM of Cholera toxin (Sigma-Aldrich, Cat. # C8052), 5.50 µg/mL of Insulin (Sigma-Aldrich, Cat.# I6634) and 0.01 µg/mL of Epidermal growth factor (Sigma-Aldrich, Cat.# E4127)) from below for 24 hours at 37°C and 5% CO₂ to let the tissue piece recover. After 24 hours, the cell culture media was replaced with cell culture media containing drug conditions and incubated for another 4 days at 37°C and 5% CO₂. One made sure that tissue piece is covered with a drop of media containing drugs (day 0 and day 2). After 4 days of treatment, tissue was fixed in 4% buffered formaldehyde followed by immunohistochemistry stainings for histopathological examination and comparison of treatment conditions to untreated controls (DMSO).

Immunohistochemistry of *ex vivo* tumor pieces: Tumor slices were embedded into paraffin blocks. Consecutive cuts were stained with antibodies of interest. Following antibodies were used for stainings: Ki67 (Dako, clone MIB-1, Cat# M7240, Dilution 1:50, Antigen Retrieval: Leica Bond ER2: 30 min at 95°C) and HE (Hämalaun nach Mayer, Artechemis, Cat# T.865.3; Eosin 1% wässrig – Morphisto, Cat# 10177) The slides were scanned at Vectra Polaris

5 T.865.3; Eosin 1% wässrig – Morphisto, Cat# 10177) The slides were scanned at Vectra Polaris Slide Scanner (Akoya Biosystems) and analyzed with Qpath software.

KI-67 staining was used as an immunohistochemical cellular marker for proliferation to visualize regions of the slice with proliferating cells.

Results:

10 Incubation of patient-derived infiltrative cSCC tumors for 4 days demonstrated a significant reduction in cell proliferation of tumor cells when exposed to inventive compound 23526 (500 nM) compared to the negative control DMSO (Two-Way ANOVA; ** $p < 0.0035$). The reduction of proliferating tumor cells is indicated by the % of ki67 positive cells (DMSO: 17.1; 23526 500nM: 1.7). Tumor region was localized by HE stainings with help of a

15 histopathologist. See FIG. 3A and FIG. 3B.

EXAMPLE 10

Efficacy of 23526 on *ex vivo* patient-derived cutaneous Squamous Cell Carcinoma (cSCC) of the patient's ear

The efficacy of inventive compound 23526 was confirmed in a further experiment using

20 fresh *ex vivo* infiltrative cSCC patient material. Tumour material was harvested from an infiltrative cutaneous squamous cell carcinoma (cSCC) from a 97 years old male patient's ear.

Fresh tumour material of said patient was cut into similar sized pieces, put on cell culture inserts (0.4µM, Millicell cell culture; Millipore, Cat# PICM03050) and incubated with 1ml of co-culture media (3 parts DMEM (Gibco, Cat. # 41966052), 1 part Ham's F-12 Nutrient Mix

25 (Gibco, Cat.# 11765054), 10% Fetal Bovine serum heat inactivated (Gibco, Cat.# 1050), 0.1 mg/ml of Normocin™ (Invivogen, Cat.# ant-nr-1), 21.8 µg/mL of Adenin (Sigma-Aldrich, Cat.# A2786), 5.45 µg/mL of Apotransferrin (Sigma-Aldrich, Cat.# T1147), 2.18 nM of Triiodothyronine (Sigma-Aldrich, Cat.# T6397), 0.44 µg/mL of Hydrocortisone (Sigma-Aldrich, Cat.# H0888), 0.11 nM of Cholera toxin (Sigma-Aldrich, Cat. # C8052), 5.50 µg/mL

30 of Insulin (Sigma-Aldrich, Cat.# I6634) and 0.01 µg/mL of Epidermal growth factor (Sigma-Aldrich, Cat.# E4127)) from below for 24 hours at 37°C and 5% CO₂ to let the tissue piece recover. After 24 hours, the cell culture media was replaced with cell culture media containing

drug conditions and incubated for another 4 days at 37°C and 5% CO₂. One made sure that tissue piece is covered with a drop of media containing drugs (day 0 and day 2). After 4 days of treatment, tissue was fixed in 4% buffered formaldehyde followed by immunohistochemistry stainings for histopathological examination and comparison of treatment conditions to untreated controls (DMSO).

Immunohistochemistry of *ex vivo* tumor pieces: Tumor slices were embedded into paraffin blocks. Consecutive cuts were stained with antibodies of interest. Following antibodies were used for stainings: Ki67 (Dako, clone MIB-1, Cat# M7240, Dilution 1:50, Antigen Retrieval: Leica Bond ER2: 30 min at 95°C). pan Cytokeratin (PanCK) (Santa Cruz Biotechnology, Sc-8018, Cat# L2420, Dilution 1:50, Antigen Retrieval: Leica Bond ER2: 30 min at 95°C) and HE (Hämalaun nach Mayer, Artechemis, Cat# T.865.3; Eosin 1% wässrig – Morphisto, Cat# 10177). The slides were scanned at Vectra Polaris Slide Scanner (Akoya Biosystems) and analyzed with Qpath software.

KI-67 staining was used as an immunohistochemical cellular marker for proliferation to visualize regions of the slice with proliferating cells. Pan Cytokeratin (PanCK) is a marker for epithelial tumors as it stains the cytoplasmic keratins of keratinocytes (FIG. 4A).

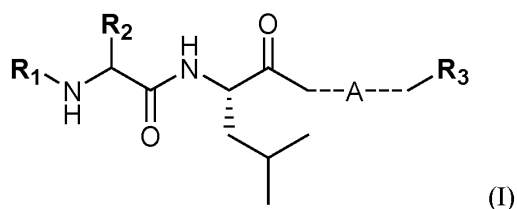
Results:

Incubation of patient-derived infiltrative cSCC tumors for 4 days demonstrated a significant reduction in cell proliferation of tumor cells when exposed to the reference compound 6027 (500 nM) as compared to the negative control DMSO but even more significantly further after treatment with the inventive compound 23526 (500 nM) (Two-Way ANOVA; ** $p < 0.004$ (23526); * $p < 0.03$ (6027)). The reduction of proliferating tumor cells is indicated by the ki67/PanCK ratios (DMSO: 0.75; 6027 500nM: 0.24; 23526 500nM: 0) as shown in FIG. 4B.

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CLAIMS

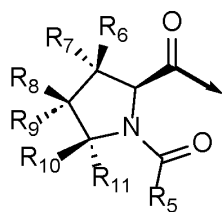
1. A compound of formula (I)



wherein

- 5 --A-- represents a peptide chain, wherein said peptide chain consists of 4 to 9 amino acids, wherein preferably said amino acids are selected from α -aminoisobutyric acid (Aib), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala);

R_1 is



, wherein the arrow indicates the attachment to the NH-moiety

- 10 depicted in formula (I), and wherein

- R_5 is selected from H, C_1 - C_{16} alkyl, C_1 - C_{16} alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl or C_1 - C_3 alkylene-heterocyclyl, wherein said C_1 - C_{16} alkyl and said C_1 - C_{16} alkenyl each independently optionally substituted with halogen, OR_{18} , $NR_{19}R_{20}$, $-[O-C_2H_4]_n-OCH_3$ wherein $n=2-20$; and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C_1 - C_4 alkyl, halogen, oxo, CF_3 , OR_{18} , $NR_{19}R_{20}$, C_6H_5 , C_6H_5 substituted with halogen, C_1 - C_3 alkyl, OR_{18} , $NR_{19}R_{20}$, wherein R_{18} , R_{19} , R_{20} are independently at each occurrence H, C_1 - C_3 alkyl, and wherein

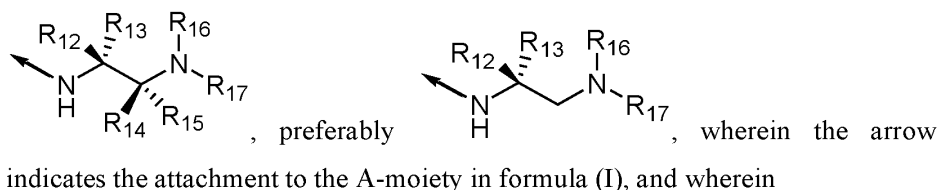
- 20 R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} are independently at each occurrence selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl, C_1 - C_3 alkylene-heterocyclyl, halogen, C_1 - C_2 haloalkyl, OR_{21} or $NR_{22}R_{23}$, wherein said R_{21} , R_{22} , R_{23} are independently at each occurrence selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, $C(O)O$ - C_1 - C_6 alkyl, $C(O)$ - C_1 - C_6 alkyl, $C(O)O$ - C_1 - C_6 alkenyl, $C(O)$ - C_1 - C_6 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_3 alkylene-carbocyclyl or C_1 - C_3 alkylene-

heterocyclyl, wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C₁-C₃alkyl, halogen, oxo, C₁-C₂haloalkyl, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle; said carbocycle and said heterocycle optionally substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀; and

wherein at least one of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ is not H; and

R₂ is selected from C₄-C₁₂alkyl, C₄-C₁₀alkoxy, C₁-C₃alkylene-cycloalkyl, C₁-C₃alkylene-aryl or C₁-C₃alkylene-heteroaryl, wherein independently in said C₁-C₃alkylene one -CH₂- moiety is optionally replaced by -CH(NH)- or -O-; and wherein said alkyl, cycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more, preferably one or two, substituents selected from C₁-C₂alkyl, C₁-C₂haloalkyl, oxo, OH, halogen, C₁-C₂alkoxy, C₆H₅ or C₆H₅ substituted with C₁-C₃alkyl or OC₁-C₃alkyl;

R₃ is

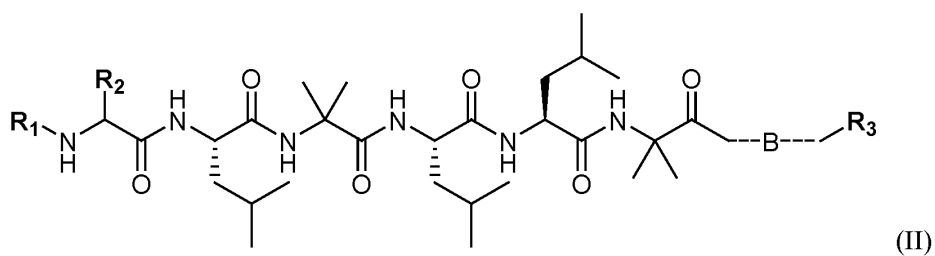


R₁₂, R₁₃, R₁₄ and R₁₅ are independently at each occurrence selected from H or C₁-C₃alkyl, preferably H or methyl, or two of said R₁₂, R₁₃, R₁₄ and R₁₅ together with the carbon atom to which they are attached form a carbocycle or heterocycle, preferably a carbocycle, and wherein

R₁₆ and R₁₇ are independently of each other selected from H or C₁-C₄alkyl optionally substituted with halogen, hydroxyl or C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a heteroaryl or a heterocyclyl, each independently optionally substituted with halogen, C₁-C₄alkyl, OR₁₈, NR₁₉R₂₀;

or a pharmaceutically acceptable salt of said compound of formula (I).

2. The compound of formula (I), wherein said compound is a compound of formula (II)

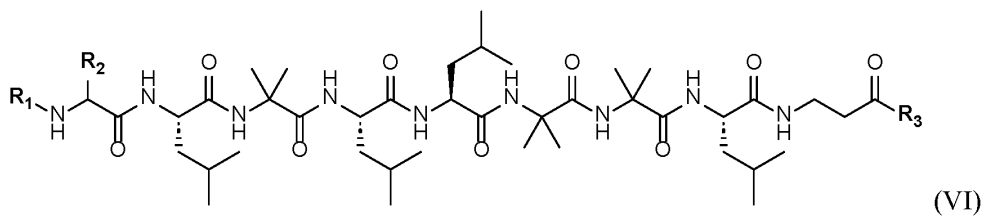
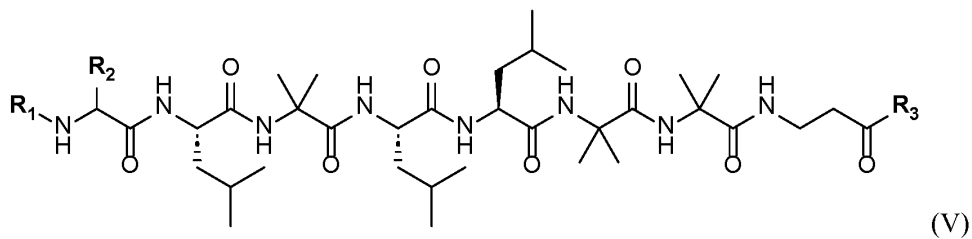
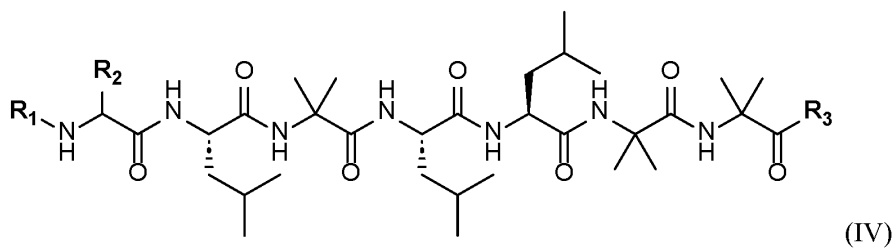
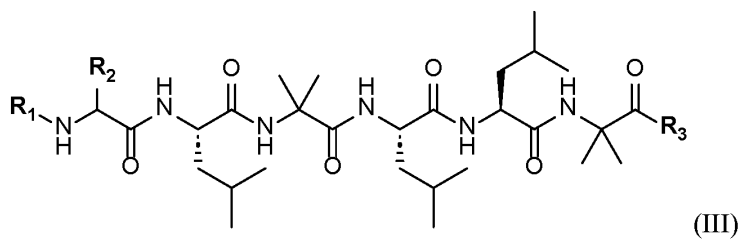


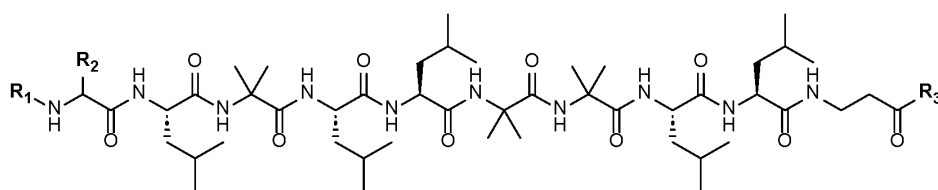
wherein

--B-- represents a peptide chain, wherein said peptide chain consists of 0 to 5 amino acids, wherein preferably said amino acids are independently selected from α -aminoisobutyric acid (Aib), leucine (Leu), preferably (*S*)-leucine, or β -alanine (β -Ala); and wherein

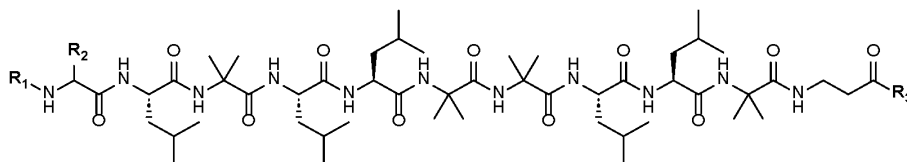
5 R_1 , R_2 and R_3 are as defined as in claim 1.

3. The compound of claim 2, wherein said compound of formula (II) is a compound selected from any one of the formulas (III) to (VIII)





(VII)



(VIII),

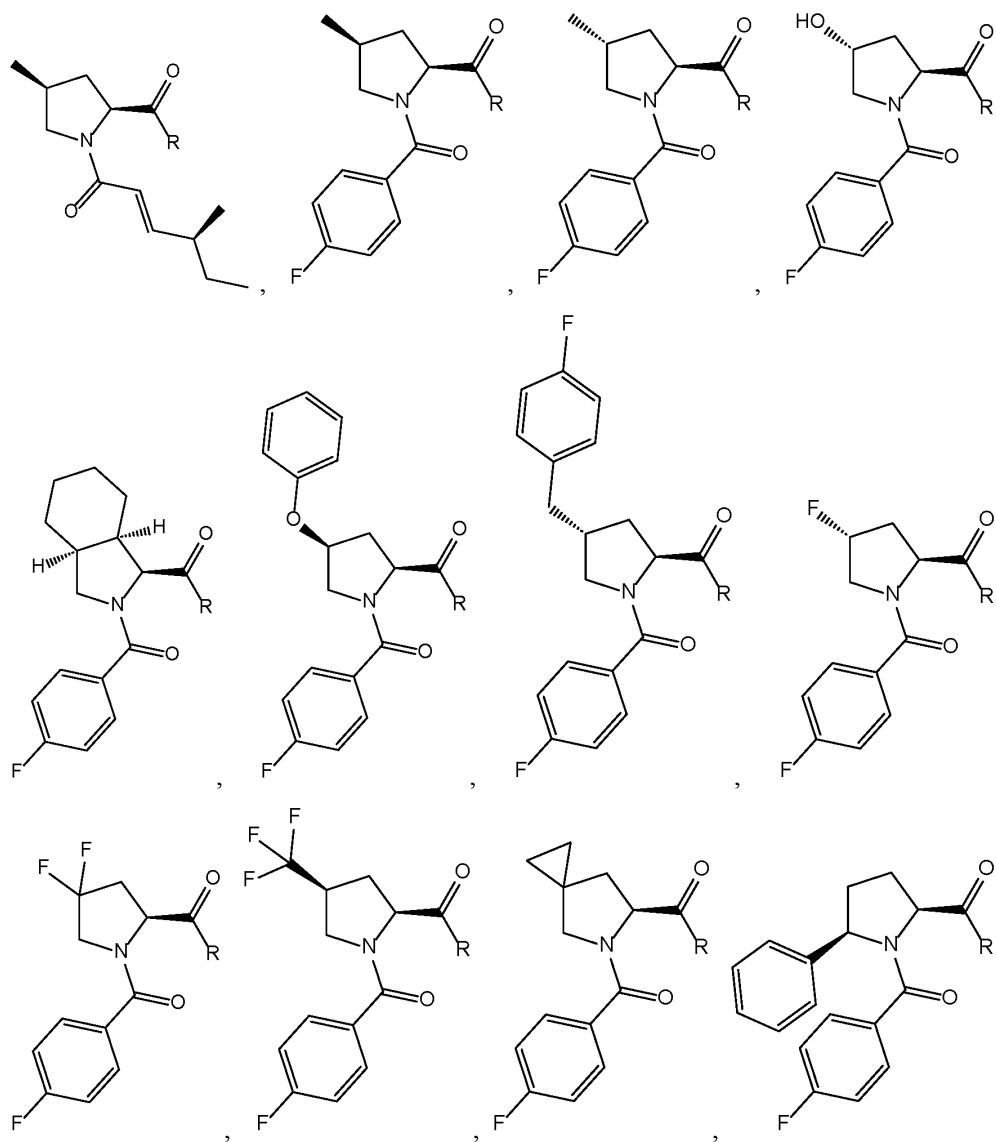
and wherein preferably said compound of formula (II) is a compound selected from any one of the formulas (IV) to (VI), and wherein further preferably said compound of formula (II) is a compound of formula (IV).

4. The compound of any one of the preceding claims, wherein said R_5 is selected from cycloalkyl, aryl, heteroaryl, C_5 - C_{12} alkyl, C_5 - C_{12} alkenyl or C_1 - C_4 alkylene- $[O-C_2H_4]_n-OCH_3$ wherein $n=5-15$, wherein said aryl, heteroaryl, cycloalkyl each independently optionally substituted with C_1 - C_4 alkyl, halogen, oxo, CF_3 , OR_{18} , $NR_{19}R_{20}$, C_6H_5 , C_6H_5 substituted with halogen, C_1 - C_3 alkyl, OR_{18} , $NR_{19}R_{20}$.
5. The compound of any one of the preceding claims, wherein R_5 is selected from C_6 - C_7 alkyl, C_6 - C_7 alkenyl, C_1 - C_4 alkylene- $[O-C_2H_4]_n-OCH_3$ wherein $n=8-12$, phenyl or a monocyclic heteroaryl comprising one or two heteroatoms selected from N, O and S, preferably oxazolyl, wherein said phenyl or said monocyclic heteroaryl preferably said oxazolyl, each independently optionally substituted with C_1 - C_4 alkyl, halogen, CF_3 , OR_{18} , $NR_{19}R_{20}$, C_6H_5 , C_6H_5 substituted with halogen, C_1 - C_3 alkyl, OR_{18} , $NR_{19}R_{20}$.
6. The compound of any one of the preceding claims, wherein R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} are independently at each occurrence selected from H, C_1 - C_3 alkyl, C_1 - C_3 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_2 alkylene-carbocyclyl, C_1 - C_2 alkylene-heterocyclyl, halogen, CF_3 , OR_{21} or $NR_{22}R_{23}$, wherein said R_{21} , R_{22} , R_{23} are independently at each occurrence selected from H, C_1 - C_3 alkyl, C_1 - C_3 alkenyl, $C(O)O$ - C_1 - C_3 alkyl, $C(O)$ - C_1 - C_3 alkyl, $C(O)O$ - C_1 - C_3 alkenyl, $C(O)$ - C_1 - C_3 alkenyl, carbocyclyl, heterocyclyl, C_1 - C_2 alkylene-carbocyclyl or C_1 - C_2 alkylene-heterocyclyl, wherein said carbocyclyl and said heterocyclyl is monocyclic, and wherein each of said carbocyclyl and said heterocyclyl independently at each occurrence optionally substituted with C_1 - C_3 alkyl, halogen, oxo,

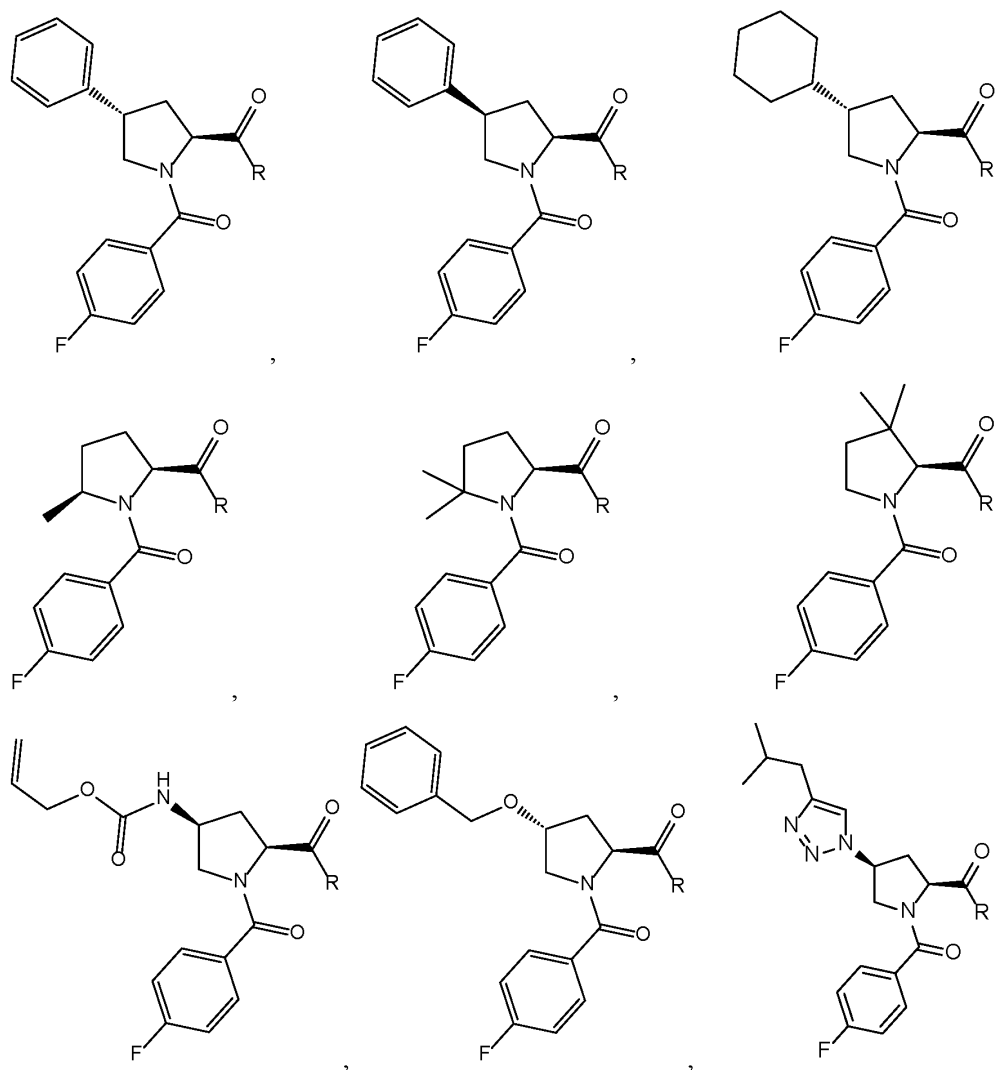
CF₃, OR₁₈, NR₁₉R₂₀, C₆H₅, C₆H₅ substituted with halogen, C₁-C₃alkyl, OR₁₈, NR₁₉R₂₀; or
wherein two of said R₆, R₇, R₈, R₉, R₁₀, and R₁₁ together with the carbon atom to which
they are attached form a monocyclic carbocycle or heterocycle, preferably a monocyclic
carbocycle; wherein said carbocycle and said heterocycle each independently optionally
substituted with C₁-C₃alkyl, halogen, CF₃, OR₁₈, NR₁₉R₂₀.

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7. The compound of any one of the preceding claims, wherein said R₁ is selected from the
formula



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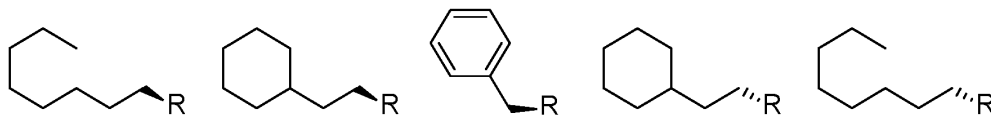


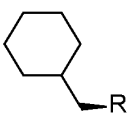
wherein R indicates the attachment to the NH-moiety depicted in formula (I).

- 5 8. The compound of any one of the preceding claims, wherein said R_2 is selected from C_5 - C_{12} alkyl, C_4 - C_{10} alkoxy, C_1 - C_3 alkylene- C_5 - C_6 cycloalkyl, C_1 - C_3 alkylene-phenyl, C_1 - C_3 alkylene-(mono- or bicyclic-heteroaryl), wherein said phenyl, C_5 - C_6 -cycloalkyl, and mono- or bicyclic-heteroaryl are each independently optionally substituted with one or more, typically and preferably with one or two, substituents selected from C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, halogen, C_1 - C_2 alkoxy.
- 10
9. The compound of any one of the preceding claims, wherein said R_2 is selected from C_5 - C_{12} alkyl, C_1 - C_2 alkylene- C_5 - C_6 cycloalkyl and CH_2 -phenyl, wherein said phenyl is

optionally substituted with one or two substituents selected from methyl, ethyl, fluorine, chlorine and methoxy.

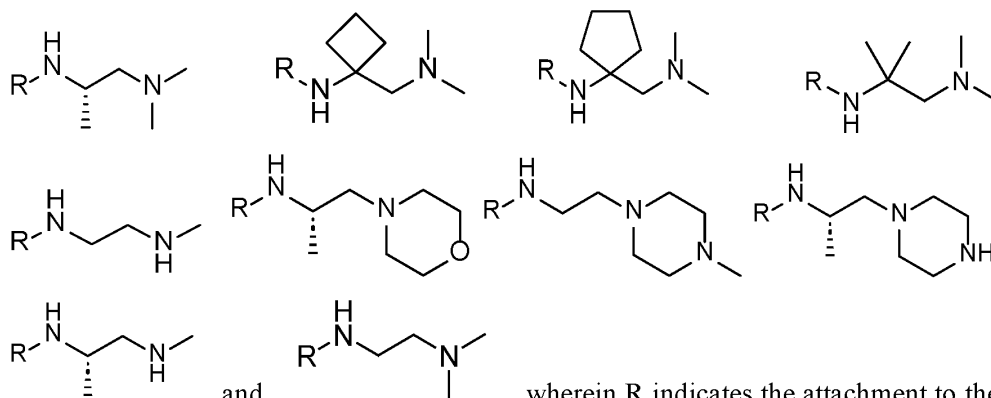
10. The compound of any one of the preceding claims, wherein said R_2 is selected from

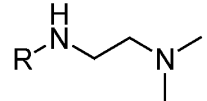


- 5 and , wherein R indicates the attachment to the CH-moiety depicted in formula (I).

11. The compound of any one of the preceding claims, wherein said R_{12} , R_{13} , R_{14} and R_{15} are independently at each occurrence H or C_1 - C_3 alkyl, preferably H or methyl, or independently at each occurrence two of said R_7 , R_8 , R_9 and R_{10} together with the carbon atom to which they are attached form a monocyclic carbocyclic or monocyclic heterocyclic ring, preferably a monocyclic carbocyclic ring, and wherein R_{16} and R_{17} are independently of each other H or C_1 - C_4 alkyl optionally substituted with halogen, hydroxyl, methoxy or C_3 - C_6 cycloalkyl; or together with the nitrogen atom to which they are attached form independently at each occurrence a monocyclic heteroaryl or a monocyclic heterocyclyl, each independently optionally substituted with halogen, C_1 - C_4 alkyl, OR_{18} , $NR_{19}R_{20}$.

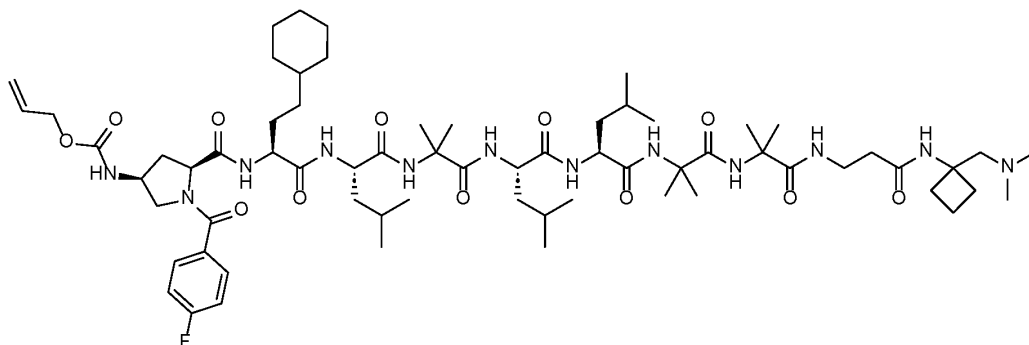
12. The compound of any one of the preceding claims, wherein said R_3 is selected from



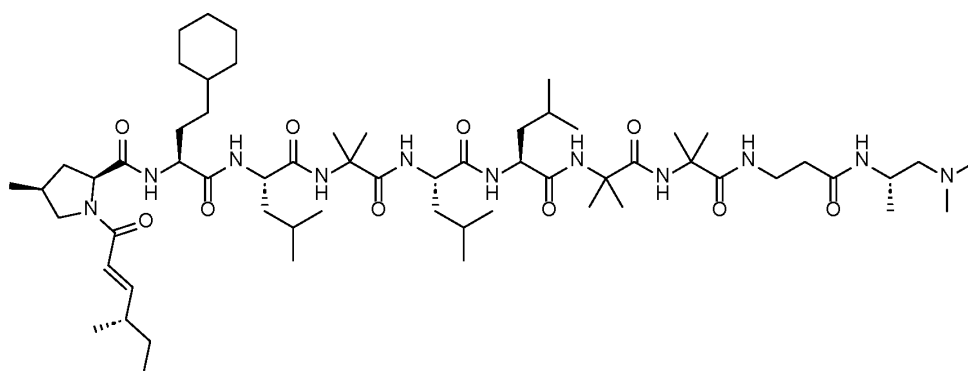
- 20 and , wherein R indicates the attachment to the A-moiety in formula (I).

13. The compound according to claim 1, wherein said compound is selected from

20762:

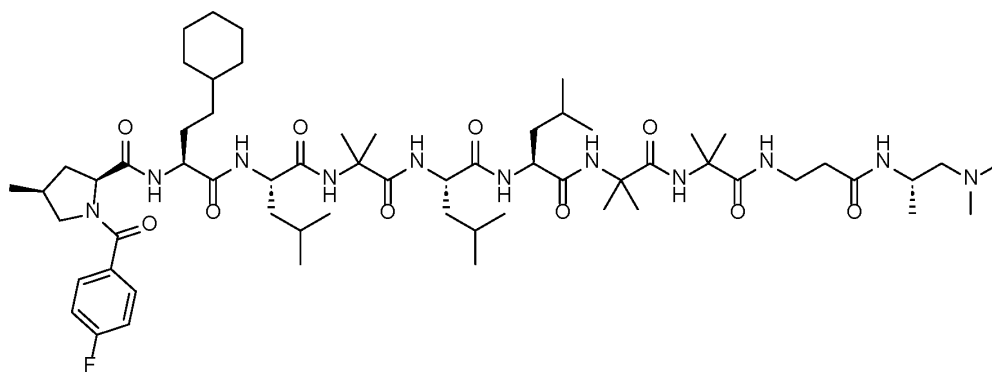


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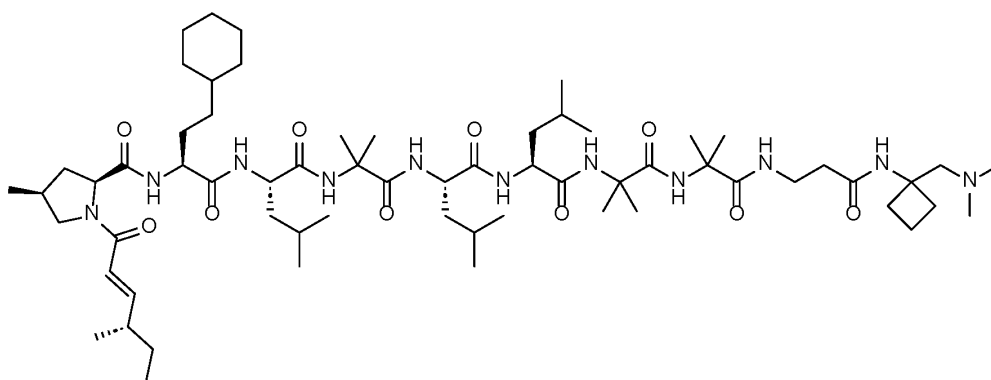


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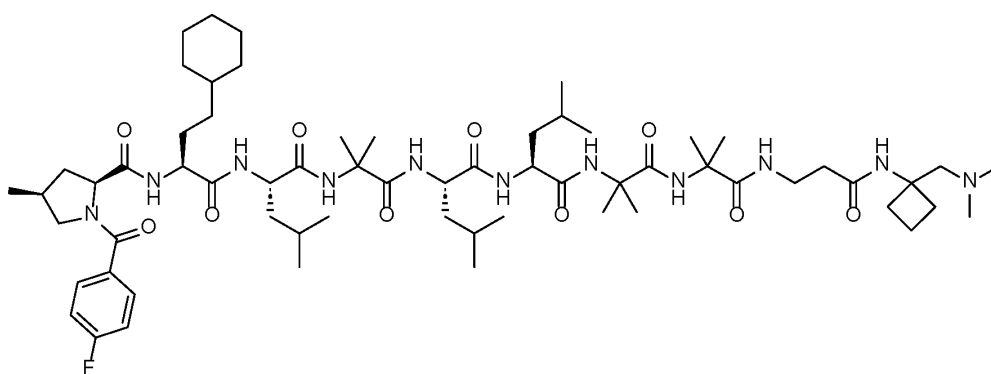
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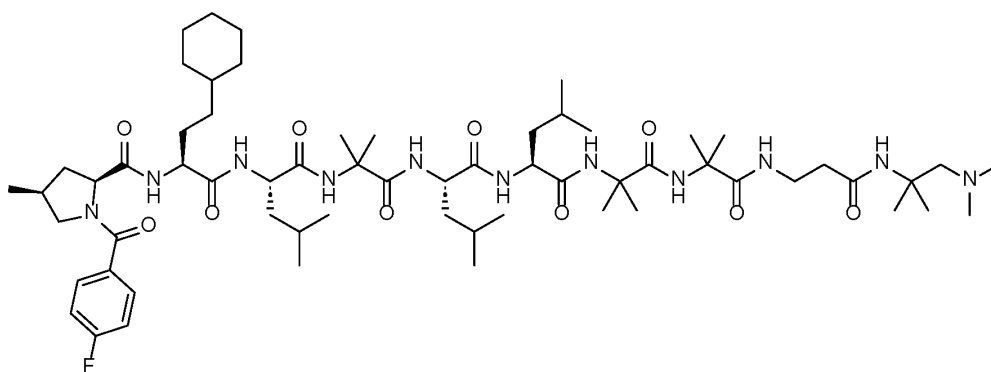
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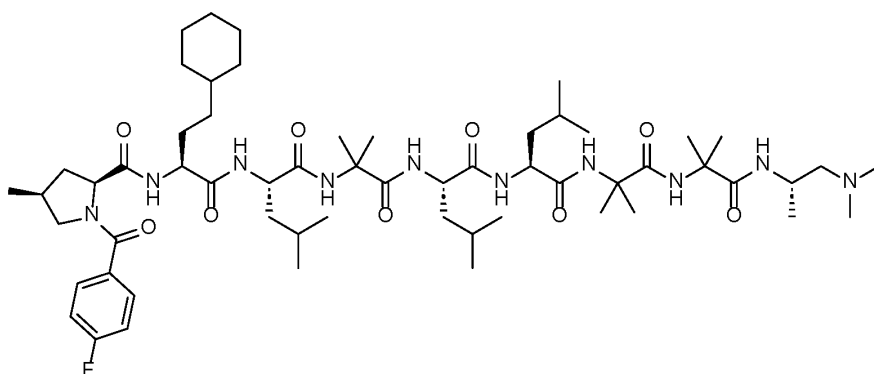
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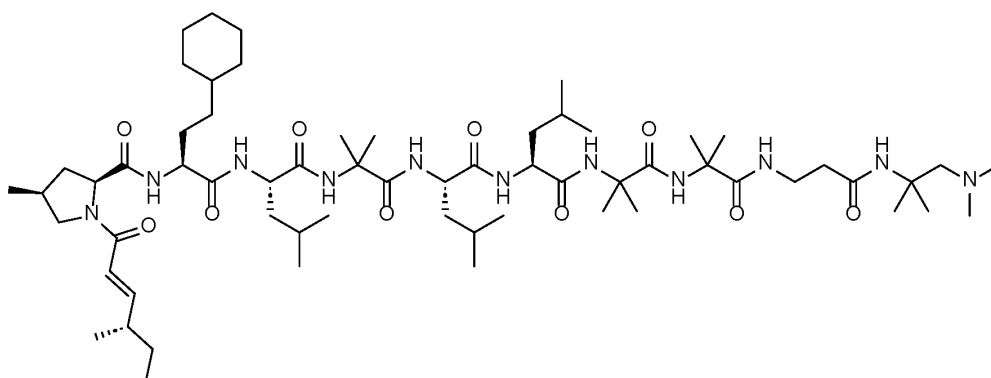
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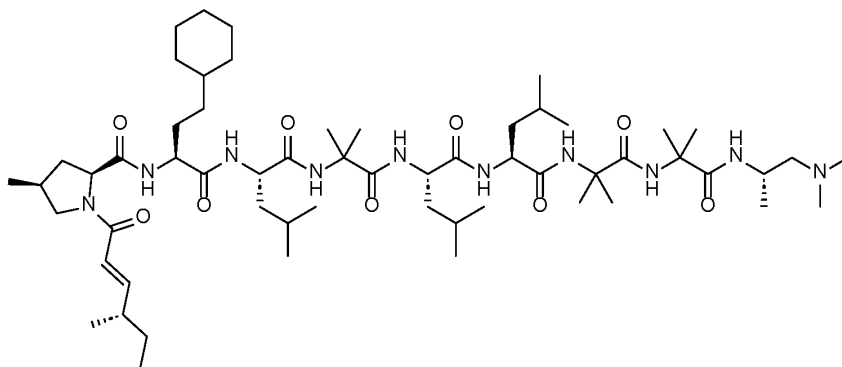
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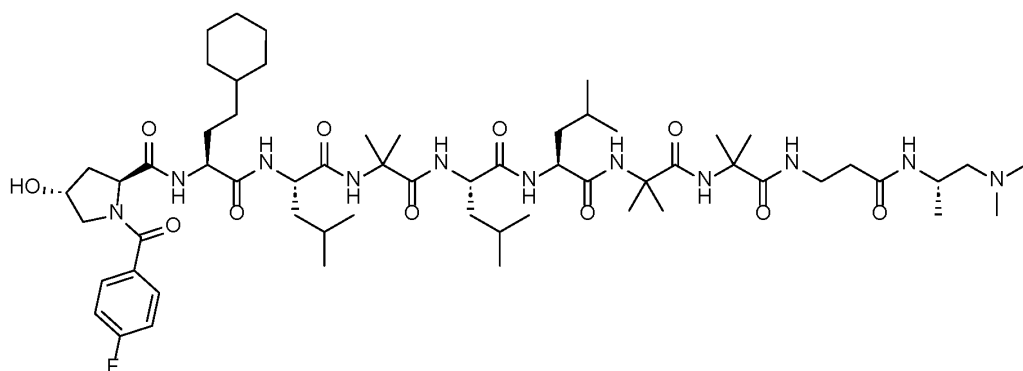
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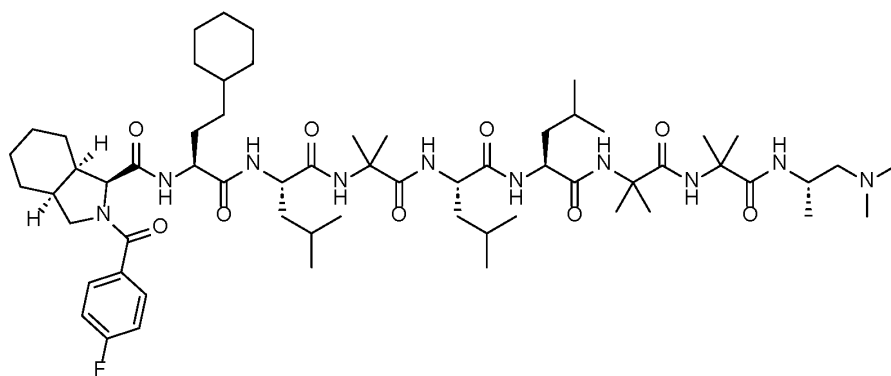
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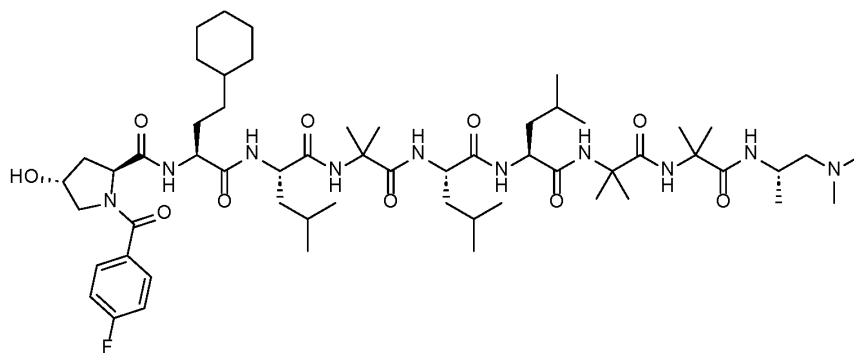
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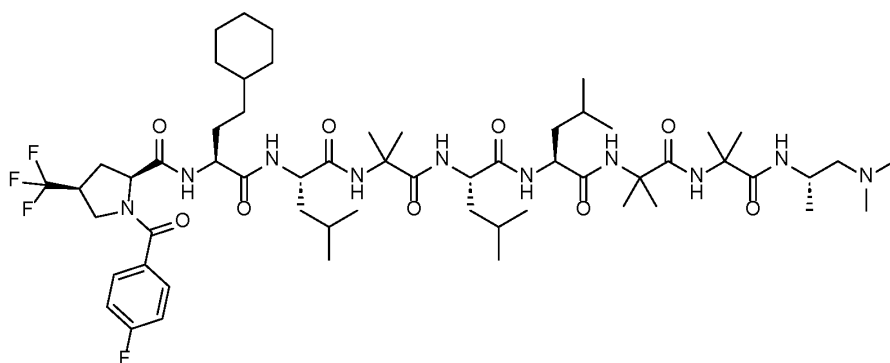
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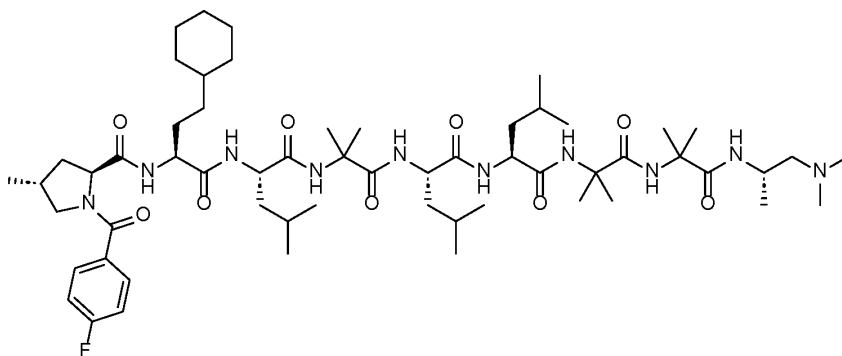
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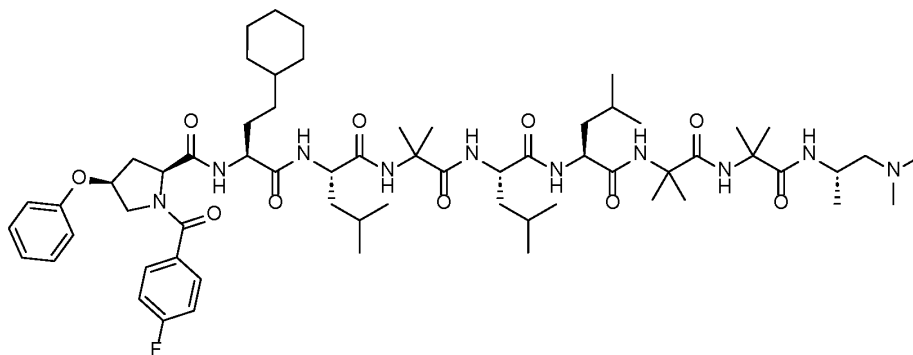
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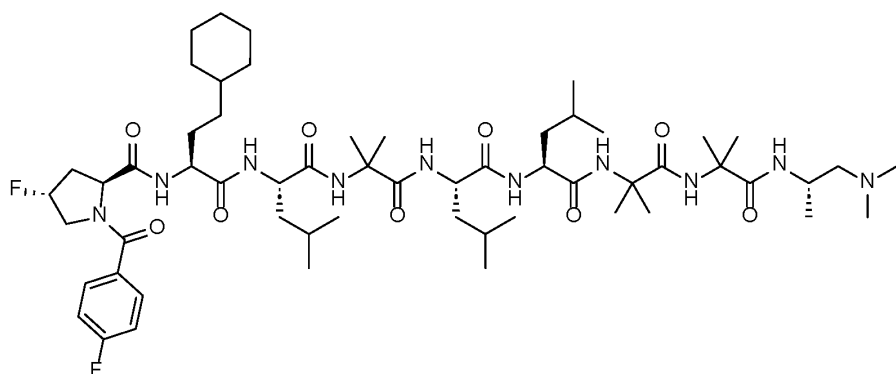


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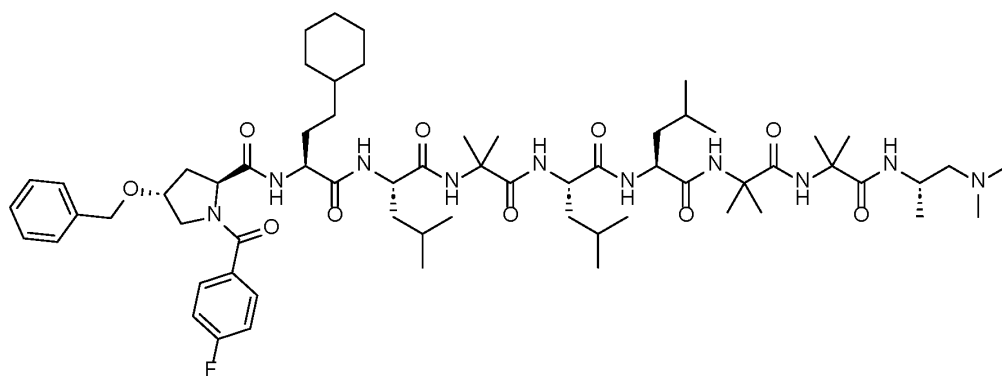


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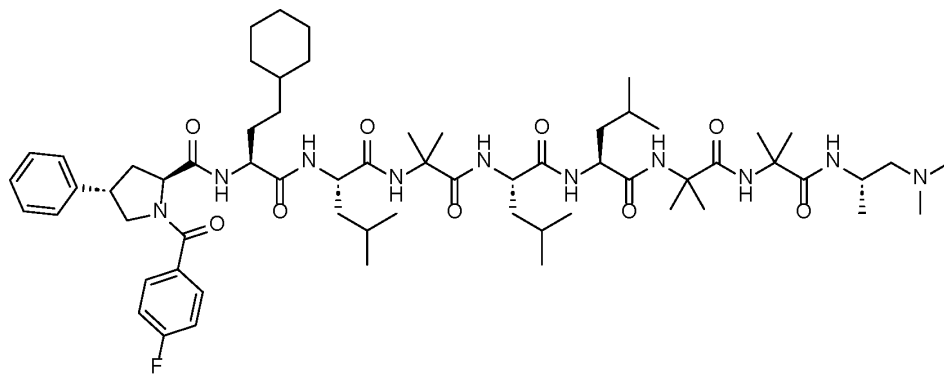
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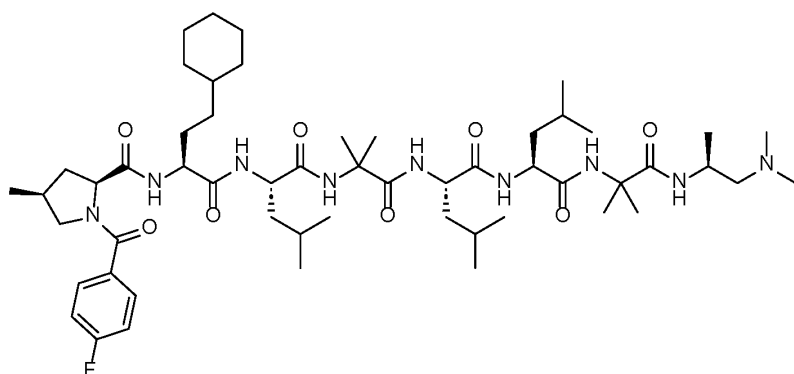
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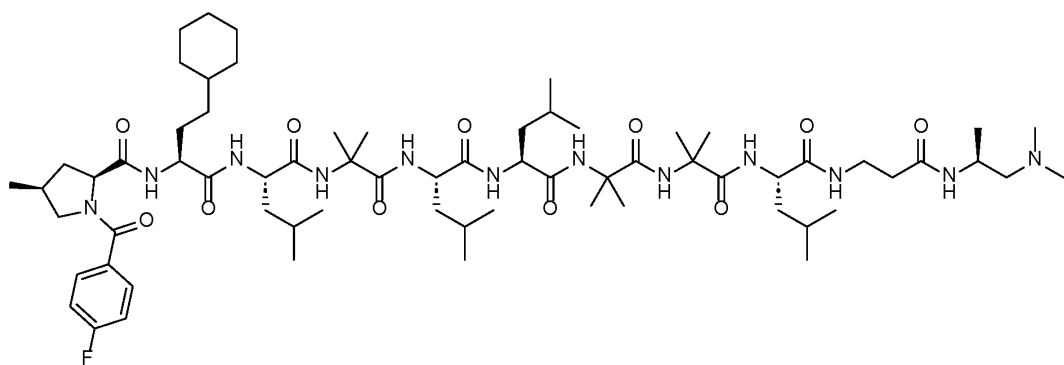
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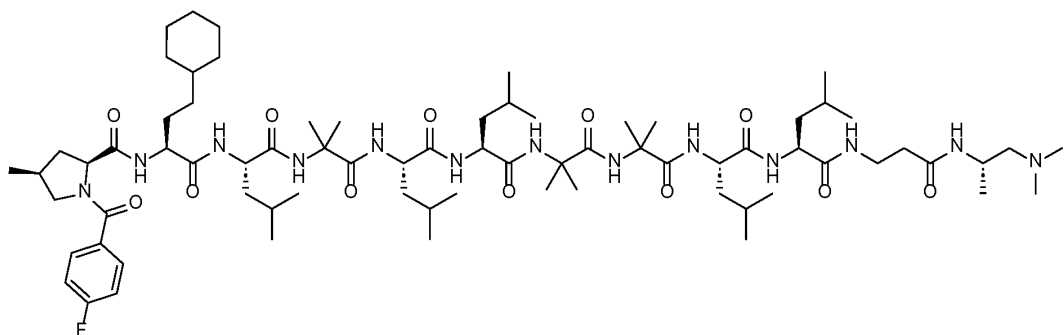
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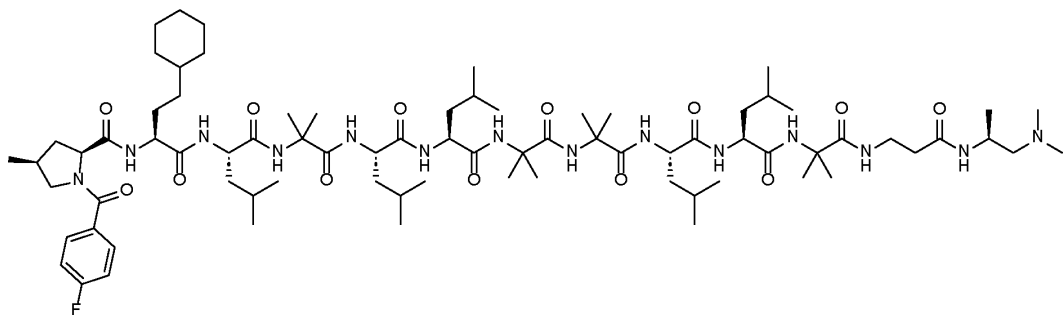


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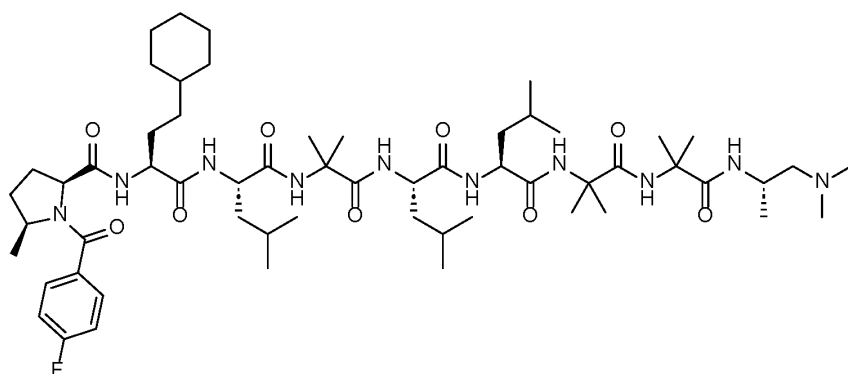


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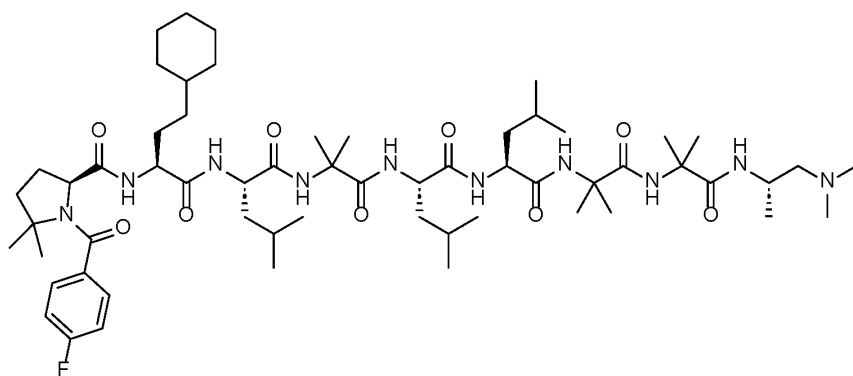
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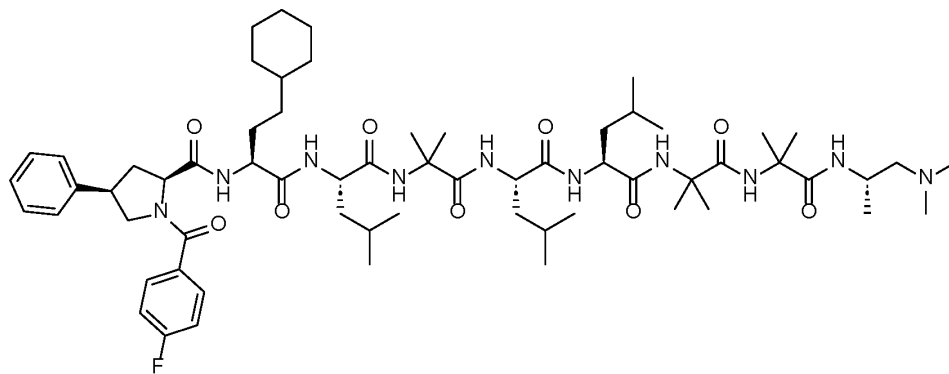
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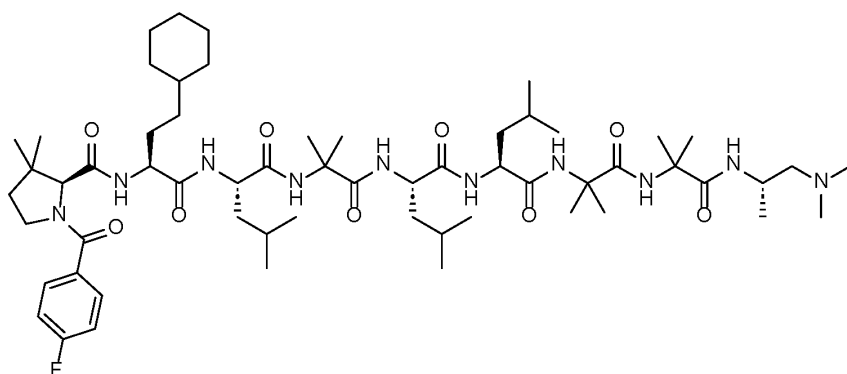
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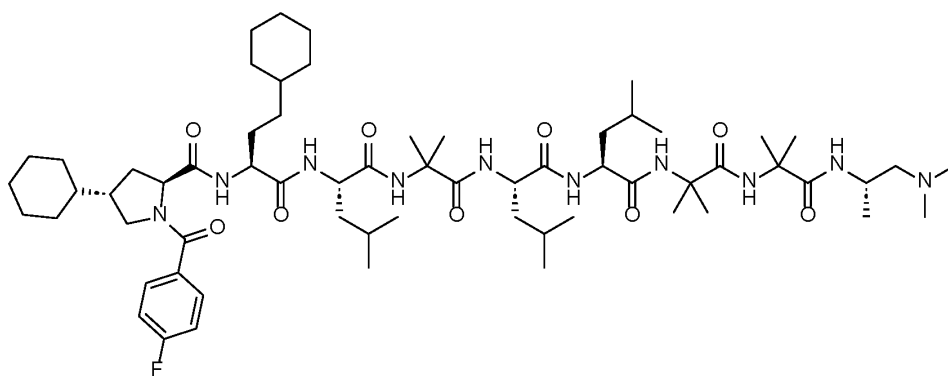
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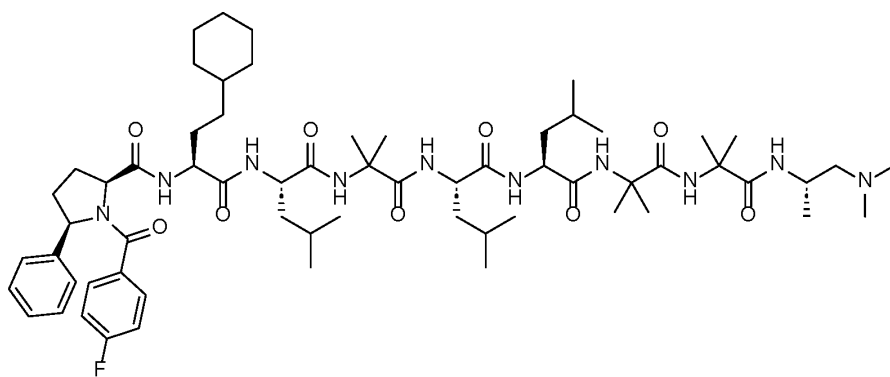
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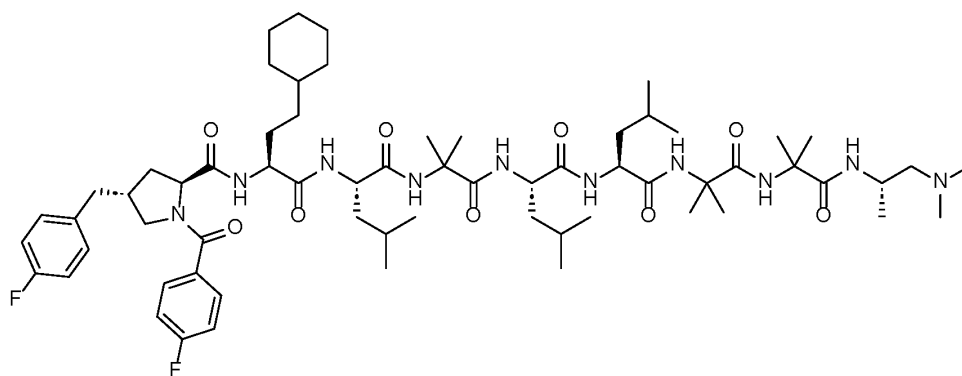
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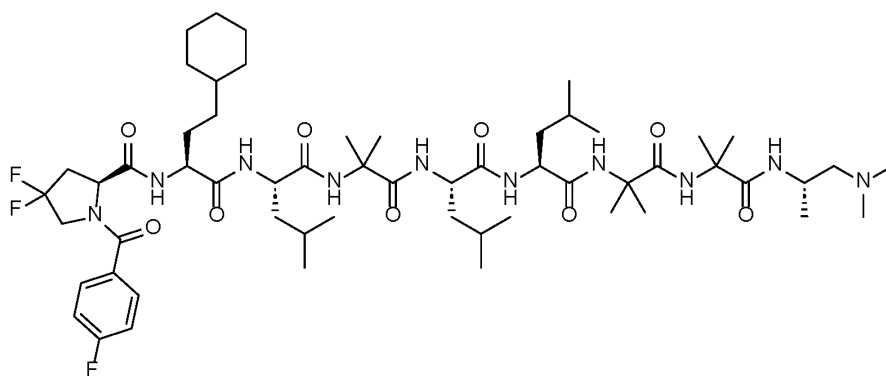
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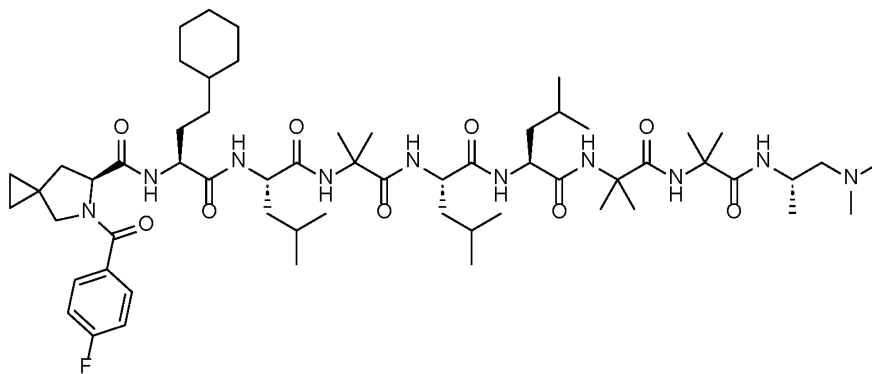
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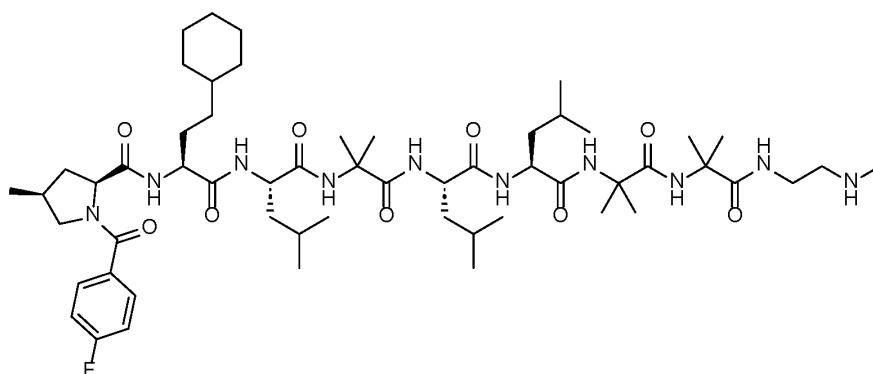
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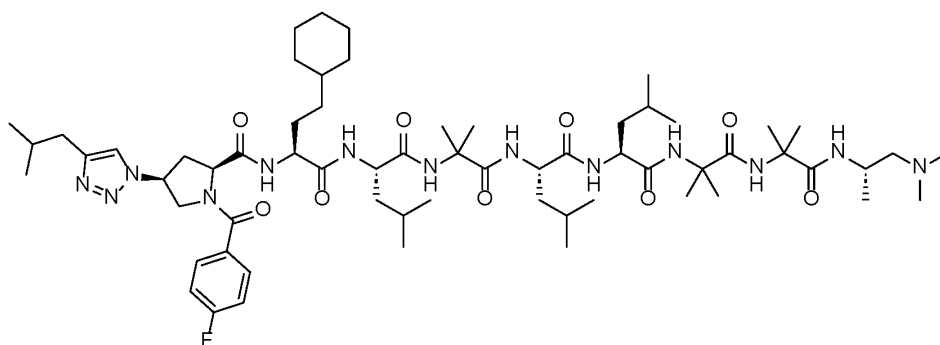
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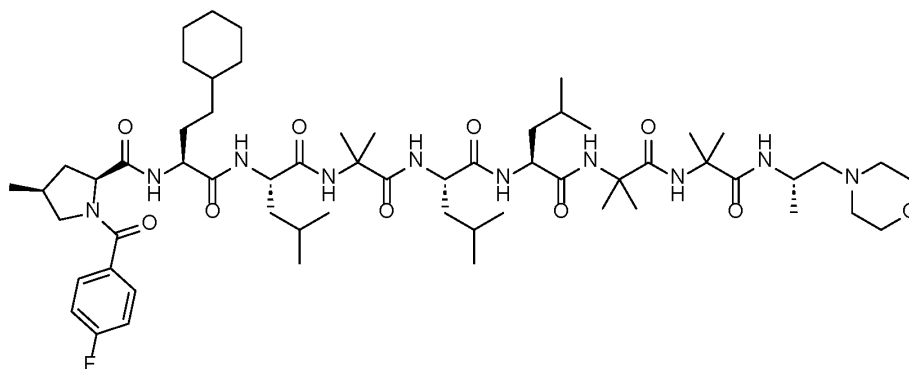
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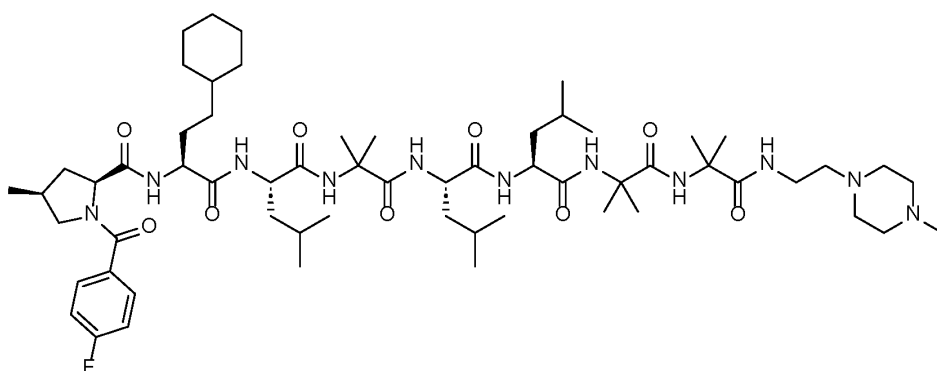
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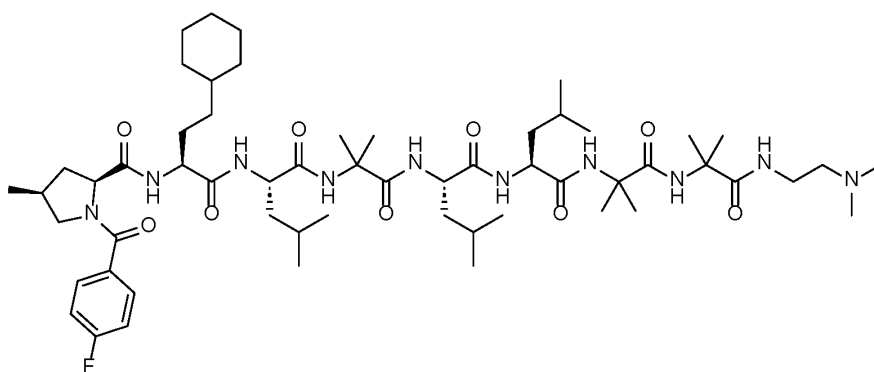
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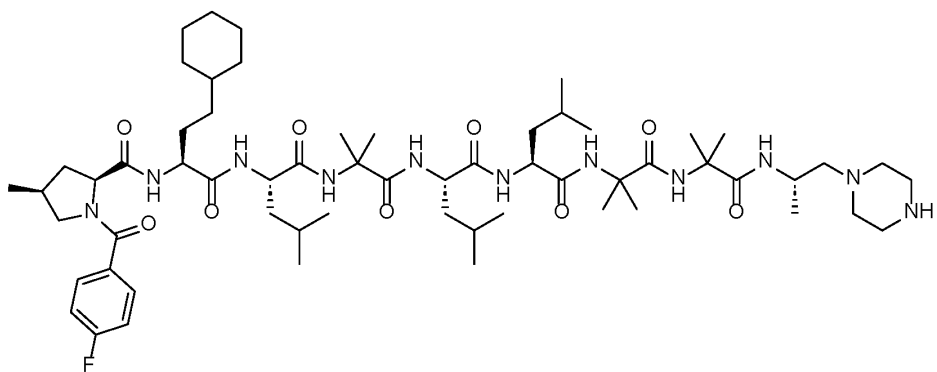
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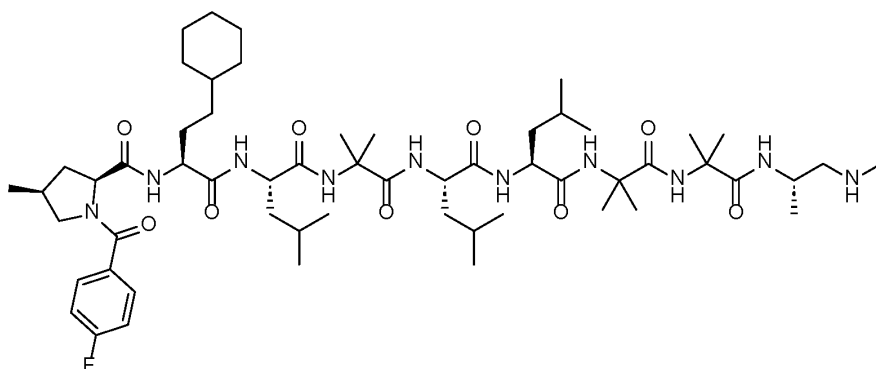
25088:



25126:



25157:



14. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of the claims 1 to 13, and a pharmaceutically acceptable carrier or adjuvant
15. The compound of any one of the claims 1 to 13, or the pharmaceutical composition of claim 14 for use in a method of treating a cancer of a mammal, preferably a human, wherein said method comprises administration of said compound or said pharmaceutical composition to said mammal, preferably to said human, and wherein preferably said method comprises administration of an effective amount of said compound or said pharmaceutical composition to said mammal, preferably to said human.