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DOLASTATIN 15 DERIVATIVES

BACKGROUND OF THE INVENTION

A number of short peptides with significant activity as inhibitors of cell growth have been isolated from the Indian Ocean sea hare *Dolabella auricularia* (Bai *et al.*, *Biochem. Pharmacology*, *40*: 1859-1864 (1990); Beckwith *et al.*, *J. Natl. Cancer Inst.*, *85*: 483-488 (1993) and references cited therein). These include Dolastatins 1-10 (U.S. Patent No. 4,816,444, issued to Pettit *et al.*) and Dolastatin-15 (European Patent Application No. 398558). Dolastatin 15, for example, markedly inhibits the growth of the National Cancer Institute's P388 lymphocytic leukemia (PS system) cell line, a strong predictor of efficacy against various types of human malignancies.

The exceedingly small amounts of the various Dolastatin peptides present in *Dolabella auricularia* (about

difficulties in purifying amounts sufficient for evaluation and use, have motivated efforts toward the synthesis of these compounds (Roux *et al.*, *Tetrahedron* 50: 5345-5360 (1994); Shioiri *et al.*, *Tetrahedron* **49**: 1913-24 (1993); Patino *et al.*, *Tetrahedron* **48**: 4115-4122 (1992) and references cited therein). Synthetic Dolastatin 15, however, suffers from drawbacks which include poor solubility in aqueous systems and the need for expensive starting materials for its synthesis. These, in turn, have led to the synthesis and evaluation of structurally modified Dolastatin 15 derivatives [cf.: *Biorg. Med. Chem. Lett.* **4**: 1947-50 (1994); WO 93 03054; JP-A-06234790; WO 93 23424].

However, there is a need for synthetic compounds with the biological activity of Dolastatin 15 which have useful aqueous solubility and can be produced efficiently and economically.

SUMMARY OF THE INVENTION

Compounds of the present invention include cell growth inhibitors which are peptides of Formula I,

$$A - B - D - E - F - (G)_r - (K)_s - L \qquad (I),$$

and acid salts thereof, wherein A, B, D, E, F, G and K are α-amino acid residues, and s and r are each, independently, 0 or 1. L is a monovalent radical, such as, for example, an amino group, an N-substituted amino group, a β-hydroxylamino group, a hydrazido group, an alkoxy group, a thioalkoxy group, an aminoxy group, or an oximato group.

Another aspect of the present invention includes pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier.

An additional embodiment of the present invention is a method for treating cancer in a mammal, such as a human, comprising administering to the mammal an effective amount of a compound of Formula I in a pharmaceutically acceptable composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to peptides having antineoplastic activity. It also includes pharmaceutical compositions comprising these compounds and methods for treating cancer in a mammal, including a human, by administration of these compositions to the mammal.

Dolastatin 15, a peptide isolated from the sea hare *Dolabella auricularia*, is a potent inhibitor of cell growth. This compound, however, is present in trace quantities in the sea hare, and is thus difficult to isolate. Dolastatin 15 is also expensive to synthesize and suffers from poor aqueous solubility. As shown herein, however, Dolastatin 15 can serve as a starting point for the development of compounds which overcome these disadvantages while retaining antineoplastic activity or exhibiting greater antineoplastic activity than the natural product. Applicants have discovered that certain structural modifications of Dolastatin 15 provide compounds with a surprisingly improved therapeutic potential for the treatment of neoplastic diseases as compared to Dolastatin 10 and Dolastatin 15. Furthermore, the compounds of the present invention can be conveniently synthesized, as described below in detail.

For the purposes of the present invention, the term "monovalent radical" is intended to mean an electrically neutral molecular fragment capable of forming one covalent bond with a second neutral molecular fragment. Monovalent radicals include the hydrogen atom, alkyl groups, such as methyl, ethyl and propyl groups, halogen atoms, such as fluorine, chlorine and bromine atoms, aryl groups, such as phenyl and naphthyl groups, and alkoxy groups, such as methoxy and ethoxy groups. Two monovalent radicals on adjacent sigma-bonded atoms can also together form a pi bond between the adjacent atoms. Two monovalent radicals may also be linked together, for example, by a polymethylene unit, to form a cyclic structure. For example, the unit -N(R)R', wherein R and R' are each a monovalent radical, can, together with the nitrogen atom, form a heterocyclic ring. In addition, two monovalent radicals bonded to the same atom can together form a divalent radical, such as an oxygen atom or an alkylidene group, for example, a propylidene group.

For the purposes of the present invention, the term "normal alkyl" refers to an unbranched, or straight chain, alkyl group, for example, normal propyl (*n*-propyl, $-CH_2CH_2CH_3$).

The compounds of the present invention can be represented by Formula I,

$$A - B - D - E - F - (G)_r - (K)_s - L \qquad (I),$$

wherein A, B, D, E, F, G, and K are α-amino acid residues; s and r are each, independently, 0 or 1; and L is a monovalent radical such as an amino group, an N-substituted amino group, a β-hydroxylamino group, a hydrazido group, an

alkoxy group, a thioalkoxy group, an aminoxy group, or an oximato group.

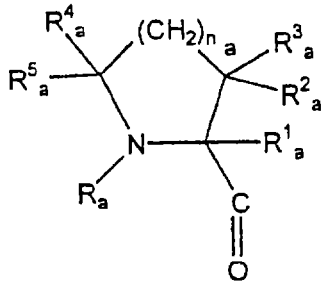
The peptides of Formula I are generally composed of L-amino acids but they can contain one or more D-amino acids. In the following discussion, reference to a particular amino acid includes both enantiomers unless a specific enantiomer is indicated. The present compounds can also be present as salts with physiologically-compatible acids, including hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, malic acid, succinic acid, malonic acid, sulfuric acid, L-glutamic acid, L-aspartic acid, pyruvic acid, mucic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

The following is a description of the present invention, including a detailed description of individual components and of methods of using the claimed compounds.

Compounds of the Present Invention

Identity of A

In one embodiment, A is a proline derivative of Formula II_a,



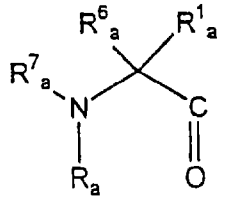
(II_a),

where n_a is an integer, preferably 0, 1, 2, or 3. R_a is a monovalent radical, such as a hydrogen atom or an unsubstituted or fluorine-substituted alkyl group, for example a normal, branched or cyclic C_1-C_3-alkyl group which is, optionally, substituted by from 1 to about 3 fluorine atoms; suitable examples include methyl, ethyl, isopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl or cyclopropyl; methyl, ethyl or isopropyl are preferred;

In this embodiment, R^1_a is a monovalent radical, such as a hydrogen atom, an alkyl group, such as a methyl, ethyl or propyl group, or a phenyl group. The phenyl group can be substituted; suitable substituents include one or more halogen atoms, with fluorine, chlorine and bromine atoms preferred, C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl or nitro groups. R_a and R^1_a together can also form a propylene bridge.

R^2_a, R^3_a, R^4_a and R^5_a are each, independently, a monovalent radical, such as a hydrogen atom or an alkyl, preferably, methyl, group.

In another embodiment, A is a substituted glycine derivative of Formula III_a,



(IIIa)

where R_a has the meaning stated for R_a in Formula II_a and, R^1_a is a monovalent radical, for example, a hydrogen atom

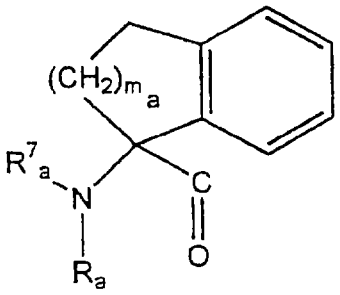
or a C_1-C_6-alkyl group, preferably a methyl, ethyl or propyl group.

In this embodiment, $R^6{}_a$ is a monovalent radical, such as an alkyl, substituted alkyl, alkenyl, phenyl or substituted phenyl group. Suitable examples include methoxymethyl, 1-methoxyethyl, 1,1-dimethyl-hydroxymethyl, 1-trifluoromethylethyl, 1-trifluoromethyl-2,2,2-trifluoroethyl, vinyl, and 1-methylvinyl. Phenyl substituents can include one or more halogen atoms, preferably fluorine, chlorine or bromine atoms, and alkyl, methoxy, ethoxy, trifluoromethyl, and nitro groups.

When $R^1{}_a$ is an alkyl group, $R^6{}_a$ can also be a C_1-C_6-alkyl, cycloalkyl, unsubstituted benzyl or substituted benzyl group. Suitable benzyl substituents include one or more halogen atoms, such as fluorine, chlorine or bromine atoms, C_1-C_4-alkyl groups, and methoxy, ethoxy, trifluoromethyl and nitro groups.

$R^7{}_a$ is a monovalent radical, preferably a methyl, ethyl or isopropyl group.

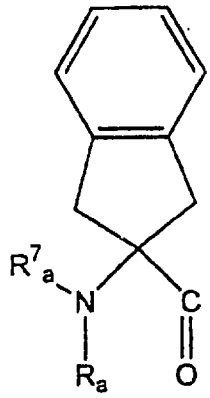
In another embodiment, A is an α-amino acid derivative of Formula IV_a,



(IV_a)

where m_a is an integer, preferably 1 or 2, and R_a and $R^7{}_a$ have the meanings stated for these substituents in Formula III_a.

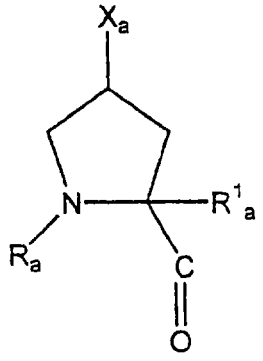
In another embodiment, A is an α-amino acid derivative of Formula V_a,



(V_a),

where R_a and $R^7{}_a$ have the meanings stated for R_a and $R^7{}_a$ in Formula III_a.

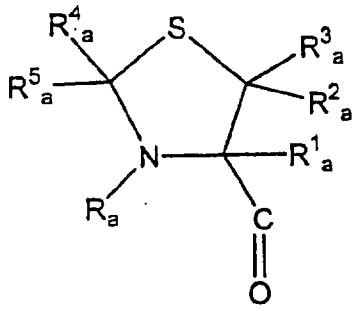
In a further embodiment, A is a substituted proline derivative of Formula VI_a,



(VI_a)

where R_a and $R^1{}_a$ have the meanings stated for R_a and $R^1{}_a$ in Formula II_a, and X_a is a monovalent radical, preferably a hydroxyl, alkoxy, for example, methoxy or ethoxy, group or a fluorine atom.

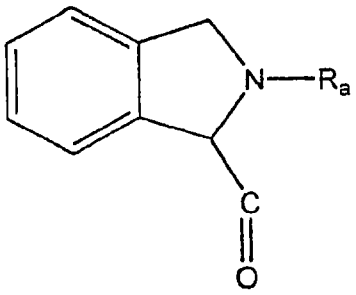
In another embodiment, A is a thiaprolyl derivative of Formula VII_a,



(VII_a)

where R_a, $R^1{}_a$, $R^2{}_a$, $R^3{}_a$, $R^4{}_a$ and $R^5{}_a$ have the meanings stated for the respective substituents in Formula II_a.

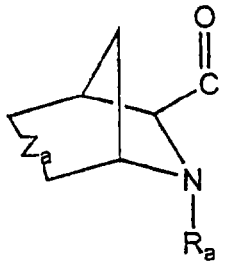
In another embodiment, A is a 1,3-dihydroisoindole derivative of Formula $VIII_a$



($VIII_a$)

where R_a has the meaning stated for R_a for Formula II_a.

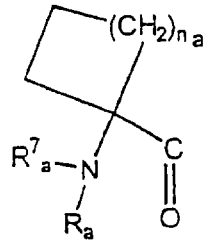
In another embodiment, A is a 2-azabicyclo[2.2.1]heptane-3-carboxylic acid derivative of Formula IX_a,



(IX_a),

where Z_a is a single or double bond and R_a has the meaning stated for Formula II_a. The 3-carbonyl substituent can have either the exo or endo orientation.

In another embodiment, A is an α-amino acid derivative of Formula X_a,

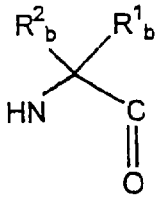


(X_a),

where n_a has the meaning as stated for n_a for Formula II_a, and $R^7{}_a$ and R_a have the meanings as stated for $R^7{}_a$ and R_a for Formula III_a.

Identity of B

B is a valyl, isoleucyl, allo-isoleucyl, norvalyl, 2-tert-butylglycyl or 2-ethylglycyl residue. B can also be an α-amino acid residue of Formula II_b,



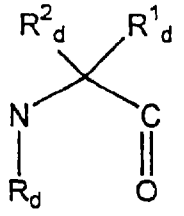
(II_b),

in which R^1_b and R^2_b are each a monovalent radical. R^1_b is, preferably, a hydrogen atom and R^2_b is, for example, an alkyl, alkoxyalkyl or alkenyl group. In preferred embodiments, R^2_b is a cyclopropyl group, a normal or branched butyl, preferably tertiary-butyl, group, a methoxymethyl group, a 1-methoxyethyl group or a 1-methylvinyl group. Additionally, R^1_b and R^2_b together can be an isopropylidene group.

Identity of D

D is an N-alkylvalyl, N-alkyl-2-ethylglycyl, N-alkyl-2-tert-butylglycyl, N-alkyl-norleucyl, N-alkyl-isoleucyl, N-alkyl-allo-isoleucyl or N-alkyl-norvalyl residue, where the N-alkyl group is preferably a methyl group or an ethyl group.

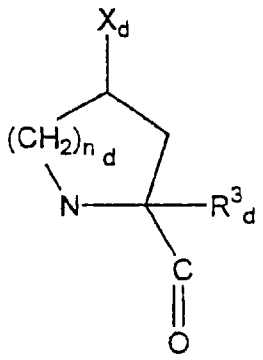
In another embodiment, D is an α-amino acid residue of Formula II_d,



(II_d),

where R_d has the meaning stated for R_a in Formula III_a, $R^1{}_d$ is a monovalent radical, preferably a hydrogen atom, and $R^2{}_d$ is a monovalent radical, for example, an alkyl, alkoxyalkyl or alkenyl group. In preferred embodiments, $R^2{}_d$ is a cyclopropyl group, a normal or branched butyl, preferably tertiary-butyl, group, a methoxymethyl group, a 1-methoxyethyl group or a 1-methylvinyl group. such as a cyclopropyl group, a methoxymethyl group, a 1-methoxyethyl group or a 1-methylvinyl group. Additionally, $R^1{}_d$ and $R^2{}_d$ together can form an isopropylidene group.

Alternatively, D can be a proline derivative of Formula III_d,

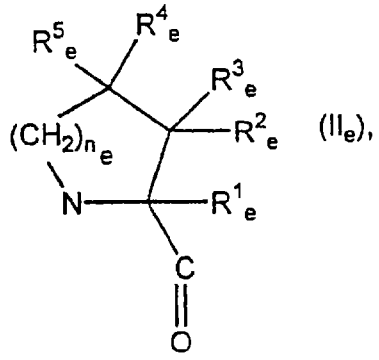


(III_d),

where n_d is an integer, for example, 1 or 2, and R^3_d has the meaning stated for R^1_a in Formula III_a. X_d is a monovalent radical, preferably a hydrogen atom, and, in the case where n_d equals 1, can also be a hydroxy or alkoxy, for example, methoxy or ethoxy, group or a fluorine atom.

Identity of E

E is a prolyl, thiazolidinyl-4-carbonyl, homoprolyl or hydroxyprolyl residue, or a cyclic α-amino carboxylic acid residue of Formula II_e,

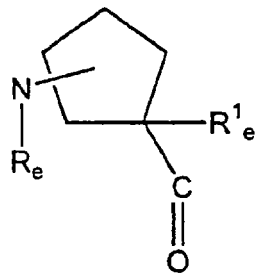


(II_e),

where n_e is an integer, preferably 0, 1 or 2. R^1_e has the meaning stated for R^1_a in Formula III_a. R^2_e and R^3_e are each a monovalent radical, and can be, independently, a hydrogen atom or an alkyl, preferably methyl, group. R^4_e is a monovalent radical, preferably a hydrogen atom, a hydroxy, alkoxy, for example, methoxy or ethoxy, group or a fluorine atom. R^5_e is a monovalent radical, preferably a hydrogen atom or a fluorine atom. In the case where n_e is 1, R^3_e and R^4_e can together form a double bond, or R^4_e and R^5_e can together be a double-bonded oxygen radical. In the

case where n_e has the value 1 or 2, R^1_e and R^2_e can together form a double bond.

In another embodiment, E is a 2- or 3-amino-cyclopentanecarboxylic acid residue of Formula III_e,

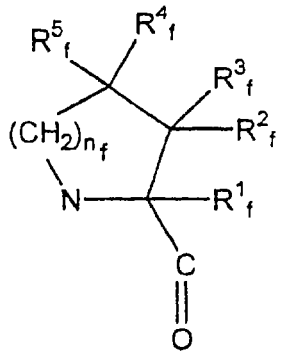


(III_e),

where R_e is an alkyl group, such as methyl or ethyl, and R^1_e has the meaning stated for R^1_a in Formula III_a.

Identity of F

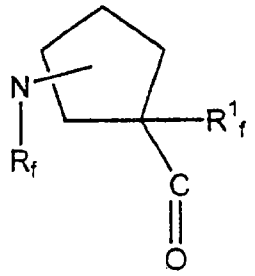
F is a prolyl, thiazolidinyl-4-carbonyl, homoprolyl or hydroxyprolyl residue. F can also be a cyclic α-amino acid residue of Formula II_f,



(II_f),

where n_f is an integer, preferably 0, 1 or 2. R^1_f has the meaning stated for R^1_a in Formula III_a. R^2_f and R^3_f are each a monovalent radical, and can be, independently, a hydrogen atom or an alkyl, preferably methyl, group. R^4_f is a monovalent radical, preferably a hydrogen atom, a hydroxy, alkoxy, for example, methoxy or ethoxy, group or a fluorine atom. R^5_f is a monovalent radical, preferably a hydrogen atom or a fluorine atom. In the case where n_f has the value 1, R^3_f and R^4_f together can form a double bond or R^4_f and R^5_f can together be a double-bonded oxygen radical. In the case where n_f has the value 1 or 2, R^1_f and R^2_f can together form a double bond.

In another embodiment, F is a 2- or 3-amino-cyclopentanecarboxylic acid residue of Formula III_f



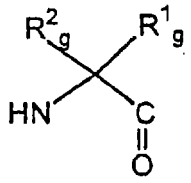
(III_f),

where R_f is a monovalent radical, such as a methyl or ethyl group, and R^1_f has the meaning stated for R^1_a in Formula III_a.

In another embodiment, F is an N-alkylglycyl or N-alkylalanyl residue, and the alkyl group is, preferably, a methyl group or an ethyl group.

Identity of G

G is an α-amino acid residue of Formula II_g,

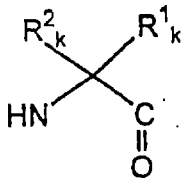


(II_g),

wherein R^1_g is a hydrogen atom, or an alkyl group, for example, methyl, ethyl or n-propyl. R^2_g can be, for example, a hydrogen atom, or an alkyl, arylalkyl, heteroarylalkyl or aryl group. Preferably, R^2_g is an ethyl, isopropyl, tert-butyl, isobutyl, 2-methylpropyl, cyclohexylmethyl, benzyl, thiazolyl-2-methyl, pyridyl-2-methyl, n-butyl, 2,2-dimethylpropyl, naphthylmethyl, or n-propyl group, or a substituted or unsubstituted phenyl group. Suitable phenyl substituents include one or more halogen, preferably fluorine, chlorine or bromine, atoms, C_1-C_4-alkyl groups, methoxy, ethoxy, nitro or trifluoromethyl groups or a dioxomethylene group. Alternately, R^1_g and R^2_g can, together with the α-carbon atom, form a cyclopentane or cyclohexane ring or a benzo-fused cyclopentane ring, such as, for example, the indanyl group.

Identity of K

K is an α-amino acid residue of Formula II_k,

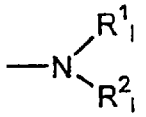


(II_k),

wherein R^1_k has the identity stated for R^1_g in Formula II_g, and R^2_k has the identity stated for R^2_g in Formula II_g.

Identity of L

In one embodiment, L is an amino or substituted amino group of Formula II_l,



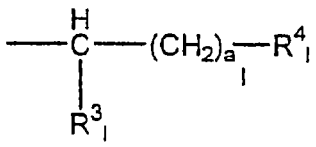
(II_l),

where R^1_l is a monovalent radical, such as a hydrogen atom, a normal or branched, saturated or unsaturated C_1-C_{18}-alkoxy group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted aryl-C_1-C_6-alkoxy group, or a substituted or unsubstituted aryloxy-C_1-C_6-alkoxy or heteroaryl-C_1-C_6-alkoxy group. The aryl group is preferably a phenyl or naphthyl group. The heteroaryl group is a 5- or 6-membered, preferably nitrogen-, oxygen- or sulfur- containing, ring system, such as, for example, a heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3- triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole,

benzopyran, benzothiazole, oxadiazole,thiadiazole or pyridine. Suitable aryl substituents include one or more halogen, preferably fluorine, bromine or chlorine, atoms, C_1-C_4-alkyl groups, methoxy, ethoxy or trifluoromethyl groups, a dioxymethylene group or nitro groups.

R^2_1 is a monovalent radical, such as a hydrogen atom, a normal or branched, saturated or unsaturated C_1-C_{18}-alkyl group, a C_3-C_{10}-cycloalkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaryl group. The aryl group is preferably a phenyl or naphthyl group. The heteroaryl group is a 5- or 6-membered, preferably nitrogen-, oxygen- or sulfur-containing, ring system, such as, for example, a heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3- triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole,thiadiazole or pyridine. Suitable aryl substituents include one or more halogen, preferably fluorine, bromine or chlorine, atoms, C_1-C_4-alkyl groups, methoxy, ethoxy or trifluoromethyl groups, a dioxymethylene group or nitro groups.

R^2_1 can, alternately, be of Formula II_r,



(II_r),

where a_1 is an integer, such as 0, 1, 2, 3, 4 or 5. R^3_1 is a monovalent radical, preferably a lower alkyl group, such as a methyl, ethyl, propyl or isopropyl group. R^4_1 is a

monovalent radical, which can be a saturated or partially unsaturated carbocyclic system comprising from about 3 to about 10 carbon atoms, a substituted or unsubstituted aryl or heteroaryl group, with aryl and heteroaryl and preferred substituents having the meaning stated for R^2_1 in Formula II_1.

R^2_1 can also be a substituent of Formula III_r,

$$-(CH_2)_2-W_1-R^5_1 \qquad (III_r),$$

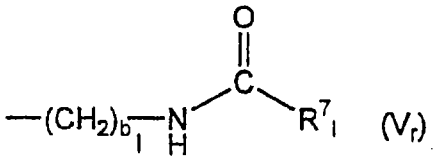
wherein W_1 is an oxygen or sulfur atom or an $N-R^6_1$ group. R^5_1 is a monovalent radical, such as a hydrogen atom, a C_1-C_4-alkyl or C_3-C_7-cycloalkyl group or a substituted or unsubstituted aryl or arylmethyl group, with aryl and its preferred substituents having the meaning stated for R^2_1 from Formula II_1. R^6_1 is a monovalent radical, preferably a hydrogen atom, a C_1-C_4-alkyl group or a C_3-C_7-cycloalkyl group, a C_1-C_{18}-alkanoyl group, a benzoyl group or a substituted or unsubstituted aryl or arylmethyl group, with aryl and its preferred substituents having the meaning stated for R^2_1 in Formula II_1.

R^2_1 can, alternately, be a substituent of Formula IV_r,

$$—(CH_2)_{b_1}—Z_1 \qquad (IV_r)$$

where b_1 is an integer, preferably 2, 3 or 4. Z_1 can be a monovalent radical such as a formyl, aminocarbonyl or hydrazinocarbonyl group, or a cyclic or acyclic acetal or thioacetal group.

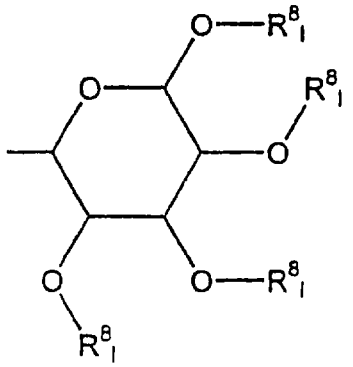
R^2_1 can also be a substituent of Formula V_r,



(Vr)

in which b_1 has the above-mentioned meaning. R^7_1 can be a monovalent radical, such as a polyglycol group of the formula $-O-(CH_2-CH_2-O)_{d1}-CH_3$, where d_1 is an integer, preferably in the range from about 2 to about 4 or from about 40 to about 90.

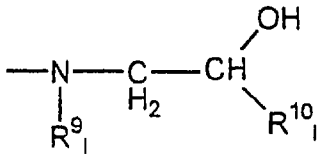
R^2_1 can further be a carbohydrate of Formula VI_r,



(VIr)

where R^8_1 is a monovalent radical, such as a hydrogen atom, a C_1-C_4-alkanoyl or alkyl group, a benzoyl group or a benzyl group.

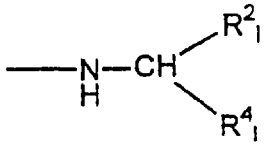
L can also be a β-hydroxylamino group of Formula III_1,



(III),

where R^9_1 is a monovalent radical such as a hydrogen atom, a C_1-C_6-alkyl group or a substituted or unsubstituted aryl group, with aryl and its preferred substituents having the meaning stated for R^2_1. R^{10}_1 is a monovalent radical, preferably a hydrogen atom, alkyl, for example, methyl, or a phenyl group.

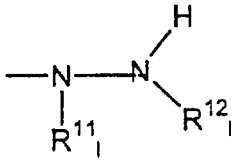
When r and/or s is 1, L can also be an amino group of Formula IV_1,



(IV_1),

where R^2_1 and R^4_1 are each a monovalent radical. R^2_1 and R^4_1 can also be linked by a carbon-carbon bond.

Another subclass of compounds of this invention includes peptides of Formula I wherein L is a hydrazido group of Formula V_1,



(V_1),

and R^{11}_1 is a monovalent radical, preferably a hydrogen atom. R^{12}_1 can be a monovalent radical such as a hydrogen atom, a normal or branched C_1-C_8-alkyl group, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4-alkyl group or a substituted or unsubstituted aryl, heteroaryl, aryl-C_1-C_4-alkyl or heteroaryl-C_1-C_4-alkyl group, where aryl, heteroaryl and their preferred substituents can be selected from among the options listed for R^2_1.

When r and/or s is 1, $R^{11}{}_1$ can also be selected from among the options listed above for $R^{12}{}_1$, and the two radicals together can additionally form a propylene or butylene bridge.

Another subclass of compounds of this invention includes peptides of Formula I wherein L is a monovalent radical of the formula $-O-R^{13}{}_1$ or the formula $-S-R^{13}{}_1$, where $R^{13}{}_1$ is a monovalent radical, such as a C_3-C_{10}-cycloalkyl group, a normal or branched C_2-C_{16}-alkenylmethyl group or a C_1-C_{16}-alkyl group which can be substituted by from 1 to about 5 halogen, preferably fluorine, atoms.

$R^{13}{}_1$ can also be the radical $-(CH_2)_e-R^{14}{}_1$, where e is an integer, preferably 1, 2 or 3. $R^{14}{}_1$ is a monovalent radical, preferably a saturated or partially unsaturated C_3-C_{10}-carbocycle.

$R^{13}{}_1$ can further be the monvalent radical $-[CH_2-CH=C(CH_3)-CH_2]_f-H$, where f is an integer, preferably 1, 2, 3 or 4.

$R^{13}{}_1$ can also be the radical $-[CH_2-CH_2-O]_g-CH_3$, where g is an integer, preferably in the range from 1 to about 5.

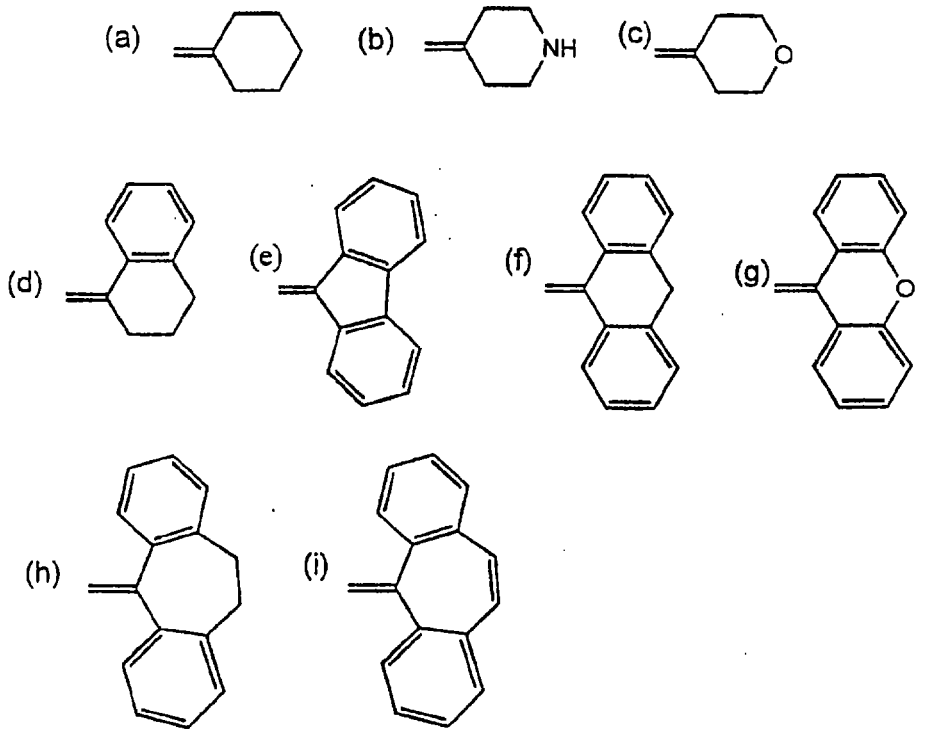
$R^{13}{}_1$ can also be the radical $-(CH_2)_h$-aryl or $-(CH_2)_h$-heteroaryl, where aryl and heteroaryl can also be substituted and, along with their preferred substituents, can be selected from the group listed for $R^2{}_1$. h is an integer, preferably 0, 1, 2 or 3.

$R^{13}{}_1$ can further be the radical $-(CH_2)_b-W_1-R^5{}_1$. b, W_1 and $R^5{}_1$ can each be selected from among the options described for Formula IV_1.

Another subclass of compounds of this invention includes peptides of Formula I in which L is an aminoxy group of the formula $-O-N(R^{15}{}_1)(R^{16}{}_1)$, where $R^{15}{}_1$ and $R^{16}{}_1$ are each a monovalent radical, which can independently be a

hydrogen atom, a normal or branched C_1-C_8-alkyl group, which can be substituted by halogen, preferably fluorine, atoms, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4-alkyl group, a substituted or unsubstituted aryl or heteroaryl group or a substituted or unsubstituted aryl-C_1-C_4-alkyl group. Aryl and heteroaryl groups and the preferred substituents thereof can be selected from the options listed for R^2_1. R^{16}_1 can be selected from among the options listed for R^{15}_1. Additionally, R^{15}_1 and R^{16}_1 can together form a 5-, 6- or 7-membered heterocycle. The compounds of the present invention further comprise the salts of the compounds described above with physiologically tolerated acids.

Another subclass of compounds of this invention includes peptides of Formula I wherein L is an oximato group of the formula -O-N=C(R^{15}_1)(R^{16}_1), R^{15}_1 and R^{16}_1 can be selected from among the options listed above and, additionally, can together form a cyclic system comprising, preferably, from about 3 to about 7 ring atoms. This cyclic system can additionally be fused to one or more aromatic rings. Particularly preferred cyclic systems are shown below.



In one embodiment, the invention provides compounds of Formula I wherein A is an amino acid derivative selected from among N-alkyl-D-prolyl, N-alkyl-L-prolyl, N-alkyl-D-piperidine-2-carbonyl, N-alkyl-L-piperidine-2-carbonyl, N,N-dialkyl-D-2-ethyl-2-phenylglycyl and N,N-dialkyl-L-2-ethyl-2-phenylglycyl, wherein alkyl is methyl, ethyl or isopropyl; and B is a valyl, isoleucyl or 2-t-butyl-L-glycyl residue.

Preferred compounds of the invention include compounds of Formula I wherein r and s are each 0. A is an amino acid derivative selected from among D-N-methyl-piperidine-2-carbonyl, L-N-methyl-piperidine-2-carbonyl, N,N-dimethylamino-isobutyryl, N-methyl-L-prolyl, N-methyl-L-thiazolidine-4-carbonyl, N,N-dimethylglycyl, L-prolyl, L-piperidine-2-carbonyl, N-propyl-D-piperidine-2-carbonyl, D-piperidine-2-carbonyl, N-ethyl-D-piperidine-2-carbonyl, N-methyl-[2,2,5,5-tetramethyl]-L-thiazolidine-2-carbonyl, N-isopropyl-D-piperidine-2-carbonyl, N,N-dimethyl-2-cyclopropylglycyl, N,N-dimethyl-L-2-ethyl-2-phenylglycyl, N,N-dimethyl-D-2-ethyl-2-phenylglycyl, D-prolyl, N-methyl-D-prolyl, N,N-dimethyl-2-(2-fluorophenyl)glycyl, 1-aza-[3,3,0]bicyclooctyl-5-carbonyl, N,N-dimethyl-2-[4-fluoro]phenyl-glycyl, N-methyl-[2,2,5,5-tetramethyl]-thiazolidine-2-carbonyl, 2-(R,S)-ethyl-2-phenylglycyl, D,L-1-aminoindane-1-carbonyl, N,N-dimethyl-2-(R,S)-methyl-2-phenylglycyl, 2-[N,N-dimethylamino]indane-2-carbonyl, 5-[N,N-dimethylamino]-5,6,7,8-tetrahydro-naphthalene-5-carbonyl, N-isopropyl-2-(R,S)-ethyl-2-phenylglycyl, 1-[N,N-dimethylamino]indane-2-carbonyl, N,N-dimethyl-2-propyl-2-phenylglycyl, N,N-dimethyl-2-[4-methoxy]phenyl-glycyl, N-methyl-3-hydroxy-D,L-valyl, N,N-dimethyl-D,L-2-isopropyl-2-phenylglycyl, N-methylpiperidine-2-carbonyl, N-methyl-L-prolyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl,

N-methylazetidine-2-carbonyl, N-isopropylazetidine-2-carbonyl, N,N-dimethyl-[O-methyl]seryl, N,N-dimethyl-[O-methyl]threonyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl, 1-[N,N-dimethylamino]cyclohexyl-1-carbonyl, 1-[N,N-dimethylamino]cyclopentyl-1-carbonyl and 1,2,3,4-tetrahydroisoquinoline-3-carbonyl. B is valyl, isoleucyl or 2-tert-butylglycyl. D is N-methylvalyl, N-methyl-2-t-butylglycyl or N-methylisoleucyl. E and F are each, independently, prolyl, thiaprolyl, homoprolyl, hydroxyprolyl, 3,4-didehydroprolyl, 4-fluoroprolyl, and 3-methylprolyl. L is an alkoxy group or an amino group of the formula R^1_1-N-R^2_1, wherein R^1_1 and R^2_1 are independently selected from the group consisting of hydrogen, alkoxy, hydroxy, alkyl and alkylaryl.

In a particularly preferred subset of the compounds of the invention, r and s are each 0. A is an amino acid derivative selected from among D-N-methyl-piperidine-2-carbonyl, N-ethyl-D-piperidine-2-carbonyl, N-isopropyl-D-piperidine-2-carbonyl, N,N-dimethyl-2-cyclopropyl-glycyl, N-methyl-D-prolyl, 1-aza-[3,3,0]bicyclooctyl-5-carbonyl, N-methyl-[2,2,5,5-tetramethyl]-thiazolidine-2-carbonyl, 2-(R,S)-ethyl-2-phenylglycyl, D,L-1-aminoindane-1-carbonyl, N,N-dimethyl-2-(R,S)-methyl-2-phenylglycyl, 5-[N,N-dimethylamino]-5,6,7,8-tetrahydro-naphthalene-5-carbonyl, 1-[N,N-dimethylamino]indane-2-carbonyl, N,N-dimethyl-2-propyl-2-phenylglycyl, N,N-dimethyl-L-2-ethyl-2-phenylglycyl, N,N-dimethyl-D-2-ethyl-2-phenylglycyl, N-methyl-3-hydroxy-D,L-valyl, N,N-dimethyl-D,L-2-isopropyl-2-phenylglycyl,

N-methyl-piperidine-2-carbonyl, N-methyl-D,L-prolyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl, N-methylazetidine-2-carbonyl, N-isopropylazetidine-2-carbonyl, N,N-dimethyl-[O-methyl]seryl, 1-[N,N-dimethylamino]cyclohexyl-1-carbonyl and 1-[N,N-dimethylamino]cyclopentyl-1-carbonyl. B is valyl; D is N-methylvalyl; and E and F are each prolyl. L is a C_1-C_6-alkoxy group or an amino group of the formula R^1_1-N-R^2_1, wherein R^1_1 and R^2_1 are each independently selected from the group consisting of hydrogen, C_1-C_6-alkoxy, hydroxy, normal, cyclic or branched C_1-C_{12}-alkyl, and phenylalkyl.

Synthetic Methods

The compounds of the present invention can be prepared by known methods of peptide synthesis. Thus, the peptides can be assembled sequentially from individual amino acids or by linking suitable small peptide fragments. In sequential assembly, the peptide chain is extended stepwise, starting at the C-terminus, by one amino acid per step. In fragment coupling, fragments of different lengths can be linked together, and the fragments in turn can be obtained by sequential assembly from amino acids or by fragment coupling of still shorter peptides.

In both sequential assembly and fragment coupling it is necessary to link the units by forming an amide linkage, which can be accomplished via a variety of enzymatic and chemical methods. Chemical methods for forming the amide linkage are described in detail in standard references on peptide chemistry, including Müller, Methoden der organischen Chemie Vol. XV/2, 1-364, Thieme Verlag, Stuttgart, (1974); Stewart and Young, Solid Phase Peptide

Synthesis, 31-34 and 71-82, Pierce Chemical Company, Rockford, IL (1984); Bodanszky *et al.*, Peptide Synthesis, 85-128, John Wiley & Sons, New York, (1976). Preferred methods include the azide method, the symmetric and mixed anhydride method, the use of *in situ* generated or preformed active esters, the use of urethane protected N-carboxy anhydrides of amino acids and the formation of the amide linkage using coupling reagents, such as carboxylic acid activators, especially dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), pivaloyl chloride, 1-ethyl-3- (3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), n-propanephosphonic anhydride (PPA), N,N-bis(2-oxo-oxazolidinyl)amidophosphoryl chloride (BOP-Cl), bromo-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBrop), diphenylphosphoryl azide (DPPA), Castro's reagent (BOP, PyBop), O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU), O-azabenzotriazolyl-N,N,N',N'-tetramethyluronium salts (HATU), diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl-2,3- dihydro-3-oxo-4- hydroxythiophene dioxide (Steglich's reagent; HOTDO), and 1,1'-carbonyldiimidazole (CDI). The coupling reagents can be employed alone or in combination with additives such as N,N-dimethyl-4-aminopyridine (DMAP), N-hydroxy-benzotriazole (HOBt), N-hydroxyazabenzotriazole (HOAt), N-hydroxybenzotriazine (HOOBt), N-hydroxysuccinimide (HOSu) or 2-hydroxypyridine.

Although the use of protecting groups is generally not necessary in enzymatic peptide synthesis, reversible protection of reactive groups not involved in formation of the amide linkage is necessary for both reactants in

chemical synthesis. Three conventional protective group techniques are preferred for chemical peptide synthesis: the benzyloxycarbonyl (Z), the t-butoxycarbonyl (Boc) and the 9-fluorenylmethoxycarbonyl (Fmoc) techniques. Identified in each case is the protective group on the α-amino group of the chain-extending unit. A detailed review of amino-acid protective groups is given by Müller, Methoden der organischen Chemie Vol. XV/1, pp 20-906, Thieme Verlag, Stuttgart (1974). The units employed for assembling the peptide chain can be reacted in solution, in suspension or by a method similar to that described by Merrifield, *J. Am. Chem. Soc.* **85**: (1963) 2149.

Solvents suitable for peptide synthesis include any solvent which is inert under the reaction conditions, especially water, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane (DCM), 1,4-dioxane, tetrahydrofuran (THF), N-methyl-2-pyrrolidone (NMP) and mixtures of these solvents.

Peptide synthesis on the polymeric support can be carried out in a suitable inert organic solvent in which the amino acid derivatives starting materials are soluble. However, preferred solvents additionally have resin-swelling properties, such as DMF, DCM, NMP, acetonitrile and DMSO, and mixtures of these solvents. Following synthesis, the peptide is removed from the polymeric support. The conditions under which this cleavage is accomplished for various resin types are disclosed in the literature. The cleavage reactions most commonly used are acid- or palladium-catalyzed, the former being conducted in, for example, liquid anhydrous hydrogen fluoride, anhydrous trifluoromethanesulfonic acid, dilute or concentrated trifluoroacetic acid, and acetic acid/

dichloromethane/trifluoroethanol mixtures. The latter can be carried out in THF or THF-DCM-mixtures in the presence of a weak base, such as morpholine. Certain protecting groups are also cleaved off under these conditions.

Partial deprotection of the peptide may also be necessary prior to certain derivatization reactions. For example, peptides dialkylated at the N-terminus can be prepared by coupling the appropriate N,N-di- alkylamino acid to the peptide in solution or on the polymeric support, by reductive alkylation of the resin-bound peptide in DMF/1% acetic acid with $NaCNBH_3$ and the appropriate aldehyde or by hydrogenation of the peptide in solution in the presence of the appropriate aldehyde or ketone and Pd/carbon.

The various non-naturally occurring amino acids as well as the various non-amino acid moieties disclosed herein can be obtained from commercial sources or synthesized from commercially available staring materials using methods known in the art. For example, amino acid building blocks with R^1 and R^2 groups can be prepared according to the method described by Wuensch and Weyl, Methoden der Organische Chemie, vol. XV, Springer Verlag: Stuttgart, p. 306 (1974) and references cited therein.

Methods of Use of the Claimed Compounds

In another embodiment, the present invention comprises a method for partially or totally inhibiting formation of, or otherwise treating (e.g., reversing or inhibiting the further development of) solid tumors (e.g., tumors of the lung, breast, colon, prostate, bladder, rectum, or endometrial tumors) or hematological malignancies (e.g., leukemias, lymphomas) in a mammal, for example, a human, by

administering to the mammal a therapeutically effective amount of a compound or a combination of compounds of Formula I. The compound(s) may be administered alone or in a pharmaceutical composition comprising the compound(s) and an acceptable carrier or diluent. Administration can be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means, such as subcutaneously, intravenously, intramuscularly and intraperitoneally, nasally or rectally. The compounds may be administered alone or in the form of pharmaceutical compositions containing a compound or compounds of Formula I together with a pharmaceutically accepted carrier appropriate for the desired route of administration. Such pharmaceutical compositions may be combination products, i.e., they may also contain other therapeutically active ingredients.

The dosage to be administered to the mammal, such as a human, will contain a therapeutically effective amount of a compound described herein. As used herein, "therapeutically effective amount" is an amount sufficient to inhibit (partially or totally) formation of a tumor or a hematological malignancy or to reverse development of a solid tumor or other malignancy or prevent or reduce its further progression. For a particular condition or method of treatment, the dosage is determined empirically, using known methods, and will depend upon factors such as the biological activity of the particular compound employed; the means of administration; the age, health and body weight of the recipient; the nature and extent of the symptoms; the frequency of treatment; the administration of other therapies; and the effect desired. A typical daily dose will be from about 0.05 to about 50 milligrams per

kilogram of body weight by oral administration and from about 0.01 to about 20 milligrams per kilogram of body weight by parenteral administration.

The compounds of the present invention can be administered in conventional solid or liquid pharmaceutical administration forms, for example, uncoated or (film-)coated tablets, capsules, powders, granules, suppositories or solutions. These are produced in a conventional manner. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, sustained release compositions, antioxidants and/or propellant gases (cf. H. Sücker *et al.*: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way typically contain from about 1 to about 90% by weight of the active substance.

The present invention will now be illustrated by the following examples, which are not limiting.

EXAMPLES

The proteinogenous amino acids are abbreviated in the examples using the known three-letter code. Other abbreviations employed are: TFA = trifluoroacetic acid, Ac = acetic acid, DCM = dichloromethane, DMSO = dimethylsulfoxide, Bu = butyl, Et = ethyl, Me = methyl, Bzl = benzyl. In the compounds listed, all proteinogenous amino acids are L-amino acids unless otherwise noted. Other abbreviations used: Me_2Val = N,N-dimethylvaline, MeVal = N-methylvaline, Bn = benzyl, Me_2Aib = [2-N,N-dimethylamino]-isobutyric acid.

General Procedures

The peptides of the invention are synthesized either by classical solution synthesis using standard Z- and Boc-methodology as described above or by standard methods of solid-phase synthesis using Boc and Fmoc protective group techniques.

In the case of solid phase synthesis, the N,N-dialkyl-penta- or hexapeptide acids are liberated from the solid support and further coupled with the corresponding C-terminal amines in solution. BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following the N-methylamino acids. The reaction times were correspondingly increased. For reductive alkylation of the N-terminus, the peptide-resin was deprotected at the N terminus and then reacted with a 3-fold molar excess of aldehyde or ketone in DMF/1% acetic acid with addition of 3 equivalents of $NaCNBH_3$. After the reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert.-butyloxycarbonyl-amino acid-N-carboxy-anhydrides), Z-protected amino acid NCAs (N-benzyloxycarbonyl-amino acid-N-carboxy-anhydrides), or the use of pivaloyl chloride as condensing agent respectively is most advantageous for coupling of the amino acid following the N-methylamino acids. Reductive alkylation of the N terminus can e.g. be achieved by reaction of the N-terminally deprotected peptides or amino acids with the corresponding aldehydes or ketones using $NaCNBH_3$ or hydrogen-Pd/C.

Valyl-N-methylvalyl-prolyl-prolylbenzylamide hydrochloride for example was prepared according to methods disclosed in German Patent Application No. DE 19527575 A1.

Purification and characterization of the peptides

Peptide purification was carried out by gel chromatography (SEPHADEX G-10, G-15/10% HOAc, SEPHADEX LH_20/MeOH), medium pressure chromatography (stationary phase: HD-SIL C-18, 20-45 micron, 100 Angstrom; mobile phase: gradient with A = 0.1% TFA/ MeOH, B = 0.1% TFA/water), preparative HPLC (stationary phase: Waters Delta-Pak C-18, 15 micron, 100 Angstrom; mobile phase: gradient with A = 0.1 % TFA/MeOH, B = 0.1 % TFA/water), or by crystallization.

The purity of the resulting products was determined by analytical HPLC (stationary phase: 100 2.1 mm VYDAC C-18, 5 micron, 300 A; mobile phase: acetonitrile-water gradient, buffered with 0.1% TFA, 40°C; or 3.9 mm VYDAC C-18, 30°C). Characterization was by fast atom bombardment mass spectroscopy and NMR-spectroscopy.

Example 1 Synthesis of [N-Methyl-L-piperidine-2-carbonyl]-Val-MeVal-Pro-Pro-NHBn (Compound 1) and [N-Methyl-D-piperidine-2-carbonyl]-Val-MeVal-Pro-Pro-NHBn (Compound 2)

Preparation of N-methyl-piperidine-2-carboxylic acid

N-Methyl-piperidine-2-carboxylic acid ethyl ester (5.1 g) was dissolved in a mixture of 100 ml methanol and 10 ml water. NaOH (8 g) was added and the reaction mixture was stirred at room temperature overnight. The solution was then neutralized with hydrochloric acid, evaporated to dryness, and evaporated four times with toluene. The resulting powdery residue was used directly in the next step.

Preparation of [N-Methyl-piperidine-2-carbonyl]-Val-MeVal-Pro-Pro-NHBn

The residue prepared as described above (5.05 g) and H-Val-MeVal-Pro-Pro-NHBn x HCl (4.88 g) were dissolved in 50 ml dry DMF. After cooling the solution in an ice bath, 1.52 g DEPCN and 2.66 ml triethylamine were added. The reaction mixture was stirred at 0°C for 2 h and then at room temperature overnight. The DMF was removed by evaporation under reduced pressure. The residue was diluted with dichloromethane and the organic phase was washed with aqueous hydrochloric acid (pH 2) and water, dried over sodium sulfate and evaporated to dryness. The diastereomeric mixture was then separated by flash chromatography with a gradient using heptane/ethyl acetate and dichloromethane/methanol. Under the HPLC conditions

described in the previous section (C-18 reverse phase) isomer 1 has a retention time of 14.9 minutes, and isomer 2 has a retention time of 15.8 minutes. Both isomers were characterized by fast atom bombardment mass spectrometry ([M+H]+ = 639).

Example 2 Preparation of Me_2Aib-Val-MeVal-Pro-Pro-NHBn (Compound 3)

Preparation of 2-[N,N-dimethylamino]-isobutyric acid

2-Amino-isobutyric acid (10.3 g) was dissolved in 200 ml methanol. After addition of 25 ml aqueous formaldehyde and 1 g 10% Pd/C, the reaction mixture was hydrogenated overnight at room temperature. The catalyst was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from isopropanol to give 4.8 g of the desired product.

Preparation of Me_2Aib-Val-MeVal-Pro-Pro-NHBn x HCl

2-[N,N-Dimethylamino]-isobutyric acid (1.3 g, 10 mmol) and 5.5 g (10 mmol) H-Val-MeVal-Pro-Pro-NHBn x HCl were dissolved in 50 ml dry DMF. After cooling to 0°C, 1.6 g DEPCN (10 mmol) and 2.9 ml triethylamine were added to the reaction mixture. The resulting mixture was stirred at 0°C for 2 h and at room temperature overnight. Ice water (50 mL) was then added, and the resulting mixture was extracted twice with diethyl ether. The ether extracts were washed with 1 N NaOH (1x) and aqueous NaCl (3x), then dried over sodium sulfate and evaporated to dryness under reduced pressure. The product was crystallized from 100 ml diethyl ether with HCl/ether, and recrystallized from acetone to give 1.2 g of the desired product, which was characterized by fast atom bombardment mass spectrometry ([M+H]+ = 627).

Example 3 Preparation of [N,N-dimethyl-2-ethyl-2-phenylglycyl]-Val-MeVal-Pro-Pro-NHBn x HCl (Compound 4)

Preparation of [N,N-dimethyl-2-ethyl-2-phenylglycyl]-Val-MeVal-Pro-Pro-NHBn x HCl

2.07 g (10 mmol) N,N-Dimethyl-2-ethyl-2-phenylglycine and 5.5 g (10 mmol) H-Val-MeVal-Pro-Pro-NHBn x HCl were dissolved in 100 ml dry DMF. After cooling to 0°C, 1.6 g DEPCN (10 mmol) and 2.9 ml triethylamine were added. The reaction mixture was stirred at 0°C for 2 h and at room temperature overnight, then worked up as described above. The crude product was crystallized from diethyl ether with HCl/ether to give 4 g of the desired product, which was characterized by fast atom bombardment mass spectrometry ([M+H]+ = 703).

Example 4 Preparation of [N-Methyl-D-Pro]-Val-MeVal-Pro-Pro-NHBn (Compound 5)

Preparation of Z-D-Pro-Val-MeVal-Pro-Pro-NHBn

3.74 g Z-D-Pro-OH (15 mmol, BACHEM) and 8.25 g H-Val-MeVal-Pro-Pro-NHBn x HCl (15 mmol) were dissolved in 80 ml dry DMF. After cooling to 0°C, 2.4 g DEPCN (2.25 ml, 15 mmol) and 4.2 ml triethylamine (30 mmol) were added. The reaction mixture was stirred at 0°C for several hours and room temperature overnight, then the DMF was evaporated under reduced pressure. The residue was diluted with ethyl acetate and thoroughly washed with dilute aqueous HCl (pH 2), water, dilute aqueous NaOH (pH 9-10), and water. The

organic phase was dried over sodium sulfate and evaporated to dryness to yield 9.2 g of the desired protected pentapeptide.

Preparation of D-Pro-Val-MeVal-Pro-Pro-NHBn x HCl

8.2 g (11 mmol) Z-D-Pro-Val-MeVal-Pro-Pro-NHBn was dissolved in 70 ml methanol. After addition of 0.7 ml concentrated hydrochloric acid and 0.3 g 10 % Palladium/charcoal to the solution, the resulting mixture was hydrogenated. Filtration and evaporation of the solvent gave a residue which was dissolved in water, adjusted to pH 2 and extracted twice with ethyl acetate. The aqueous phase was adjusted to pH 9-10 and extracted twice with dichloromethane. The organic extracts were evaporated and the residue was redissolved in diethylether and crystallized by addition of HCl/ether as the hydrochloride salt to give 6.5 g of the desired product.

Preparation of [N-methyl-D-Pro]-Val-MeVal-Pro-Pro-NHBn x HCl

1.94 g (3 mmol) of D-Pro-Val-MeVal-Pro-Pro-NHBn x HCl was dissolved in 30 ml methanol. To this solution was then added 0.3 g 10% Pd/charcoal and 1.5 ml aqueous formaldehyde solution and the reaction mixture was hydrogenated. Following filtration and evaporation of the solvents, the resulting residue was dissolved in water, adjusted to pH 2 and extracted twice with diethyl ether and several additional times with dichloromethane. The aqueous phase was adjusted to pH 9-10 and extracted twice with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated to dryness. The residue was crystallized as the hydrochloride salt to give 0.5 g of the

desired product which was characterized by fast atom bombardment mass spectrometry ([M+H]+ = 625).

The compounds listed in Table 1 were prepared according to the methods described in Examples 1-4. Where compounds are referred to as "isomer 1" or "isomer 2", isomer 1 is the diastereomer with the shorter retention time on the reversed phase analytical HPLC system. Fast atom bombardment-mass spectrometry results for selected compounds are provided in Table 2.

Table 1

Compound No.		
6	Xah Val Xaa Pro Xab	
7	Xai Val Xaa Pro Xab	
8	Xae Val Xaa Pro Xab	
9	Xad Val Xaa Pro Xbr	
10	Xam Val Xaa Pro Xab	
11	Xaw Ile Xaa Pro Xbx	
12	Xao Val Xaa Pro Xab	
13	Xad Val Xaa Pro Xap	
14	Xaq Val Xaa Pro Xab	
15	Xar Val Xaa Pro Xab	
16	Xas Val Xaa Pro Xab	
17	Xat Val Xaa Pro Xab	isomer 1
18	Xat Val Xaa Pro Xab	isomer 2
19	Xaf Val Xaa Pro Xab	
20	Xav Val Xaa Pro Xab	
21	Xag Val Xaa Pro Xab	
22	Xax Val Xaa Pro Xab	isomer 1
23	Xax Val Xaa Pro Xab	isomer 2
24	Xay Val Xaa Pro Xab	
25	Xaz Val Xaa Pro Xab	isomer 1
26	Xaz Val Xaa Pro Xab	isomer 2
27	Xba Val Xaa Pro Xab	
28	Xbb Val Xaa Pro Xab	
29	Xbc Val Xaa Pro Xab	

Table 1

Compound No.					
30	Xbd	Val	Xaa	Pro	Xab isomer 1
31	Xbd	Val	Xaa	Pro	Xab isomer 2
32	Xbe	Val	Xaa	Pro	Xab isomer 1
33	Xbe	Val	Xaa	Pro	Xab isomer 2
34	Xbf	Val	Xaa	Pro	Xab isomer 1
35	Xbg	Val	Xaa	Pro	Xab
36	Xbh	Val	Xaa	Pro	Xab isomer 1
37	Xbh	Val	Xaa	Pro	Xab isomer 2
38	Xbi	Val	Xaa	Pro	Xab isomer 1
39	Xbi	Val	Xaa	Pro	Xab isomer 2
40	Xbk	Val	Xaa	Pro	Xab isomer 1
41	Xbk	Val	Xaa	Pro	Xab isomer 2
42	Xbl	Val	Xaa	Pro	Xab
43	Xbf	Val	Xaa	Pro	Xab isomer 2
44	Xbm	Val	Xaa	Pro	Xab
45	Xaw	Val	Xaa	Pro	Xbn
46	Xbo	Val	Xaa	Pro	Xbn isomer 1
47	Xbo	Val	Xaa	Pro	Xbn isomer 2
48	Xaw	Val	Xaa	Pro	Xbp
49	Xbo	Val	Xaa	Pro	Xbp isomer 1
50	Xbo	Val	Xaa	Pro	Xbp isomer 2
51	Xaw	Val	Xaa	Pro	Xbq
52	Xaw	Val	Xaa	Pro	Xbr
53	Xbs	Val	Xaa	Pro	Xbt isomer 1
54	Xbl	Val	Xaa	Pro	Xab isomer 1
55	Xbl	Val	Xaa	Pro	Xab isomer 2
56	Xbu	Val	Xaa	Pro	Xab isomer 1
57	Xbv	Val	Xaa	Pro	Xab
58	Xbw	Val	Xaa	Pro	Xab isomer 1
59	Xbw	Val	Xaa	Pro	Xab isomer 2
60	Xbs	Val	Xaa	Pro	Xbt isomer 2
61	Xbu	Val	Xaa	Pro	Xab isomer 2
62	Xbo	Val	Xaa	Pro	Xbr isomer 1
63	Xbo	Val	Xaa	Pro	Xbr isomer 2
64	Xbo	Val	Xaa	Pro	Xbq isomer 1
65	Xbo	Val	Xaa	Pro	Xbq isomer 2
66	Xaw	Val	Xaa	Pro	Xbx

Table 1

Compound No.	
67	Xby Val Xaa Pro Xab
68	Xbz Val Xaa Pro Xab
69	Xca Val Xaa Pro Xab isomer 1
70	Xca Val Xaa Pro Xab isomer 2
71	Xbo Val Xaa Pro Xbx isomer 1
72	Xbo Val Xaa Pro Xbx isomer 2
73	Xau Val Xaa Pro Xbp
74	Xau Val Xaa Pro Xbx
75	Xbi Val Xaa Pro Xbx isomer 2
76	Xau Val Xaa Pro Xab isomer 1
77	Xau Val Xaa Pro Xab isomer 2
78	Xau Val Xaa Pro Xcb
79	Xbi Val Xaa Pro Xcb isomer 1
80	Xbi Val Xaa Pro Xcb isomer 2
81	Xbi Val Xaa Pro Xcc isomer 1
82	Xbi Val Xaa Pro Xcc isomer 2
83	Xbi Val Xaa Pro Xcd
84	Xbk Val Xaa Pro Xcc isomer 1
85	Xbk Val Xaa Pro Xcc isomer 2
86	Xax Val Xaa Pro Xbp isomer 1
87	Xax Val Xaa Pro Xbp isomer 2
88	Xbk Val Xaa Pro Xcb isomer 1
89	Xbk Val Xaa Pro Xcb isomer 2
90	Xau Val Xaa Pro Xcc
91	Xau Val Xaa Pro Xcd
92	Xba Val Xaa Pro Xcb isomer 1
93	Xba Val Xaa Pro Xcb isomer 2
94	Xbo Val Xaa Pro Xbp isomer 1
95	Xbo Val Xaa Pro Xbp isomer 2
96	Xau Val Xaa Pro Xbp isomer 1
97	Xau Val Xaa Pro Xbp isomer 2
98	Xbi Val Xaa Pro Xcd isomer 2
99	Xbk Val Xaa Pro Xcd
100	Xba Val Xaa Pro Xbp isomer 1
101	Xba Val Xaa Pro Xbp isomer 2
102	Xba Val Xaa Pro Xcc isomer 1

Table 1

Compound No.					
103	Xba	Val	Xaa	Pro	Xcc isomer 2
104	Xba	Val	Xaa	Pro	Xcd
105	Xce	Val	Xaa	Pro	Xab
106	Xcf	Val	Xaa	Pro	Xab
107	Xcg	Val	Xaa	Pro	Xab isomer 1
108	Xcg	Val	Xaa	Pro	Xab isomer 2
109	Xaw	Val	Xaa	Pro	Xch
110	Xaw	Val	Xaa	Pro	Xci
111	Xaw	Val	Xaa	Pro	Xck
112	Xaw	Val	Xaa	Pro	Xcl
113	Xaw	Val	Xaa	Pro	Xcm
114	Xaw	Val	Xaa	Pro	Xcn
115	Xaw	Val	Xaa	Pro	Xco
116	Xaw	Val	Xaa	Pro	Xcp
117	Xaw	Val	Xaa	Pro	Xcq
118	Xaw	Val	Xaa	Pro	Xcr
119	Xad	Val	Xaa	Pro	Xch
120	Xad	Val	Xaa	Pro	Xci
121	Xad	Val	Xaa	Pro	Xck
122	Xad	Val	Xaa	Pro	Xcl
123	Xad	Val	Xaa	Pro	Xcm
124	Xad	Val	Xaa	Pro	Xcn
125	Xad	Val	Xaa	Pro	Xco
126	Xad	Val	Xaa	Pro	Xcp
127	Xad	Val	Xaa	Pro	Xcq
128	Xad	Val	Xaa	Pro	Xcr
129	Xad	Val	Xaa	Pro	Xbx
130	Xau	Val	Xaa	Pro	Xch
131	Xau	Val	Xaa	Pro	Xci
132	Xau	Val	Xaa	Pro	Xck
133	Xau	Val	Xaa	Pro	Xcl
134	Xau	Val	Xaa	Pro	Xcm
135	Xau	Val	Xaa	Pro	Xcn
136	Xau	Val	Xaa	Pro	Xco
137	Xau	Val	Xaa	Pro	Xcp
138	Xau	Val	Xaa	Pro	Xcq
139	Xau	Val	Xaa	Pro	Xcr

Table 1

Compound No.					
140	Xau	Val	Xaa	Pro	Xbr
141	Xad	Val	Xaa	Xal	Xbx
142	Xau	Val	Xaa	Xal	Xbx
143	Xaw	Val	Xaa	Xal	Xbx
144	Xad	Val	Xaa	Xal	Xch
145	Xau	Val	Xaa	Xal	Xch
146	Xaw	Val	Xaa	Xal	Xch
147	Xad	Val	Xaa	Xal	Xcr
148	Xau	Val	Xaa	Xal	Xcr
149	Xaw	Val	Xaa	Xal	Xcr
150	Xad	Val	Xaa	Xan	Xbx
151	Xau	Val	Xaa	Xan	Xbx
152	Xaw	Val	Xaa	Xan	Xbx
153	Xad	Val	Xaa	Xan	Xch
154	Xau	Val	Xaa	Xan	Xch
155	Xaw	Val	Xaa	Xan	Xch
156	Xad	Val	Xaa	Xan	Xcr
157	Xau	Val	Xaa	Xan	Xcr
158	Xaw	Val	Xaa	Xan	Xcr
159	Xau	Ile	Xaa	Pro	Xbx
160	Xad	Ile	Xaa	Pro	Xbx
161	Xaw	Ile	Xaa	Pro	Xch
162	Xad	Ile	Xaa	Pro	Xch
163	Xau	Ile	Xaa	Pro	Xch
164	Xaw	Xcs	Xaa	Pro	Xch
165	Xad	Xcs	Xaa	Pro	Xch
166	Xau	Xcs	Xaa	Pro	Xch
167	Xaw	Xcs	Xaa	Pro	Xbx
168	Xad	Xcs	Xaa	Pro	Xbx
169	Xau	Xcs	Xaa	Pro	Xbx
170	Xaw	Val	Xct	Pro	Xch
171	Xad	Val	Xct	Pro	Xch
172	Xau	Val	Xct	Pro	Xch
173	Xaw	Val	Xct	Pro	Xbx

Table 1

Compound No.	
174	Xad Val Xct Pro Xbx
175	Xau Val Xct Pro Xbx

The symbols Xaa in Table 1 represent the following amino acids or residues thereof:

Xaa: N-methyl-valine

Xab: Prolyl N-benzylamide

Xac: L-N-methyl-piperidine-2-carboxylic acid

Xad: D-N-methyl-piperidine-2-carboxylic acid

Xae: N-methyl-L-proline

Xaf: N-methyl-L-thiazolidine-4-carboxylic acid

Xag: N,N-dimethylglycine

Xah: L-proline

Xai: L-piperidine-2-carboxylic acid

Xak: 2-[N,N-dimethylamino]-isobutyric acid

Xal: L-thiazolidine-4-carboxylic acid

Xam: N-propyl-D-piperidine-2-carboxylic acid

Xan: L-3,4-didehydroproline

Xao: D-piperidine-2-carboxylic acid

Xap: proline tert.butylester

Xaq: N-ethyl-D-piperidine-2-carboxylic acid

Xar: N-methyl-[2,2,5,5-tetramethyl]-L-thiazolidine-2-carboxylic acid

Xas: N-isopropyl-D-piperidine-2-carboxylic acid

Xat: N,N-dimethyl-2-cyclopropyl-glycine

Xau: N,N-dimethyl-2-ethyl-2-phenyl-glycine

Xav: D-proline

Xaw: N-methyl-D-proline

Xax: N,N-dimethyl-2-[2-fluoro]phenyl-glycine

Xay: 1-aza-[3,3,0]bicyclooctyl-5-carboxylic acid

Xaz: N,N-dimethyl-2-[4-fluoro]phenyl-glycine

Xba: N-methyl-[2,2,5,5-tetramethyl]-thiazolidine-2-carboxylic acid

Xbb: 2-(R,S)-ethyl-2-phenyl-glycine

Xbc: D,L-1-aminoindane-1-carboxylic acid

Xbd: N,N-dimethyl-2-(R,S)-methyl-2-phenyl-glycine

Xbe: 2-[N,N-dimethylamino]indane-2-carboxylic acid

Xbf: 5-[N,N-dimethylamino]-5,6,7,8-tetrahydro-naphthalene-5-carboxylic acid

Xbg: N-isopropyl-2-(R,S)-ethyl-2-phenyl-glycine

Xbh: 1-[N,N-dimethylamino]indane-2-carboxylic acid

Xbi: N,N-dimethyl-2-propyl-2-phenyl-glycine

Xbk: N,N-dimethyl-2-[4-methoxy]phenyl-glycine

Xbl: N-methyl-3-hydroxy-D,L-valine

Xbm: N,N-dimethyl-D,L-2-isopropyl-2-phenyl-glycine

Xbn: proline-N-methoxy-N-methyl-amide

Xbo: N-methyl-piperidine-2-carboxylic acid

Xbp: proline-isopropylamide

Xbq: proline-isoxazolidinyl

Xbr: proline-N-methoxy-N-benzylamide

Xbs: N-methyl-D,L-proline

Xbt: proline-[5-phenyl]isoxazolidinyl

Xbu: N-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid

Xbv: N-methyl-azetidine-2-carboxylic acid

Xbw: N-isopropyl-azetidine-2-carboxylic acid

Xbx: proline-tert-butylamide

Xby: N,N-dimethyl-[O-methyl]serine

Xbz: N,N-dimethyl-[O-methyl]threonine

Xca: N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Xcb: proline-pentyl(3)amide

Xcc: proline-(R)-phenethylamide

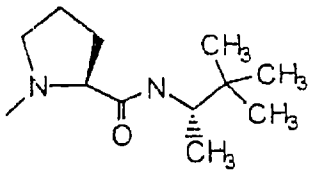
Xcd: proline-(S)-phenethylamide

Xce: 1-[N,N-dimethylamino]cyclohexyl-1-carboxylic acid

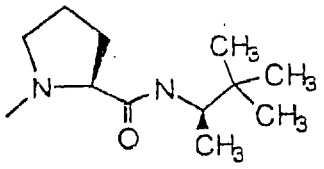
Xcf: 1-[N,N-dimethylamino]cyclopentyl-1-carboxylic acid

Xcg: 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

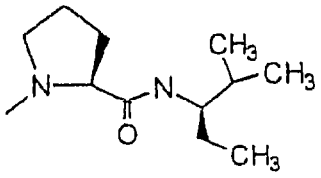
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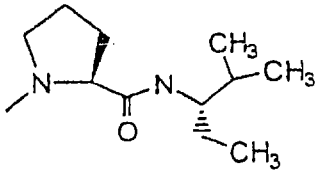
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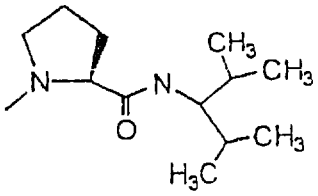
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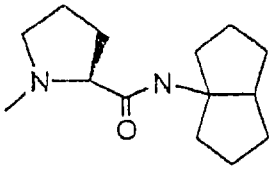
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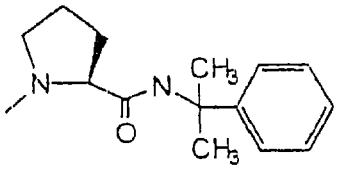
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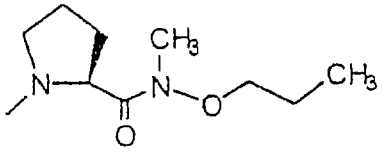
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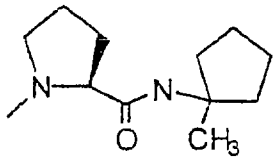


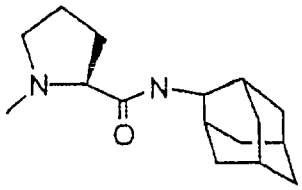
Xco:



Xcp:



Xcq: 

Xcr: 

Xcs: L-2-tert-butyl-glycine

Xct: N-methyl-L-Isoleucine

Table 2: Results of FAB-MS analysis of selected compounds

Compound No.	Mol. weight measured
1	639
2	639
3	627
4	703
5	625
6	611
7	625
8	625
10	667
12	625
13	606
14	653
15	699
16	667
17	639
18	639
19	643
20	611
21	599
22	693
23	693

Compound No.	Mol. weight measured
24	651
25	693
26	693
27	699
28	675
29	673
30	689
31	689
32	701
33	701
34	715
35	717
36	701
37	701
38	717
39	717
40	705
41	705
42	643
43	715
44	703
45	579
46	593
47	593
48	577
49	591
50	591
51	591
52	655
53	667
54	657
55	657
56	687
57	611
58	639
59	639
60	667
61	687
62	669
63	669
64	605
65	605

Compound No.	Mol. weight measured
66	591
67	643
68	657
69	687
70	687
71	605
72	605
73	655
74	669
75	683
76	703
77	703
78	683
79	697
80	697
81	731
82	731
83	731
84	719
85	719
86	645
87	645
88	685
89	685
90	717
91	717
92	679
93	679
94	591
95	591
96	655
97	655
98	731
99	719
100	651
101	651
102	713
103	713
104	713
105	666
106	653
107	687

Compound No.	Mol. weight measured
108	687

Example 5 Evaluation of Biological Activity

In vitro Methodology

Cytotoxicity was measured using a standard methodology for adherent cell lines, such as the microculture tetrazolium assay (MTT). Details of this assay have been published (Alley, M.C. *et al.*, *Cancer Research* 48: 589-601, (1988)). Exponentially growing cultures of HT-29 colon carcinoma cells were used to make microtiter plate cultures. Cells were seeded at 5000-20,000 cells per well in 96-well plates (in 150 mL of media), and grown overnight at 37°C. Test compounds were added, in 10-fold dilutions varying from 10^{-4} M to 10^{-10} M. Cells were then incubated for 48 hours. To determine the number of viable cells in each well, the MTT dye was added (50 mL of a 3 mg/mL solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide in saline). This mixture was incubated at 37°C for 5 hours, and then 50 mL of 25% SDS, pH 2, was added to each well. After an overnight incubation, the absorbance of each well at 550 nm was read using an ELISA reader. The values for the mean +/- SD of data from replicated wells were calculated, using the formula % T/C (% viable cells treated/control). The concentration of test compound which gives a T/C of 50% growth inhibition was designated as the IC_{50}.

Table 3 presents the IC_{50} values determined in the HT-29 assay for a series of compounds of the invention.

Table 3

Compound No.	HT-29 [IC_{50}]
1	4.7×10^{-8}
2	6.8×10^{-10}
3	3.5×10^{-8}
4	1.2×10^{-9}
5	5.0×10^{-9}
8	5.1×10^{-7}
10	1.3×10^{-7}
12	3.7×10^{-7}
13	1.0×10^{-9}
14	1.5×10^{-9}
15	1.7×10^{-7}
16	7.3×10^{-10}
17	6.3×10^{-8}
18	8.8×10^{-9}
22	6.4×10^{-7}
24	2.8×10^{-8}
27	3.7×10^{-8}
28	4.9×10^{-8}
29	3.6×10^{-8}
30	6.1×10^{-9}
31	2.0×10^{-7}
32	8.5×10^{-7}
33	1.2×10^{-6}
34	5.0×10^{-9}

Compound No.	HT-29 [IC_{50}]
35	1.4×10^{-7}
36	6.2×10^{-9}
37	1.9×10^{-7}
38	7.3×10^{-7}
39	2.5×10^{-8}
40	5.6×10^{-7}
41	7.3×10^{-6}
42	3.4×10^{-7}
43	5.9×10^{-8}
44	4.8×10^{-8}
45	5.6×10^{-8}
46	7.2×10^{-7}
47	2.3×10^{-8}
48	2.5×10^{-8}
49	8.8×10^{-8}
50	8.9×10^{-8}
51	4.6×10^{-8}
52	3.4×10^{-7}
53	5.0×10^{-9}
54	4.2×10^{-9}
55	5.6×10^{-8}
57	2.5×10^{-8}
58	6.3×10^{-8}
59	1.9×10^{-7}
60	1.8×10^{-9}

Compound No.	HT-29 [IC_{50}]
62	9.9×10^{-8}
63	5.6×10^{-8}
64	1.7×10^{-6}
65	9.7×10^{-8}
66	3.4×10^{-7}
67	3.4×10^{-7}
68	4.2×10^{-7}
70	7.1×10^{-6}
72	1.2×10^{-7}
73	1.4×10^{-9}
74	5.1×10^{-8}
75	8.5×10^{-7}
76	2.3×10^{-10}
77	7.2×10^{-9}
78	4.3×10^{-9}
79	1.7×10^{-6}
80	6.7×10^{-8}
81	1.3×10^{-7}
82	1.1×10^{-8}
83	1.3×10^{-7}
84	1.2×10^{-6}
85	9.5×10^{-6}
90	9.3×10^{-10}
91	8.3×10^{-10}
92	1.5×10^{-6}

Compound No.	HT-29 [IC_{50}]
93	1.8×10^{-6}
94	3.0×10^{-6}
95	1.1×10^{-8}
96	1.7×10^{-9}
97	3.2×10^{-8}
98	6.0×10^{-9}
99	3.8×10^{-6}
100	2.3×10^{-6}
101	2.1×10^{-6}
102	1.2×10^{-7}
103	1.1×10^{-7}
104	3.5×10^{-6}
105	1.8×10^{-8}
106	9.7×10^{-8}
108	7.1×10^{-6}

In vivo Methodology

Compounds of this invention may be further tested in any of the various preclinical assays for *in vivo* activity which are indicative of clinical utility. Such assays are conducted with nude mice into which tumor tissue, preferably of human origin, has been transplanted ("xenografted"), as is well known in this field. Test compounds are evaluated for their anti-tumor efficacy following administration to the xenograft-bearing mice.

More specifically, human tumors grown in athymic nude mice can be transplanted into new recipient animals, using

tumor fragments which are about 50 mg in size. The day of transplantation is designated as day 0. Six to ten days later, the mice are treated with the test compounds given as an intravenous or intraperitoneal injection, in groups of 5-10 mice at each dose. Compounds are given daily for 5 days, 10 days or 15 days, at doses from 10-100 mg/kg body weight. Tumor diameters and body weights are measured twice weekly. Tumor masses are calculated using the diameters measured with Vernier calipers, and the formula:

$$(\text{length} \times \text{width}^2) / 2 = \text{mg of tumor weight}$$

Mean tumor weights are then calculated for each treatment group, and T/C values are determined for each group relative to the untreated control tumors.

The compounds provided as examples herein correspond to the SEQ ID NOs. as follows: SEQ ID NO: 1: compounds 1-4, 7, 9, 10, 12-19, 22-44, 46, 47, 49, 50, 54-59, 61-65, 67-108, 119-142, 144, 145, 147, 148, 150, 151, 153, 154, 156, 157, 159, 160, 162, 163, 165, 166, 168, 169, 171, 172, 174, 175; SEQ ID NO: 2: compounds 5, 6, 8, 20, 45, 48, 51-53, 60, 66, 109-118, 143, 146, 149, 152, 155, 158, 161, 167, 170, 173; SEQ ID NO: 3: compound 11; SEQ ID NO: 4: compound 21.

EQUIVALENTS

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

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CLAIMS

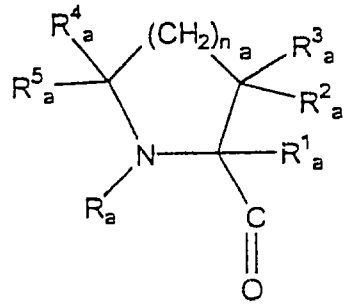
We claim:

1. A compound of the formula

$$A\text{-}B\text{-}D\text{-}E\text{-}F\text{-}(G)_r\text{-}(K)_s\text{-}L,$$

wherein

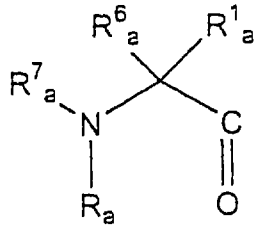
A is a proline derivative of Formula II_a,



(II_a),

wherein n_a is 0 to 3; R_a is hydrogen, or unsubstituted or fluorine-substituted normal, branched or cyclic C_1-C_3-alkyl; R^1_a is hydrogen, C_1-C_3-alkyl, phenyl, or substituted phenyl; or R_a and R^1_a together form a propylene bridge; and R^2_a, R^3_a, R^4_a and R^5_a are each, independently, hydrogen or alkyl; or

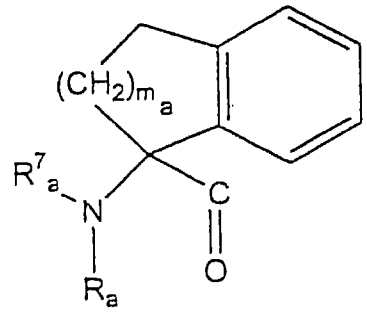
an α-amino acid derivative of Formula III_a,



(III_a),

wherein R_a is hydrogen or unsubstituted or fluorine-substituted C_1-C_3-alkyl; R^1_a is C_1-C_4-alkyl; R^6_a is alkyl, substituted alkyl, alkenyl, phenyl or substituted phenyl; or R^1_a is an alkyl group and R^6_a is C_1-C_6-alkyl, cycloalkylmethyl, benzyl or substituted benzyl; and R^7_a is hydrogen or alkyl; or

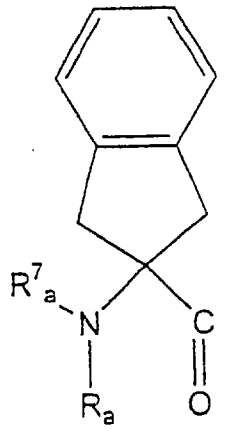
an α-amino acid derivative of Formula IV_a,



(IV_a),

wherein m_a is 1 or 2; R^7_a is hydrogen or alkyl; R_a is hydrogen, or unsubstituted or fluorine-substituted alkyl; or

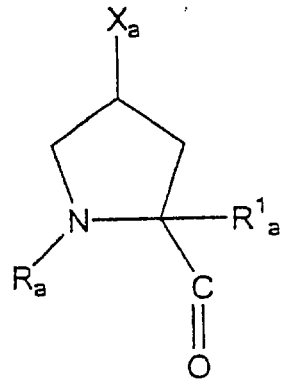
an α-amino acid derivative of Formula V_a,



(V_a),

wherein R^7_a is hydrogen or alkyl and R_a is hydrogen, or unsubstituted or fluorine-substituted alkyl; or

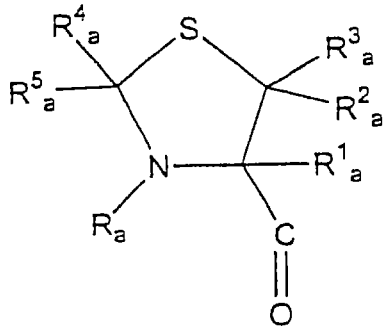
an α-amino acid of Formula VI_a,



(VI_a),

wherein R_a is hydrogen, or unsubstituted or fluorine-substituted alkyl; R^1_a is hydrogen, alkyl, phenyl, or substituted phenyl; or R_a and R^1_a together form a propylene bridge; and X_a is hydroxy, alkoxy or fluorine; or

an α-amino acid of Formula VII_a,

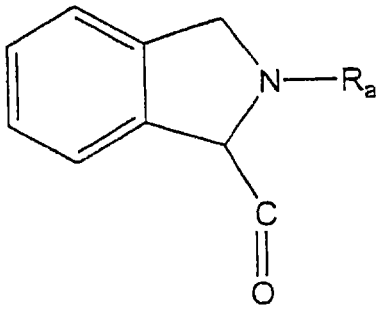


(VII_a),

wherein R_a is hydrogen, or unsubstituted or

fluorine-substituted alkyl; R^1_a is hydrogen, alkyl, phenyl, or substituted phenyl; or R_a and R^1_a together form a propylene bridge; and R^2_a, R^3_a, R^4_a and R^5_a are each, independently, hydrogen or alkyl; or

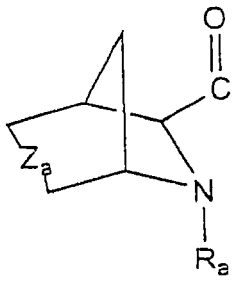
an α-amino acid residue of Formula $VIII_a$,



($VIII_a$),

wherein R_a is hydrogen, or unsubstituted or fluorine-substituted alkyl; or

a 2-azabicyclo[2.2.1]heptane-3-carboxylic acid derivative of Formula IX_a,

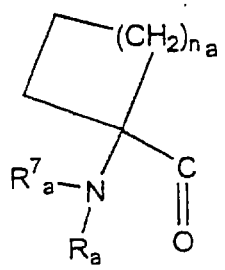


(IX_a),

wherein the 3-carbonyl moiety is in the endo or exo position, Z_a is a single bond or a double bond, and R_a is hydrogen or

unsubstituted or fluorine-substituted alkyl; or

an α-amino acid residue of Formula X_a,

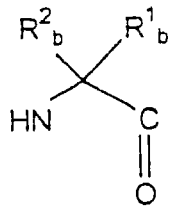


(X_a)

wherein n_a is 1, 2 or 3, and R^7_a is hydrogen or alkyl and R_a is hydrogen, unsubstituted alkyl or fluorine-substituted alkyl;

B is a valyl, isoleucyl, allo-isoleucyl, norvalyl,
2-tert-butylglycyl or 2-ethylglycyl residue; or

an α-amino acid residue of Formula II_b,



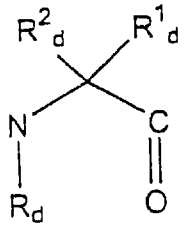
(II_b),

wherein R^1_b is hydrogen, and R^2_b is alkyl or alkenyl; or R^1_b and R^2_b together form an isopropylidene group;

07 MAR 2005

D is an N-alkylvalyl, N-alkyl-2-ethylglycyl, N-alkyl-2-tert-butylglycyl, N-alkylnorleucyl, N-alkylisoleucyl, N-alkyl-allo-isoleucyl or N-alkylnorvalyl residue; or

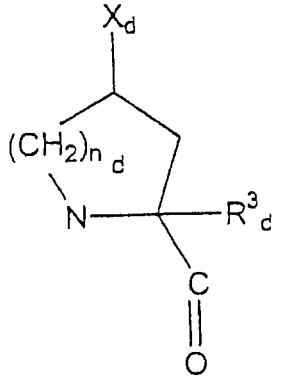
an α-amino acid residue of Formula II_d,



(II_d),

wherein R_d is hydrogen, or unsubstituted or fluorine-substituted alkyl; R^1_d is hydrogen; and R^2_d is alkyl, substituted alkyl or alkenyl; or R^1_d and R^2_d together form an isopropylidene group; or

an α-amino acid residue of Formula III_d,



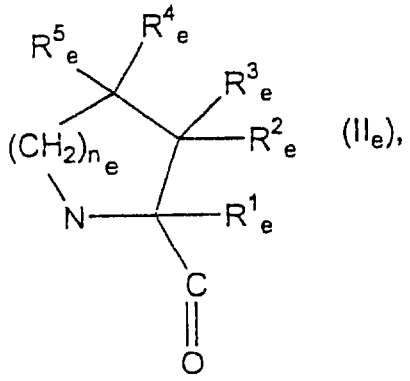
(III_d),

wherein n_d is 1 or 2; R^3_d is hydrogen, alkyl or fluorine-substituted alkyl; and X_d is hydrogen; or n_d is 1 and X_d is fluorine, hydroxy,

methoxy, or ethoxy;

E is a prolyl, thiazolidinyl-4-carbonyl, homoprolyl,or hydroxyprolyl residue; or

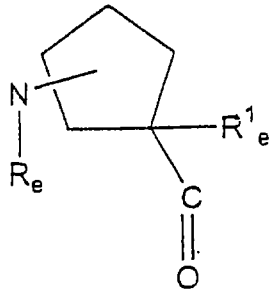
an α-amino acid residue of Formula II_e,



(II_e),

wherein n_e is 0, 1 or 2, R^1_e is hydrogen, or unsubstituted or fluorine-substituted alkyl; R^2_e and R^3_e are each, independently, hydrogen or alkyl; R^4_e is hydrogen, hydroxy or alkoxy; and R^5_e is hydrogen or fluorine; or n_e is 1 and R^3_e and R^4_e together form a double bond; or n_e is 1 and R^4_e and R^5_e together form a double-bonded oxygen diradical; or n_e is 1 or 2 and R^1_e and R^2_e together form a double bond; or

an aminocyclopentanecarboxylic acid residue of Formula III_e,

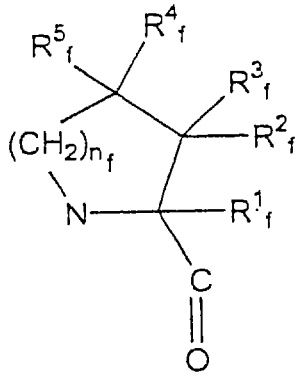


(III_e),

wherein R_e is alkyl and R^1_e is hydrogen, or unsubstituted or fluorine-substituted alkyl;

F is a prolyl, thiazolidinyl-4-carbonyl, homoprolyl or hydroxyprolyl residue; or

an α-amino acid residue of Formula II_f,

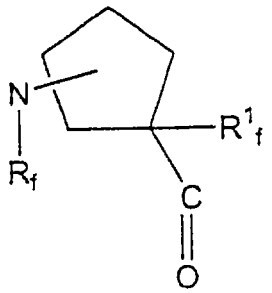


(II_f),

wherein n_f is 0, 1 or 2, R^1_f is hydrogen, or unsubstituted or fluorine-substituted alkyl; R^2_f and R^3_f are each, independently, hydrogen or methyl; R^4_f is hydrogen, hydroxy, alkoxy, or fluorine; R^5_f is hydrogen or fluorine; or n_f is 1 and R^2_f and R^4_f together form a double bond;

or n_f is 1 and R^4_f and R^5_f together form a double-bonded oxygen diradical; or n_f is 1 or 2 and R^1_f and R^2_f together form a double bond; or

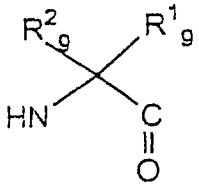
a 2- or 3-aminocyclopentanecarboxylic acid residue of Formula III_f,



(III_f),

wherein R_f is alkyl and R^1_f is hydrogen, or unsubstituted or fluorine-substituted alkyl; or an N-alkylglycyl or N-alkylalanyl residue;

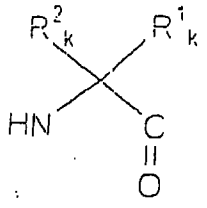
G is an α-amino acid residue of Formula II_g,



(II_g),

wherein R^1_g is hydrogen or alkyl and R^2_g is hydrogen, alkyl, arylalkyl, heteroarylalkyl, phenyl or substituted phenyl; or R^1_g and R^2_g, together with the α-carbon atom, form a C_5-C_6 ring or a benzo-fused C_5 ring;

K is an α-amino acid of Formula II_k,



(II_k),

wherein R^1_k is hydrogen, or alkyl; and R^2_k is hydrogen, alkyl, arylalkyl, heteroarylalkyl, phenyl or substituted phenyl; or R^1_g and R^2_g, together with the α-carbon atom, form a cyclopentane ring or a benzo-fused cyclopentane ring;

L is a substituted or unsubstituted amino, hydrazido, aminoxy or oximato group; and

r and s are, independently 0 or 1, provided that when s and r are each 0 and A is of formula II_a where n_a is 0 or 1 and R^1_a, R^2_a, R^3_a, R^4_a, and R^5_a are each hydrogen, L is a substituted or unsubstituted amino or hydrazido group.

2. The compound of Claim 1 wherein A is a proline derivative of Formula II_a; R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl; R^1_a is hydrogen, methyl, ethyl, propyl, phenyl, or substituted phenyl, wherein the phenyl substituents comprise one or more alkyl, alkoxy, trifluoromethyl or nitro groups; or Ra and R1a together form a propylene bridge; and R^2_a, R^3_a, R^4_a and R^5_a are each, independently, hydrogen or methyl.

3. The compound of Claim 1 wherein A is an α-amino acid residue of Formula III_a, wherein R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl,

1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl; R^1_a is a C_1-C_3-alkyl group; R^6_a is methoxymethyl, 1-methoxyethyl, vinyl, 1-methylvinyl, 1-trifluoromethylvinyl, 1-trifluoromethylethyl, 1-trifluoromethyl-2,2,2-trifluoroethyl, 1,1-dimethylhydroxymethyl, phenyl or substituted phenyl, wherein the phenyl substituents comprise one or more halogen atoms or one or more C_1-C_4-alkyl, methoxy, trifluoromethyl or nitro groups; or R^1_a is C_1-C_3-alkyl and R^6_a is C_1-C_6-alkyl, cycloalkylmethyl, benzyl or substituted benzyl, wherein the benzyl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl, methoxy, ethoxy, trifluoromethyl or nitro groups; and R^7_a is methyl, ethyl or isopropyl.

4. The compound of Claim 1 wherein A is an α-amino acid residue of Formula IV_a, wherein R^7_a is methyl, ethyl or isopropyl; and R_a is hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl.

5. The compound of Claim 1 wherein A is an α-amino acid residue of Formula V_a, wherein R^7_a is methyl, ethyl or isopropyl and R_a is hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl.

6. The compound of Claim 1 wherein A is an α-amino

acid residue of Formula VI_a, wherein R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl; R^1_a is hydrogen, methyl, ethyl, propyl, phenyl, or substituted phenyl, wherein the phenyl substituents comprise one or more alkyl, alkoxy, trifluoromethyl or nitro groups; or R_a and R^1_a together form a propylene bridge; and X_a is a hydroxy, methoxy, or ethoxy group, or a fluorine atom.

7. The compound of Claim 1 wherein A is an α-amino acid residue of Formula VII_a, wherein R_a is hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl; R^1_a is hydrogen, methyl, ethyl, propyl, phenyl, or substituted phenyl, wherein the phenyl substituents comprise one or more alkyl, alkoxy, trifluoromethyl or nitro groups; or R_a and R^1_a together form a propylene bridge; and R^2_a, R^3_a, R^4_a and R^5_a are each, independently, hydrogen or methyl.

8. The compound of Claim 1 wherein A is an α-amino acid residue of Formula $VIII_a$, wherein R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl.

9. The compound of Claim 1 wherein A is an amino acid residue of Formula IX_a, wherein R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl.

10. The compound of Claim 1 wherein A is an α-amino acid residue of Formula X_a, wherein R^7_a is methyl, ethyl or isopropyl and R_a is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-2-fluoroethyl, 1-fluoromethyl-2-fluoroethyl, or 1-methyl-2-fluoroethyl.

11. The compound of Claim 1 wherein B is a residue of Formula II_b, wherein R^1_b is hydrogen and R^2_b is cyclopropyl, n-butyl, isobutyl, tertiary butyl, methoxymethyl, 1-methoxyethyl, or 1-methylvinyl.

12. The compound of Claim 1 wherein D is an N-alkylvalyl residue, an N-alkyl-2-ethylglycyl residue, an N-alkyl-2-tert-butylglycyl residue, an N-alkylnorleucyl residue, an N-alkylisoleucyl residue, an N-alkyl-allo-isoleucyl residue or an N-alkylnorvalyl residue, wherein the N-alkyl group is methyl or ethyl.

13. The compound of Claim 1 wherein D is an α-amino acid residue of Formula II_d, R^1_d is hydrogen and R^2_d is cyclopropyl, methoxymethyl, 1-methoxyethyl, or 1-methylvinyl.

14. The compound of Claim 1 wherein D is an α-amino acid residue of Formula III_d, wherein R^3_d is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2,-trifluoroethyl, 1-methyl-2-fluoroethyl, or 1-fluoromethyl-2-fluoroethyl; and X_d is a hydrogen atom; or n_d is 1 and X_d is a fluorine atom, or a hydroxy, methoxy, or ethoxy group.

15. The compound of Claim 1 wherein E is an α-amino acid residue of Formula II_e, and R^1_e is hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2,-trifluoroethyl, 1-methyl-2-fluoroethyl, or 1-fluoromethyl-2-fluoroethyl; R^2_e and R^3_e are each, independently, hydrogen or methyl; R^4_e is a hydrogen atom or a hydroxy, methoxy or ethoxy group;

and R^5_e is hydrogen or fluorine; or n_e is 1 and R^3_e and R^4_e together form a double bond; or n_e is 1 and R^4_e and R^5_e together form a double-bonded oxygen diradical; or n_e is 1 or 2 and R^1_e and R^2_e together form a double bond.

16. The compound of Claim 1 wherein E is an aminocyclopentanecarboxylic acid residue of Formula III_e, wherein R_e is methyl or ethyl group and R^1_e is hydrogen, or methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2,-trifluoroethyl, 1-methyl-2-fluoroethyl, or 1-fluoromethyl-2-fluoroethyl.

17. The compound of Claim 1 wherein F is an α-amino acid residue of Formula II_f, wherein R^1_f is a hydrogen atom, or methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2,-trifluoroethyl, 1-methyl-2-fluoroethyl, or 1-fluoromethyl-2-fluoroethyl; R^2_f is a hydrogen atom or a methyl group; R^3_f is a hydrogen atom or a methyl group; R^4_f is a hydrogen atom, a hydroxy, methoxy, ethoxy, or a fluorine atom; R^5_f is a hydrogen atom or a fluorine atom; or n_f is 1 and R^3_f and R^4_f together form a double bond; or n_f is 1 and R^4_f and R^5_f together form a double-bonded oxygen radical; or n_f is 1 or 2 and R^1_f and R^2_f together form a double bond.

18. The compound of Claim 1 wherein F is a 2- or 3-aminocyclopentanecarboxylic acid residue of Formula III_f, wherein R_f is methyl or ethyl and R^1_f is hydrogen, methyl, ethyl, normal propyl, isopropyl, cyclopropyl, 2-fluoroethyl, 2,2,2,-trifluoroethyl, 1-methyl-2-fluoroethyl, or 1-fluoromethyl-2-fluoroethyl.

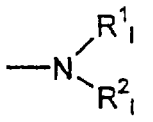
19. The compound of Claim 1 wherein F is an N-alkylglycyl residue or an N-alkylalanyl residue and the N-alkyl group is methyl or ethyl.

20. The compound of Claim 1 wherein G is an α-amino acid residue of Formula II_g, wherein R^1_g is hydrogen, methyl, ethyl or n-propyl, and R^2_g is hydrogen, ethyl, isopropyl, tert-butyl, isobutyl, 2-methylpropyl, cyclohexylmethyl, benzyl, thiazolyl-2-methyl, pyridyl-2-methyl, n-butyl, 2,2-dimethylpropyl, naphthylmethyl, n-propyl, phenyl or substituted phenyl, wherein the phenyl substituents are one or more halogen atoms, one or more C_1-C_4-alkyl, methoxy, ethoxy, nitro or trifluoromethyl groups or a dioxomethylene group.

21. The compound of Claim 1 wherein K is an α-amino acid of Formula II_k, wherein R^1_k is hydrogen, methyl, ethyl or normal propyl, and R^2_k is hydrogen, ethyl, isopropyl, tert-butyl, isobutyl, 2-methylpropyl, cyclohexylmethyl, benzyl, thiazolyl-2-methyl, pyridyl-2-methyl, normal butyl, 2,2-dimethylpropyl, naphthylmethyl, n-propyl, phenyl or substituted phenyl, wherein the phenyl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl, methoxy, ethoxy, nitro or trifluoromethyl groups or a dioxomethylene group; or R^1_g and R^2_g, together with the

α-carbon atom, form a cyclopentane ring or a benzo-fused cyclopentane ring.

22. The compound of Claim 1 wherein L is an amino group of Formula II_1,



(II_1),

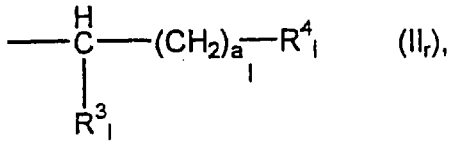
wherein

R^1_1 is a hydrogen atom, a normal or branched, saturated or unsaturated C_1-C_{18}-alkoxy group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted aryl-C_1-C_6-alkoxy group, a substituted or unsubstituted aryloxy-C_1-C_6-alkoxy group, wherein the aryl substituents comprise one or more halogen atoms or one or more C_1-C_4-alkyl, methoxy, ethoxy, trifluoromethyl, dioxymethylene, or nitro groups; or a heteroaryl-C_1-C_6-alkoxy group; and

R^2_1 is a hydrogen atom, a normal or branched C_1-C_{18}-alkyl group, a normal or branched C_1-C_{18} alkenyl group, a C_3-C_{10}-cycloalkyl group, an aryl group or a substituted aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group or a substituted heteroaryl group derived

from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups.

23. The compound of Claim 22 wherein R^2_1 is of Formula II_r,

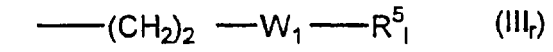


(II_r),

wherein a_1 is 0, 1, 2, 3, 4, or 5; R^3_1 is methyl, ethyl, normal propyl or isopropyl; and R^4_1 is a saturated or partially unsaturated carbocyclic system comprising from about 3 to about 10 carbon atoms, an aryl group or a substituted aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group or a substituted heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine,

pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups.

24. The compound of Claim 22 wherein R^2_1 is of Formula III_r,



$$\text{——}(CH_2)_2\text{—}W_1\text{——}R^5_1 \qquad (III_r)$$

wherein

W_1 is an $N(R^6_1)$ group, an oxygen atom or a sulfur atom;

R^5_1 and R^6_1 are each, independently, a hydrogen atom or a C_1-C_4-alkyl, C_3-C_7-cycloalkyl, aryl, arylmethyl, substituted aryl, or substituted arylmethyl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; or R^6_1 is a C_1-C_{18}-alkanoyl group or a benzoyl group.

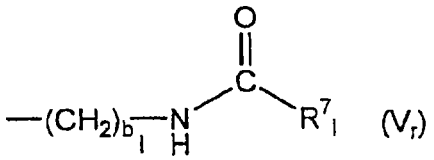
25. The compound of Claim 22 wherein R^2_1 is a monovalent radical of Formula IV_r,



$$\text{—}(CH_2)_{b_1}\text{—}Z_1 \qquad (IV_r)$$

wherein b_1 is 2, 3, or 4 and Z_1 is a formyl, aminocarbonyl, hydrazinocarbonyl, cyclic acetal, cyclic thioacetal, acyclic acetal or acyclic thioacetal group.

26. The compound of Claim 22 wherein $R^2{}_1$ is of Formula V_r,



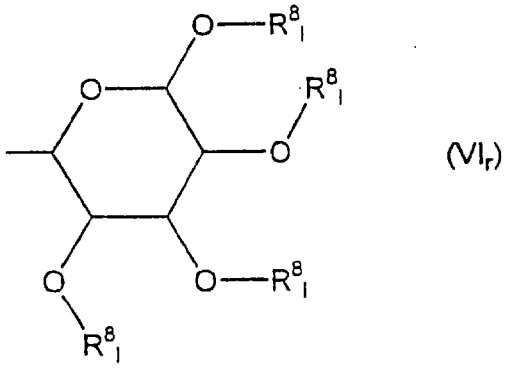
(V_r)

wherein

b_1 is 2, 3, or 4; and

$R^7{}_1$ is a polyglycol group of the formula $-O-(CH_2CH_2O)_{d1}-CH_3$, wherein d_1 is between about 2 and about 4, or between about 40 and about 90.

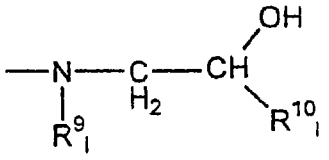
27. The compound of Claim 22 wherein $R^2{}_1$ is of Formula VI_r,



(VI_r)

and $R^8{}_1$ is a hydrogen atom, or a C_1-C_4 alkanoyl, C_1-C_4 alkyl, benzoyl, or benzyl group.

28. The compound of Claim 1 wherein L is a β-hydroxylamino group of Formula III_1,



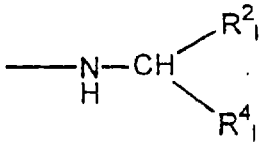
(III_1),

wherein

$R^9{}_1$ is a hydrogen atom, or a C_1-C_6-alkyl, an aryl group or a substituted aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; and

$R^{10}{}_1$ is a hydrogen atom, a methyl group or a phenyl group.

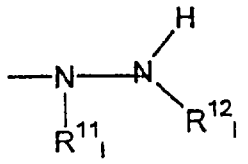
29. The compound of Claim 1 wherein at least one of r and s is 1, and L is an amino group of Formula IV_1,



(IV_1),

wherein $R^2{}_1$ and $R^4{}_1$ are each, independently, hydrogen or C_1-C_{10}-alkyl; or $R^2{}_1$, $R^4{}_1$ and the α-carbon together form a C_5-C_6-carbocycle.

30. The compound of Claim 1 wherein L is a hydrazido group of Formula V_1,



(V_1),

wherein

$R^{12}{}_1$ is a hydrogen atom, a normal or branched C_1-C_8-alkyl group, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4-alkyl group, an aryl group, an aryl-C_1-C_4-alkyl group, or a substituted aryl or aryl-C_1-C_4-alkyl group wherein the aryl substituents comprise one or more halogen atoms, or one or more methoxy, ethoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C_1-C_7-alkoxycarbonyl, C_1-C_7- alkylsulfonyl, amino, or C_1-C_7-dialkylamino groups; or a heteroaryl-C_1-C_4-alkyl group, wherein the heteroaryl group is derived from imidazole, pyrrole, thiophene, furan, thiazole, oxazole, pyrazole, 1,2,4- or 1,2,3- triazole, oxadiazole, thiadiazole, isoxazole, isothiazole, pyrazine, pyridazine, pyrimidine, pyridine, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzopyran, indole, isoindole, indazole or quinoline and the heteroaryl substituents

comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups; and

$R^{11}{}_1$ is a hydrogen atom; or r is 1, s is 1 or both r and s are 1, and $R^{11}{}_1$ is a normal or branched C_1-C_8-alkyl group, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4-alkyl group, an aryl-C_1-C_4-alkyl group, an aryl group or a substituted aryl-C_1-C_4-alkyl or aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group a heteroaryl-C_1-C_4-alkyl group or a substituted heteroaryl or heteroaryl-C_1-C_4-alkyl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups; or

$R^{11}{}_1$ and $R^{12}{}_1$ together form a propylene bridge or a butylene bridge.

31. The compound of Claim 1 wherein L is a monovalent radical of the formula -W-$R^{13}{}_1$, wherein

W is oxygen or sulfur;

$R^{13}{}_1$ is a C_3-C_{10}-cycloalkyl, straight-chain or branched C_2-C_{16}-alkenylmethyl, C_1-C_{16}-alkyl or halogen-substituted C_1-C_{16}-alkyl group or $R^{13}{}_1$ is a monovalent radical of the formula $-(CH_2)_e-R^{14}{}_1$, e is 1, 2, or 3, and $R^{14}{}_1$ is a saturated or partially unsaturated C_3-C_{10}- carbocyclic group; or $R^{13}{}_1$ is a monovalent radical of the formula $-[CH_2-CH=C(CH_3)-CH_2]_f-H$, and f is 1, 2, 3, or 4; or $R^{13}{}_1$ is a monovalent radical of the formula $-[CH_2-CH_2-O]_g-CH_3$, and g is 1, 2, 3, 4, or 5; or $R^{13}{}_1$ is a monovalent radical of the formula $-(CH_2)_h-X$, wherein h is 0, 1, 2, or 3, X is an aryl group or a substituted aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; or X is a heteroaryl group or a substituted heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups, an

aryl-C_1-C_4-alkyl group or a heteroaryl-C_1-C_4-alkyl group,; or

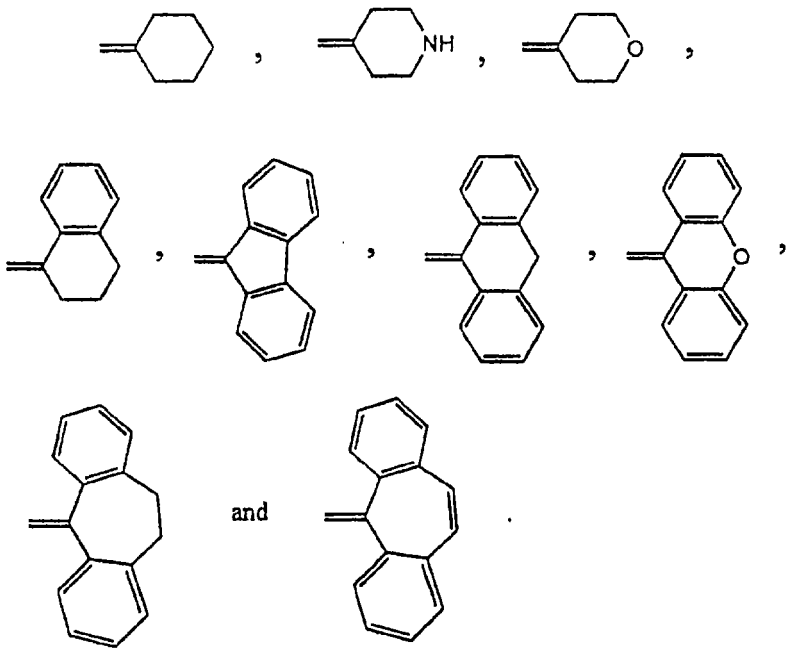
$R^{13}{}_1$ is a monovalent radical of the formula $-(CH_2)_b-W_1-R^5{}_1$, b is an integer, W_1 is an oxygen atom, a sulfur atom, or an $NR^6{}_1$ group, b_1 is 2, 3, or 4; $R^5{}_1$ is a saturated or partially unsaturated carbocyclic system which contains from about 3 to about 10 carbon atoms, an aryl or substituted aryl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group or a substituted heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups; $R^6{}_1$ is a hydrogen atom, or a C_1-C_4-alkyl, C_3-C_7-cycloalkyl, C_1-C_{18}-alkanoyl, benzoyl, aryl or arylmethyl group or a substituted aryl or arylmethyl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a

dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group.

32. The compound of Claim 1 wherein L is an aminoxy group of the formula -O-N(R^{15}_1)(R^{16}_1) wherein R^{15}_1 and R^{16}_1 are each, independently, a hydrogen atom, a normal or branched C_1-C_8-alkyl group, a halogen-substituted normal or branched C_1-C_8-alkyl group, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4 alkyl group, an aryl group, an aryl-C_1-C_4-alkyl group or a substituted aryl or aryl-C_1-C_4-alkyl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group, a heteroaryl-C_1-C_4-alkyl group or a substituted heteroaryl or heteroaryl-C_1-C_4-alkyl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, enzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups; or R^{15}_1 and R^{16}_1 together with the nitrogen atom form a heterocyclic ring structure comprising 5, 6, or 7 atoms.

33. The compound of Claim 1 wherein L is a oximato group of the formula $-O-N=C(R^{15}{}_1)(R^{16}{}_1)$, wherein $R^{15}{}_1$ and $R^{16}{}_1$ are each, independently, a hydrogen atom, a normal or branched C_1-C_8-alkyl group, a halogen-substituted normal or branched C_1-C_8-alkyl group, a C_3-C_8-cycloalkyl group, a C_3-C_8-cycloalkyl-C_1-C_4-alkyl group, an aryl group, an aryl-C_1-C_4-alkyl group or a substituted aryl or aryl-C_1-C_4-alkyl group, wherein the aryl substituents comprise one or more halogen atoms, or one or more C_1-C_4-alkyl groups, methoxy, ethoxy, trifluoromethyl, cyano or nitro groups, a C_1-C_7-alkoxycarbonyl group, a dioxymethylene group, a C_1-C_7-alkylsulfonyl group, an amino group or a C_1-C_6-dialkylamino group; a heteroaryl group or a substituted heteroaryl group derived from imidazole, isoxazole, isothiazole, thiazole, oxazole, pyrazole, thiophene, furan, pyrrole, 1,2,4- or 1,2,3-triazole, pyrazine, indole, benzofuran, benzothiophene, indole, isoindole, indazole, quinoline, pyridazine, pyrimidine, benzimidazole, benzopyran, benzothiazole, oxadiazole, thiadiazole or pyridine, wherein the heteroaryl substituents comprise one or more C_1-C_6-alkyl, hydroxyl or phenyl groups; or $R^{15}{}_1$ and $R^{16}{}_1$, together with the carbon atom, form a cyclic system or a cyclic system which is fused to an aromatic ring system.

34. The compound of Claim 33 wherein the cyclic system is selected from the group consisting of



35. The compound of Claim 1 wherein

A is an amino acid derivative selected from the group consisting of N-alkyl-D-prolyl, N-alkyl-L-prolyl, N-alkyl-D-piperidine-2-carbonyl, N-alkyl-L-piperidine-2-carbonyl, N,N-dialkyl-D-2-ethyl-2-phenylglycyl and N,N-dialkyl-L-2-ethyl-2-phenylglycyl, wherein alkyl is methyl, ethyl or isopropyl; and

B is valyl, isoleucyl or 2-t-butyl-L-glycyl.

36. A compound of the formula

A-B-D-E-F-L,

wherein

A is an amino acid derivative selected from the group consisting of D-N-methyl-piperidine-2-carbonyl, L-N-methyl-piperidine-2-carbonyl, N,N-dimethylamino-isobutyryl, N-methyl-L-prolyl, N-methyl-L-thiazolidine-4-carbonyl, N,N-dimethylglycyl, L-prolyl, L-piperidine-2-carbonyl, N-propyl-D-piperidine-2-carbonyl, D-piperidine-2-carbonyl, N-ethyl-D-piperidine-2-carbonyl, N-methyl-[2,2,5,5-tetramethyl]-L-thiazolidine-2-carbonyl, N-isopropyl-D-piperidine-2-carbonyl, N,N-dimethyl-2-cyclopropylglycyl, N,N-dimethyl-D-2-ethyl-2-phenylglycyl, N,N-dimethyl-L-2-ethyl-2-phenylglycyl, D-prolyl, N-methyl-D-prolyl, N,N-dimethyl-2-(2-fluorophenyl)glycyl, 1-aza-[3,3,0]bicyclooctyl-5-carbonyl, N,N-dimethyl-2-[4-fluoro]phenyl-glycyl, N-methyl-[2,2,5,5-tetramethyl]-thiazolidine-2-carbonyl, 2-(R,S)-ethyl-2-phenylglycyl, D,L-1-aminoindane-1-carbonyl, N,N-dimethyl-2-(R,S)-methyl-2-phenylglycyl, 2-[N,N-dimethylamino]indane-2-carbonyl, 5-[N,N-dimethylamino]-5,6,7,8-tetrahydro-naphthalene-5-carbonyl, N-isopropyl-2-(R,S)-ethyl-2-phenylglycyl, 1-[N,N-dimethylamino]indane-2-carbonyl,

N,N-dimethyl-2-propyl-2-phenylglycyl, N,N-dimethyl-2-[4-methoxy]phenyl-glycyl, N-methyl-3-hydroxy-D,L-valyl, N,N-dimethyl-D,L-2-isopropyl-2-phenylglycyl, N-methylpiperidine-2-carbonyl, N-methyl-L-prolyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl, N-methylazetidine-2-carbonyl, N-isopropylazetidine-2-carbonyl, N,N-dimethyl-[O-methyl]seryl, N,N-dimethyl-[O-methyl]threonyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl, 1-[N,N-dimethylamino]cyclohexyl-1-carbonyl, 1-[N,N-dimethylamino]cyclopentyl-1-carbonyl and 1,2,3,4-tetrahydroisoquinoline-3-carbonyl;

B is an amino acid residue selected from the group consisting of valyl, isoleucyl and 2-tert-butylglycyl;

D is an amino acid residue selected from the group consisting of N-methylvalyl, N-methylisoleucyl and N-methyl-L-2-t-butylglycyl;

E and F are each an amino acid residue independently selected from the group consisting of prolyl, thiaprolyl, homoprolyl, hydroxyprolyl, 3,4-didehydroprolyl, 4-fluoroprolyl, and 3-methylprolyl; and

L is an alkoxy group or an amino group of the formula R^1_1-N-R^2_1, wherein R^1_1 and R^2_1 are independently selected from the group consisting of hydrogen, alkoxy, hydroxy, alkyl and alkylaryl.

37. A compound of the formula

A-B-D-E-F-L,

wherein

A is an amino acid derivative selected from the group consisting of D-N-methyl-piperidine-2-carbonyl, N-ethyl-D-piperidine-2-carbonyl, N-isopropyl-D-piperidine-2-carbonyl, N,N-dimethyl-2-cyclopropyl-glycyl, N-methyl-D-prolyl, 1-aza-[3,3,0]bicyclooctyl-5-carbonyl, N-methyl-[2,2;5,5-tetramethyl]-thiazolidine-2-carbonyl, 2-(R,S)-ethyl-2-phenylglycyl, D,L-1-aminoindane-1-carbonyl, N,N-dimethyl-2-(R,S)-methyl-2-phenylglycyl, 5-[N,N-dimethylamino]-5,6,7,8-tetrahydro-naphthalene-5-carbonyl, 1-[N,N-dimethylamino]indane-2-carbonyl, N,N-dimethyl-2-propyl-2-phenylglycyl, N-methyl-3-hydroxy-D,L-valyl, N,N-dimethyl-D,L-2-isopropyl-2-phenylglycyl, N-methyl-piperidine-2-carbonyl, N-methyl-D,L-prolyl, N-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl, N-ethylazetidine-2-carbonyl, N-isopropylazetidine-2-carbonyl, N,N-dimethyl-[O-methyl]seryl, 1-[N,N-dimethylamino]cyclohexyl-1-carbonyl, N,N-dimethyl-D-2-ethyl-2-phenylglycyl, N,N-dimethyl-L-2-ethyl-2-phenylglycyl, and 1-[N,N-dimethylamino]cyclopentyl-1-carbonyl;

B is valyl;

D is N-methylvalyl;

E and F are each prolyl; and

L is a C_1-C_6-alkoxy group or an amino group of the formula R^1_1-N-R^2_1, wherein R^1_1 and R^2_1 are independently selected from the group consisting of hydrogen, C_1-C_6-alkoxy, hydroxy, normal, cyclic or branched C_1-C_{10}-alkyl, and phenylalkyl.

38. The use of a therapeutically effective amount of a compound of Claim 1 for the preparation of a medicament for the treatment of cancer in a mammal.

39. The use of Claim 38 wherein the mammal is a human.