



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07K 7/02, 5/103, 5/117, A61K 38/07, 38/08	A1	(11) International Publication Number: WO 00/02906 (43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/US99/14099 (22) International Filing Date: 23 June 1999 (23.06.99) (30) Priority Data: 09/112,249 8 July 1998 (08.07.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/112,249 (CON) Filed on 8 July 1998 (08.07.98) (71) Applicants (for all designated States except US): BASF AKTIENGESSELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE). BASF BIORESEARCH CORPORATION [US/US]; 100 Research Drive, Worcester, MA 01605 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): RITTER, Kurt [DE/US]; 9 Burton Avenue, Newton, MA 02158 (US). JANSSEN, Bernd [DE/US]; 114 Applebriar Lane, Marlborough, MA 01752 (US). HAUPT, Andreas [DE/US]; Schalzizigweg 52, D-68723 Schwetzingen (DE). KLING, Andreas [DE/DE]; Riegeler Weg 14, D-68239 Mannheim (DE). BARLOZZARI, Teresa [IT/US]; 24 South Woodside Avenue, Welles-		ley, MA 02181 (US). AMBERG, Wilhelm [DE/DE]; Stettiner Ring 24, D-61381 Friedrichsdorf (DE). (74) Agents: ELMORE, Carolyn, S. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DOLASTATIN 15 DERIVATIVES (57) Abstract Compounds of the present invention include cell growth inhibitors which are peptides of Formula (I): A - B - D - E - F - G and acid salts thereof, wherein A, D and E are α-amino acid residues, B is an α-amino acid residue or an α-hydroxy acid residue, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue, and G is a monovalent radical, such as, for example, a hydrogen atom, an amino group, an alkyl group, an alkylene alkyl ether, an alkylene alkyl thioether, an alkylene aldehyde, an alkylene amide, a β-hydroxylamino group, a hydrazido group, an alkoxy group, a thioalkoxy group, an aminoxy group, an oximato group, an alkylene aryl group, an alkylene ester, an alkylene sulfoxide or an alkylene sulfone. 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.		

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-1-

DOLASTATIN 15 DERIVATIVES

RELATED APPLICATIONS

This is a continuation of, and claims priority to, Serial No. 09/112,249, filed July 8, 1998, the teachings of which are incorporated herein by reference in their entirety.

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 1 mg each per 100 kg sea hare) and the consequent 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 (see, for example,

-2-

Bioorg. Med. Chem. Lett. **4** : 1947-50 (1994); WO 93 03054; JP-A-06234790).

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

10 A - B - D - E - F - G (I)

and acid salts thereof, wherein A, D, and E are α -amino acid residues, B is an α -amino acid residue, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue, and G is a monovalent radical, such as, for example, a hydrogen atom, an amino group, an alkyl group, an alkylene alkyl ether, an alkylene alkyl thioether, an alkylene aldehyde, an alkylene amide, a β -hydroxylamino group, a hydrazido group, an alkoxy group, a thioalkoxy group, an aminoxy group, an oximato group, an alkylene aryl group, an alkylene ester, an alkylene sulfoxide or an alkylene sulfone.

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

25 An additional embodiment of the present invention is a method for treating cancer in a mammal, such as a human,

-3-

comprising administering to the mammal an effective amount of a compound of Formula I in a pharmaceutically acceptable composition.

The present invention provides compounds with
5 antineoplastic activity as well as increased metabolic stability relative to Dolastatin 15.

DETAILED DESCRIPTION OF THE INVENTION

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

The invention is based on the discovery that Dolastatin 15, a peptide isolated from the sea hare
15 *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 and expensive to synthesize and suffers from poor aqueous solubility. As shown herein, however, Dolastatin
20 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
25 modifications of Dolastatin 15 provide compounds with a surprisingly improved therapeutic potential for the treatment of neoplastic diseases as compared to Dolastatins-10 and -15. The Dolastatin-15 derivatives

-4-

exhibit activity even in multiple drug-resistant tumor systems and an unpredicted high solubility in aqueous solvents. Furthermore, the compounds of the present invention can be conveniently synthesized, as described
5 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
10 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
15 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, in the unit $-N(R)R'$, R and R' are each a
20 monovalent radical, and can, together with the nitrogen atom, form a heterocyclic ring. In addition, two monovalent radicals bonded to the same atom can also together form a divalent radical, such as an alkylidene group, for example, a propylidene group, or an oxygen atom.

25 For the purposes of the present invention, the term "residue" refers to the molecular fragment remaining after the removal of the elements of a water molecule (one oxygen atom, two hydrogen atoms) from a molecule, such as an amino acid or a hydroxy acid.

-5-

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, -CH₂CH₂CH₃).

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



wherein A, D and E are α -amino acid residues; B is an α -amino acid residue or an α -hydroxy acid residue; F is an
10 aminobenzoic acid residue, or an aminocycloalkanecarboxylic acid residue, such as an aminocyclobutanecarboxylic acid residue, an aminocyclopentanecarboxylic acid residue, or an aminocyclohexanecarboxylic acid residue; and G is a monovalent radical.

15 The peptides of Formula I are generally composed of L-amino acids but they can contain one or more D-amino acids. They can also be present as salts with physiologically-compatible acids, including hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric
20 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.

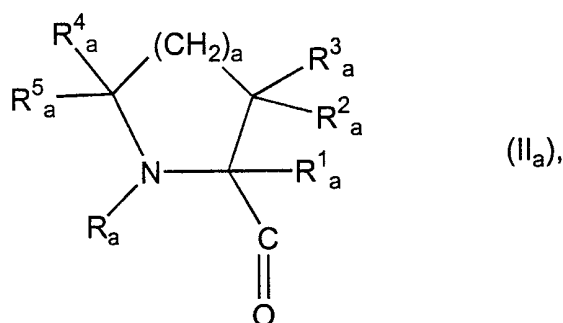
25 The following is a description of the present invention, including a detailed description of individual components and of methods of using the claimed compounds.

-6-

Compounds of the Present Invention

Identity of A

In one embodiment, A is an amino acid derivative of Formula II_a,



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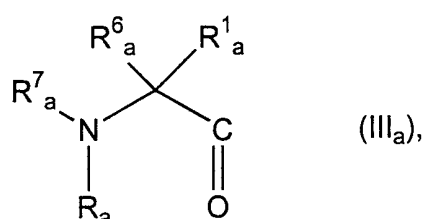
where n_a is an integer, preferably 0, 1, 2, or 3. R_a is a monovalent radical, such as a hydrogen atom or a C_1 - C_3 -alkyl group which can be normal, branched or cyclic and can be substituted by one or more, preferably 1 to
 10 about 3, fluorine atoms; suitable examples include methyl, ethyl, isopropyl, 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
 15 as a hydrogen atom or a methyl, ethyl, propyl or phenyl group. The phenyl group can be substituted; suitable substituents include one or more halogen atoms, with fluorine, chlorine and bromine being preferred, C_1 - C_4 -alkyl groups, methoxy, ethoxy, trifluoromethyl or nitro groups.

-7-

R_a^2 , R_a^3 , R_a^4 and R_a^5 are each, independently, a monovalent radical, such as a hydrogen atom or a methyl group. R_a and R_a^1 together can also form a propylene bridge.

5 In another embodiment, A is an amino acid derivative of Formula III_a,



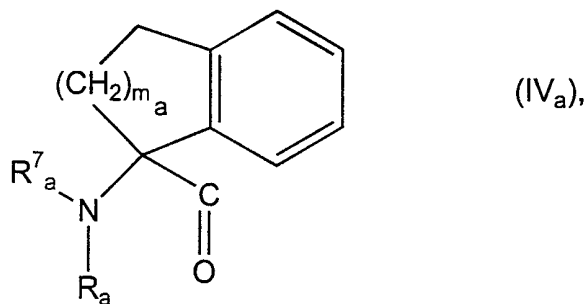
where R_a has the meaning stated for Formula II_a, R_a^1 is a monovalent radical, for example, a hydrogen atom or a lower alkyl group, preferably a methyl, ethyl or propyl group.

In this embodiment, R_a^6 is a monovalent radical, such as a hydrogen atom, a normal or branched C₁-C₈-alkyl group, which can be substituted by one or more halogen, preferably fluorine, atoms, or a C₃-C₈-cycloalkyl or C₃-C₈-cycloalkyl-C₁-C₄-alkyl group, a C₁-C₄-oxoalkyl group such as a methoxymethyl, 1-methoxyethyl or 1,1-dimethylhydroxymethyl group, a C₂-C₅ alkenyl group, such as a vinyl or 1-methylvinyl group, or a substituted or unsubstituted phenyl group. Suitable phenyl substituents include one or more halogen atoms, preferably fluorine, chlorine or bromine atoms, and alkyl, methoxy, ethoxy, trifluoromethyl, or nitro groups. R_a^7 is a monovalent radical, preferably a

-8-

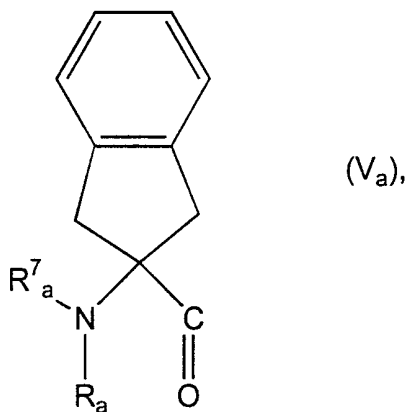
methyl group or an ethyl group.

In another embodiment, A is an amino acid residue of Formula IV_a,



5 where m_a is an integer, preferably 1 or 2. R_a and R_a^7 have the meanings stated for R_a and R_a^7 in Formula III_a.

In another embodiment, A is an amino acid residue of Formula V_a,

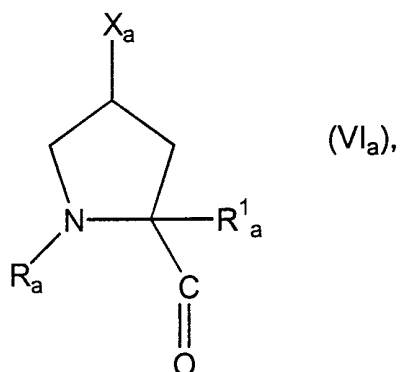


10 where R_a and R_a^7 have the meanings stated for R_a and R_a^7 in Formula III_a.

In a further embodiment, A is a substituted proline

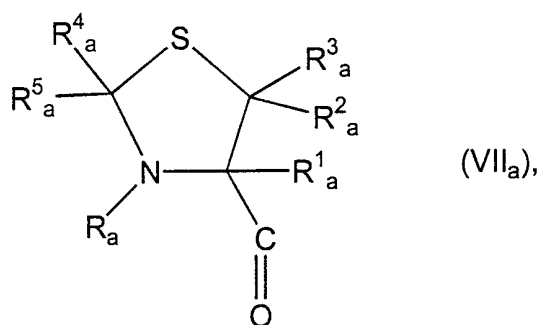
- 9 -

derivative of Formula VI_a,



where R_a and R¹_a have the meanings stated for R_a and R¹_a in Formula II_a, and X_a is a monovalent radical, preferably a hydroxyl, methoxy or ethoxy group or a fluorine atom.

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

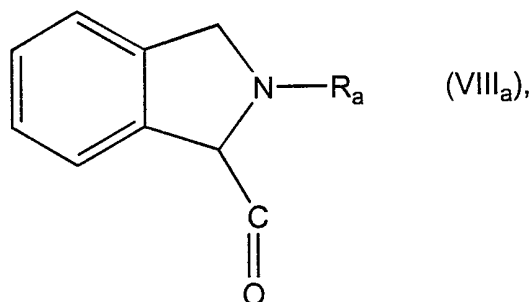


where R_a, R¹_a, R²_a, R³_a, R⁴_a and R⁵_a have the meanings stated

-10-

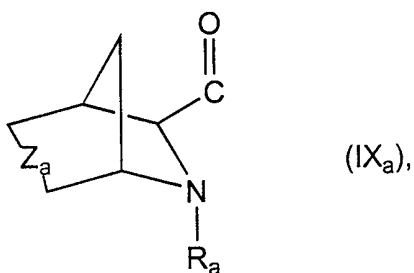
for these variables in Formula II_a.

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



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

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

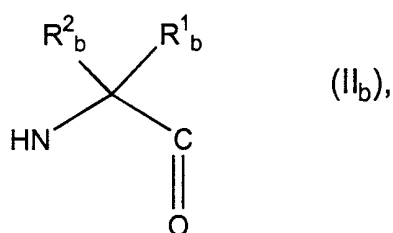


10 where Z_a is a single or double bond and R_a has the meaning stated for this variable in Formula II_a. The 3-carbonyl substituent can have either the exo or endo orientation.

-11-

Identity of B

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



5

wherein R¹_b and R²_b are each a monovalent radical. R¹_b is, preferably, a hydrogen atom and R²_b is, for example, 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, R¹_b and R²_b together can be an isopropylidene group.

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Identity of D

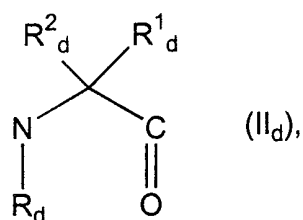
D is an N-alkylvalyl, N-alkyl-2-ethylglycyl, N-alkyl-2-tert-butylglycyl, N-alkyl-norleucyl, N-alkyl-isoleucyl, N-alkyl-allo-isoleucyl or N-alkyl-norvalyl residue, where the alkyl group is preferably methyl or ethyl.

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

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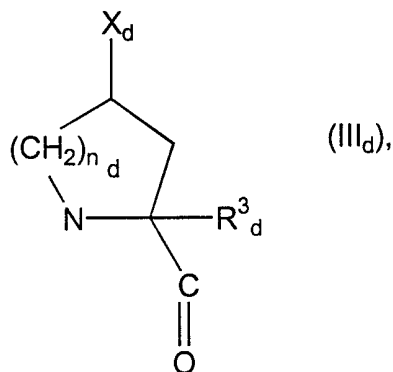
-12-



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 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,

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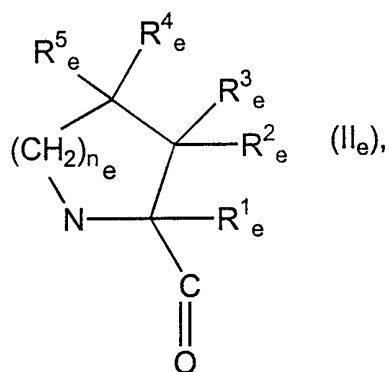
where n_d is an integer, for example, 1 or 2, and R^3_d has the meaning stated for R^1_a in Formula III_a. X_d is a monovalent radical, preferably a hydrogen atom, and, in the

-13-

case where n_d equals 1, can also be a hydroxyl, methoxy or ethoxy group or a fluorine atom.

Identity of E

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

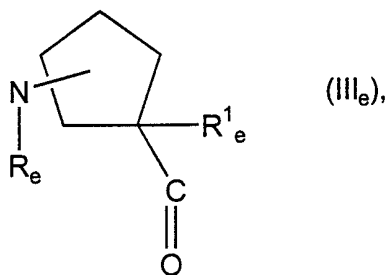


- where n_e is an integer, preferably 0, 1 or 2. R^1_e has the
 10 meaning stated for R^1_a in Formula III_a. R^2_e and R^3_e are
 each a monovalent radical, and can be, independently, a
 hydrogen atom or a methyl group. R^4_e is a monovalent
 radical, preferably a hydrogen atom, a hydroxyl, methoxy or
 ethoxy group or a fluorine atom. R^5_e is a monovalent
 15 radical, preferably a hydrogen atom. In the case where n_e
 has the value 1, R^3_e and R^4_e together can 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

-14-

and R_e^2 can together form a double bond.

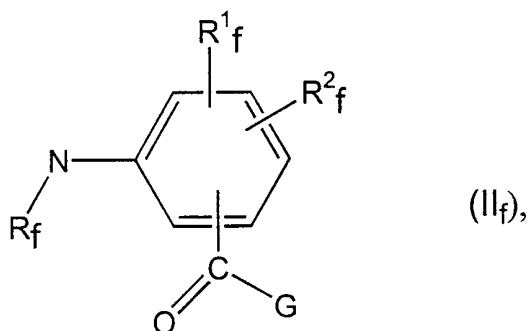
In another embodiment, E is a 2- or 3-amino-cyclopentanecarboxylic acid residue of Formula III_e,



5 where R_e is a monovalent radical, such as a methyl or ethyl group and R_e^1 has the meaning stated for R_a^1 in Formula III_a.

Identity of F

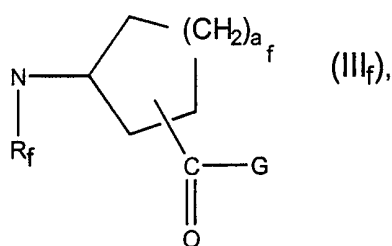
10 In one embodiment, F is an aminobenzoyl derivative of Formula II_f,



-15-

where R_f is a hydrogen atom or an alkyl group, preferably a methyl, ethyl or propyl group. The carbonyl group can be in position 1 (ortho), 2 (meta), or 3 (para) of the phenyl ring relative to the nitrogen atom. R_f^1 and R_f^2 are each, independently, a hydrogen atom; a halogen atom, for example, a fluorine, chlorine, bromine, or iodine atom; a C_1 - C_4 -alkyl group; a methoxy, ethoxy, trifluoromethyl, nitro, cyano, amino or dimethylamino group. Additionally, R_f^1 and R_f^2 can together form a dioxymethylene group.

10 In another embodiment, F is an aminocyclo-
alkanecarboxylic acid residue of Formula III_f,

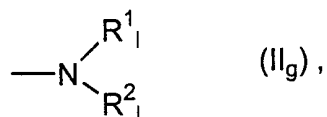


where R_f is a monovalent radical, such as a hydrogen atom or a lower alkyl group, preferably a methyl, ethyl or propyl group. a_f is an integer, for example, 0, 1 or 2. The carbonyl group is in position 2 or position 3 of the cycloalkane ring relative to the nitrogen atom at position 1. The stereogenic centers can be, independently of each other, R or S. For a five-membered ring ($a_f = 1$), the combinations R1,S2 and S1,R2 would be referred to as cis-pentacin derivatives, while the combinations R1,R2 and S1,S2 are trans-pentacin derivatives.

-16-

Identity of G

In one embodiment, G is an amino or substituted amino group of Formula II_g,

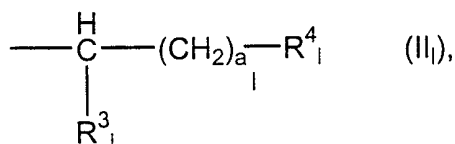


- 5 where R₁¹ is a monovalent radical, such as a hydrogen atom, a normal or branched, saturated or unsaturated C₁-C₁₈-alkoxy group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted aryl-C₁-C₆-alkoxy group, or a substituted or unsubstituted
- 10 aryloxy-C₁-C₆-alkoxy or heteroaryl-C₁-C₆-alkoxy 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, imidazolyl, isoxazolyl, isothiazolyl,
- 15 thiazolyl, oxazolyl, pyrazolyl, thiophenyl, furanyl, pyrrolyl, 1,2,4- or 1,2,3- triazolyl, pyrazinyl, indolyl, benzofuranyl, benzothiophenyl, isoindolyl, indazolyl, quinolinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzopyranyl, benzothiazolyl, oxadiazolyl, thiadiazolyl or
- 20 pyridinyl group. Suitable aryl or heteroaryl substituents include one or more halogen atoms, preferably fluorine, bromine or chlorine; C₁-C₄-alkyl groups; methoxy, ethoxy or trifluoromethyl groups, a dioxymethylene group or a nitro group.
- 25 R₁² is a monovalent radical, such as a hydrogen atom,

-17-

a normal or branched, saturated or unsaturated C₁-C₁₈-alkyl group, a C₃-C₁₀-cycloalkyl group, a substituted or unsubstituted aryl group, where aryl is preferably phenyl or naphthyl. Suitable aryl substituents include one or
 5 more halogen, preferably fluorine, chlorine or bromine, atoms, C₁-C₄-alkyl groups, methoxy, ethoxy or trifluoromethyl groups, a dioxymethylene group, nitro or cyano groups, a C₁-C₇-alkoxycarbonyl group, a C₁-C₇-alkylsulfonyl group, an amino or C₁-C₇-dialkylamino
 10 group, where the alkyl groups can, together with the nitrogen atom, also form a 5- or 6-membered heterocycle, or an unsubstituted or substituted heteroaryl group. The heteroaryl group can be a 5- or 6-membered, preferably nitrogen-, oxygen- or sulfur-containing, ring system which
 15 can be fused to a benzene ring, such as, for example, imidazolyl, pyrrolyl, thiophenyl, furanyl, thiazolyl, oxazolyl, pyrazolyl, 1,2,4- or 1,2,3-triazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridinyl,
 20 benzofuranyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzopyranyl, indolyl, isoindolyl, indazolyl or quinolinyl group, with preferred substituents being C₁-C₆-alkyl groups, or hydroxyl or phenyl groups.

R²₁ can additionally be of Formula II₁,



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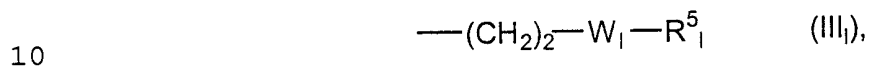
-18-

wherein a_1 is an integer, preferably 0, 1, 2, 3, 4, or 5.

R^3_1 is a monovalent radical, such as a lower alkyl group, for example, a methyl, ethyl, propyl or isopropyl group.

R^4_1 is a saturated or partially unsaturated carbocyclic group containing from 3 to about 10 carbon atoms, or a substituted or unsubstituted aryl or heteroaryl group, where the preferred aryl and heteroaryl groups and suitable substituents are as stated for R^2_1 in Formula II_g.

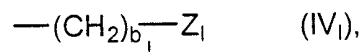
R^2_1 can also be a monovalent radical of Formula III₁,



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 $\text{C}_1\text{--C}_4$ -alkyl or $\text{C}_3\text{--C}_7$ -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_g. R^6_1 is a monovalent radical, preferably a hydrogen atom, a $\text{C}_1\text{--C}_4$ -alkyl group or a $\text{C}_3\text{--C}_7$ -cycloalkyl group, a $\text{C}_1\text{--C}_{18}$ -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_g.

R^2_1 can alternately be a substituent of Formula IV₁,



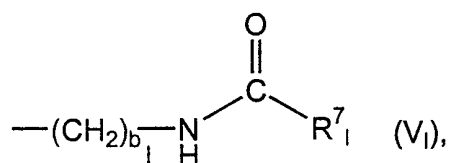
where b_1 is an integer, preferably 2, 3 or 4. Z_1 is a

-19-

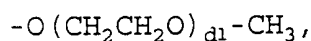
monovalent radical, such as a formyl, aminocarbonyl or hydrazinocarbonyl group, or a cyclic or acyclic acetal or thioacetal group.

R^2_1 can also be a substituent of Formula V_1 ,

5

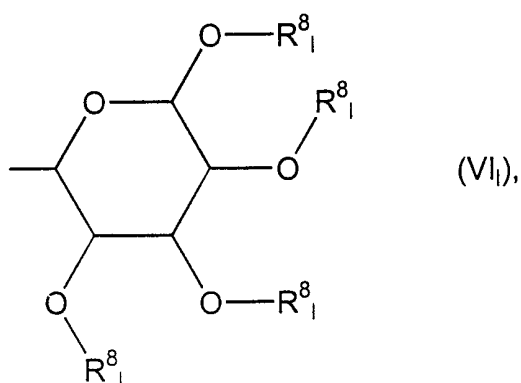


in which b_1 is an integer, preferably 2, 3 or 4. R^7_1 is a monovalent radical, such as a glycol oligomer of the formula



10 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_1 ,

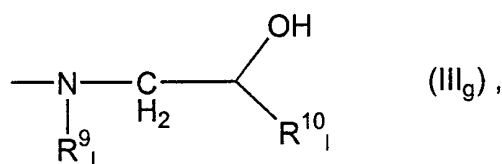


where R^8_1 is a monovalent radical, such as a hydrogen atom,

-20-

a C₁-C₄-alkanoyl or alkyl group, a benzoyl group or a benzyl group.

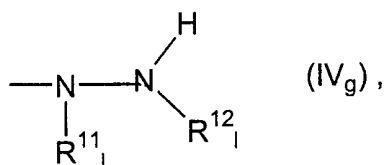
In another embodiment, G is an β -hydroxy amine of Formula III_g,



5

where R⁹₁ is a monovalent radical such as a hydrogen atom, a C₁-C₆-alkyl group or a substituted or unsubstituted aryl group, with aryl and its preferred substituents having the meaning stated for R²₁ in Formula II_g. R¹⁰₁ is a monovalent
10 radical, preferably a hydrogen atom, alkyl, for example, methyl, or a phenyl group.

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



15

where R¹¹₁ and R¹²₁ are each, independently, a monovalent radical such as a hydrogen atom, a normal or branched C₁-C₈-alkyl group, a C₃-C₈- cycloalkyl group, a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group or a substituted or

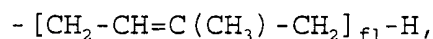
-21-

unsubstituted aryl, heteroaryl, aryl-C₁-C₄-alkyl or heteroaryl-C₁-C₄-alkyl group, where aryl, heteroaryl and their preferred substituents can be selected from among the options listed for R²₁ in Formula II_g. R¹¹₁ and R¹²₁ can
 5 also together form a propylene or butylene bridge.

Another subclass of compounds of this invention includes peptides of Formula I wherein G is a monovalent radical of the formula -O-R¹³₁ or -S-R¹³₁, where R¹³₁ is a monovalent radical, such as a C₃-C₁₀-cycloalkyl group, a
 10 normal or branched C₂-C₁₆-alkenylmethyl group or a C₁-C₁₆-alkyl group which can be substituted by from 1 to about 5 halogen, preferably fluorine, atoms.

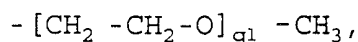
R¹³₁ can also be the radical -(CH₂)_{e₁}-R¹⁴₁ where e₁ is an integer, preferably 1, 2 or 3. R¹⁴₁ is a monovalent
 15 radical, preferably a saturated or partially unsaturated C₃-C₁₀-carbocycle.

R¹³₁ can further be the radical



where f₁ is an integer, preferably 1, 2, 3 or 4.

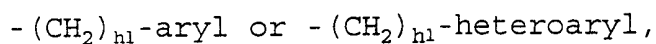
20 R¹³₁ can also be the radical



where g₁ is an integer, preferably from about 2 to about 4, or from about 40 to about 90.

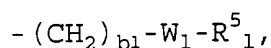
-22-

R^{13}_1 can also be the radical



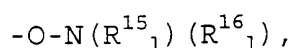
where aryl and heteroaryl can also be substituted and, along with their preferred substituents, can be selected
5 from the group listed for R^2_1 in Formula II_g. h_1 is an integer, preferably 0, 1, 2 or 3.

R^{13}_1 can further be the radical



where b_1 , W_1 and R^5_1 are each selected from among the
10 options described for Formula III₁.

Another subclass of compounds of this invention includes peptides of Formula I in which G is an aminoxy group of the formula

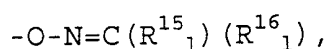


15 where R^{15}_1 and R^{16}_1 are each a monovalent radical, and can independently be a hydrogen atom, a normal or branched C_1 - C_8 -alkyl group, which can be substituted by halogen, preferably fluorine, atoms, a C_3 - C_8 -cycloalkyl group, a C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group, a substituted or
20 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

-23-

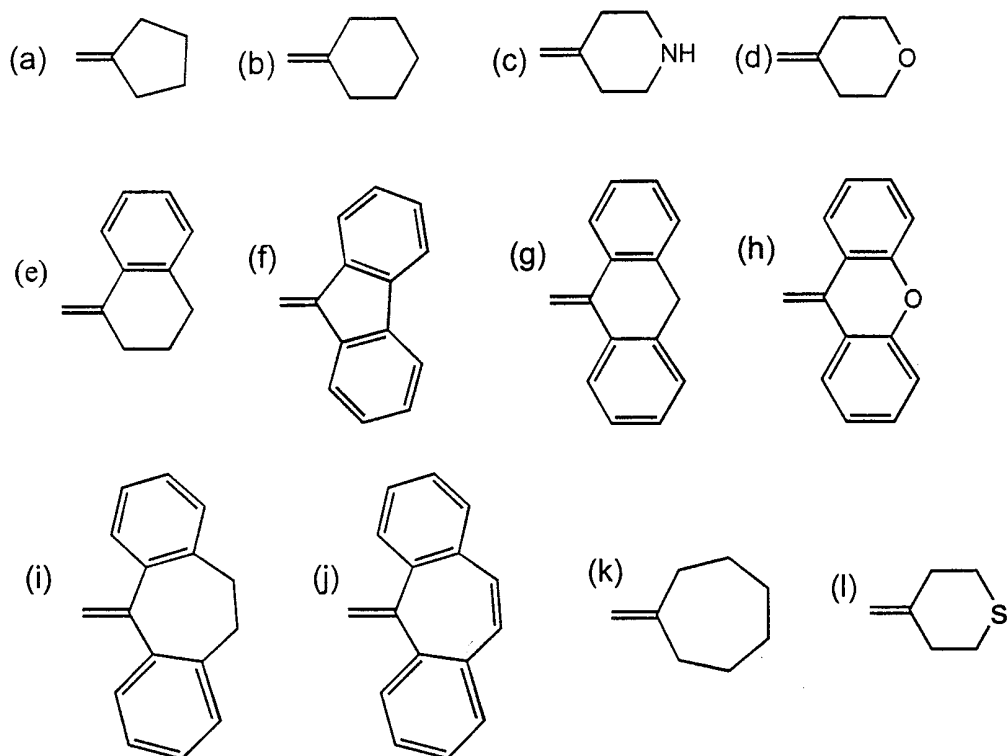
selected from the options listed for R^2_1 in Formula II_g.
Additionally, R^{15}_1 and R^{16}_1 can together form a 5-, 6- or
7-membered heterocycle.

Another subclass of compounds of this invention
5 includes peptides of Formula I wherein G is an oximato
group of the formula



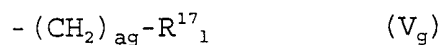
where R^{15}_1 and R^{16}_1 are selected from among the options
listed above and, additionally, can together form a cyclic
10 system comprising, preferably, from about 3 to about 7 ring
atoms. This cyclic system can additionally be fused to one
or more aromatic rings. Particularly preferred cyclic
systems are shown below.

-24-



A further subclass of compounds of this invention includes peptides of Formula I wherein G is a hydrogen atom, a normal or branched C₁-C₈-alkyl group, which can be substituted by up to six halogen, preferably fluorine, atoms, a C₃-C₈-cycloalkyl group or a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group.

G can also be an arylalkyl, heteroarylalkyl, aryl or heteroaryl group of Formula V_g,

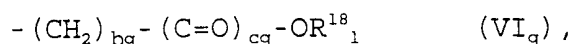


where a_g is an integer, such as 0, 1 or 2. R^{17}_1 is a

-25-

substituted or unsubstituted aryl or heteroaryl group. Preferred aryl groups include phenyl and naphthyl groups. Suitable aryl substituents include halogen, preferably fluorine, bromine or chlorine, atoms, C₁-C₄-alkyl groups, methoxy, ethoxy or trifluoromethyl groups, a dioxymethylene group, a nitro or cyano group, a C₁-C₇-alkoxycarbonyl group, a C₁-C₇-alkylsulfonyl group, an amino group or a C₁-C₆-dialkylamino group, where the alkyl groups can, together with the nitrogen atom, also form a 5- or 6-membered heterocycle. R¹⁷₁ can also be a 5- or 6-membered, preferably nitrogen-, oxygen- or sulfur-containing, ring system which can be fused to a benzene ring. Suitable heteroaryl groups include imidazolyl, pyrrolyl, thiophenyl, furanyl, thiazolyl, oxazolyl, pyrazolyl, 1,2,4- or 1,2,3- triazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridinyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzopyranyl, indolyl, isoindolyl, indazolyl and quinolinyl groups. Preferred heteroaryl substituents are C₁-C₆-alkyl groups, a hydroxyl group or a phenyl group.

Another subclass of compounds of this invention includes compounds of Formula I wherein G is a monovalent radical of Formula VI_g,



where b_g is an integer, preferably 0, 1, 2 or 3, and c_g

-26-

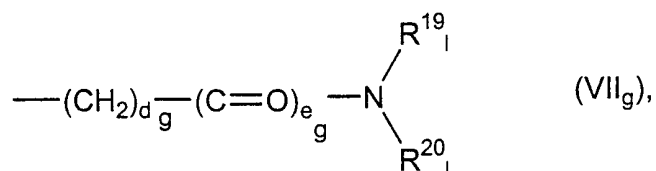
is an integer, preferably 0 or 1. b_g and c_g are not both simultaneously 0. R^{18}_1 is a monovalent radical, such as a hydrogen atom, a straight-chain or branched C_1 - C_8 -alkyl group which can be substituted by halogen, preferably

5 fluorine, atoms, especially a CF_2 -moiety, a C_3 - C_8 -cycloalkyl group, a C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group, a substituted or unsubstituted aryl, preferably phenyl or naphthyl, group. Suitable aryl substituents are halogen, preferably fluorine, bromine or chlorine, atoms,

10 C_1 - C_4 -alkoxy, trifluoromethyl, nitro or cyano groups, a dioxymethylene moiety, a C_1 - C_7 -alkoxycarbonyl moiety, a C_1 - C_7 -alkylsulfonyl moiety, an amino group or a C_1 - C_6 -dialkylamino group, where the alkyl groups can, together with the nitrogen atom, also form a 5- or

15 6-membered heterocycle.

G can also be a monovalent radical of Formula VII_g



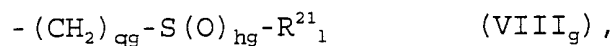
where d_g is an integer, preferably 0, 1, 2 or 3, and e_g is an integer such as 0 or 1. d_g and e_g cannot both

20 simultaneously take the value 0. R^{19}_1 and R^{20}_1 are each, independently, a monovalent radical, such as a hydrogen atom, a straight-chain or branched C_1 - C_8 -alkyl group, which can further be substituted by halogen, preferably fluorine, atoms, especially a CF_2 -moiety, a C_3 - C_8 -cycloalkyl group,

-27-

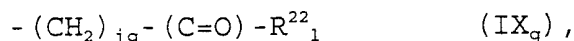
a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group, a substituted or unsubstituted aryl, preferably phenyl or naphthyl group. Suitable aryl substituents include one or more halogen, preferably fluorine, bromine or chlorine, atoms, C₁-C₄-alkoxy, trifluoromethyl, nitro or cyano groups, a dioxymethylene moiety, a C₁-C₇-alkoxycarbonyl moiety, a C₁-C₇-alkylsulfonyl group, an amino group or a C₁-C₆-dialkylamino group, where the alkyl groups can, together with the nitrogen atom, also form a 5- or 6-membered heterocycle. N(R¹⁹₁)R²⁰₁ can additionally form a ring system of the formula N(CH₂)_{f_g}, where f_g is an integer selected from among 4, 5 or 6.

Another subclass of compounds of this invention includes peptides of Formula I, wherein G is a monovalent radical of Formula VIII_g,



where g_g is an integer, for example, 1 or 2, and h_g is 1 or 2. R²¹₁ is a monovalent radical, preferably a methyl group, a trifluoromethyl group, an ethyl group or a phenyl group.

G can also be an alkyl- or arylcarbonylalkyl group of Formula IX_g,



where R²²₁ is a monovalent radical, such as a hydrogen atom, a straight-chain or branched C₁-C₈-alkyl group which

-28-

can be substituted by up to six halogen, preferably fluorine, atoms, especially a CF_2 -moiety, a C_3 - C_8 -cycloalkyl group, a C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group, a substituted or unsubstituted aryl, preferably phenyl or naphthyl, group. Suitable aryl substituents are halogen, preferably fluorine, bromine or chlorine, atoms, C_1 - C_4 -alkoxy, trifluoromethyl, nitro or cyano groups, a dioxymethylene moiety, a C_1 - C_7 -alkoxycarbonyl moiety, a C_1 - C_7 -alkylsulfonyl moiety, an amino group or a C_1 - C_6 -dialkylamino group, where the alkyl groups can, together with the nitrogen atom, also form a 5- or 6-membered heterocycle.

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 assemblage, 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 assemblage 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

-29-

peptide chemistry, including Müller, *Methoden der organischen Chemie* Vol. XV/2, pages 1-364, Thieme Verlag, Stuttgart, Germany (1974); Stewart and Young, *Solid Phase Peptide Synthesis*, pages 31-34 and 71-82, Pierce Chemical Company, Rockford, IL (1984); Bodanszky et al., *Peptide Synthesis*, pages 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-propane-phosphonic anhydride (PPA), N,N-bis(2-oxo-oxazolidinyl)imido-phosphoryl chloride (BOP-Cl), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrop), diphenyl-phosphoryl azide (DPPA), Castro's reagent (BOP, PyBop), O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU), diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl-2,3-dihydro-3-oxo-4-hydroxy-thiophene dioxide (Steglich's reagent; HOTDO), and 1,1'-carbonyl-diimidazole (CDI). The coupling reagents can be employed alone or in combination with additives such as N,N-dimethyl-4-aminopyridine (DMAP), N-hydroxybenzotriazole (HOBt), N-hydroxybenzotriazine (HOObt), N-hydroxysuccinimide (HOSu) or 2-hydroxypyridine.

-30-

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** : 2149 (1963)). Particularly preferred methods are those in which peptides are assembled sequentially or by fragment coupling using the Z, Boc or Fmoc protective group technique, with one of the reactants in the said Merrifield technique being bonded to an insoluble polymeric support (also called resin hereinafter). This typically entails assembling the peptide sequentially on the polymeric support using the Boc or Fmoc protective group technique, with the growing peptide chain covalently bonded at the C terminus to the insoluble resin particles. This procedure allows the removal of reagents and byproducts by filtration, eliminating the need to recrystallize intermediates.

The protected amino acids can be linked to any

-31-

suitable polymer, which must be insoluble in the solvents used and have a stable physical form which permits filtration. The polymer must contain a functional group to which the first protected amino acid can be covalently
5 attached. A wide variety of polymers are suitable for this purpose, including cellulose, polyvinyl alcohol, polymethacrylate, sulfonated polystyrene, chloromethylated styrene/divinylbenzene copolymer (Merrifield resin), 4-methylbenzhydrylamine resin (MBHA-resin),
10 phenylacetamidomethyl resin (Pam-resin), p-benzyloxy-benzyl-alcohol-resin, benzhydryl-amine-resin (BHA-resin), 4-(hydroxymethyl)-benzoyl-oxymethyl-resin, the resin of Breipohl et al. (*Tetrahedron Letters* **28** (1987) 565; supplied by BACHEM), 4-(2,4-dimethoxyphenylaminomethyl)
15 phenoxy resin (supplied by Novabiochem) or o-chlorotrityl-resin (supplied by Biohellas).

Solvents suitable for peptide synthesis include any solvent which is inert under the reaction conditions, especially water, N,N-dimethylformamide (DMF), dimethyl
20 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
25 the amino acid derivatives starting materials are soluble. However, preferred solvents additionally have resin-swelling properties and include DMF, DCM, NMP, acetonitrile, DMSO, and mixtures of these solvents. Following synthesis, the peptide is removed from the

-32-

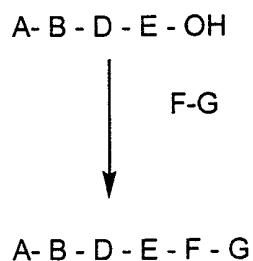
polymeric support. The conditions under which this cleavage is accomplished for various resin types are disclosed in the literature. The cleavage reactions most commonly used are acid- or palladium-catalyzed, the former
5 being conducted in, for example, liquid anhydrous hydrogen fluoride, anhydrous 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
10 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
15 prepared either by coupling the appropriate N,N-di-alkylamino acid to the peptide in solution or on the polymeric support or by reductive alkylation of the resin-bound peptide in DMF/1% acetic acid with NaCNBH_3 and the appropriate aldehyde.

20 The two schemes which follow present a more detailed description of the synthesis of the compounds of the present invention.

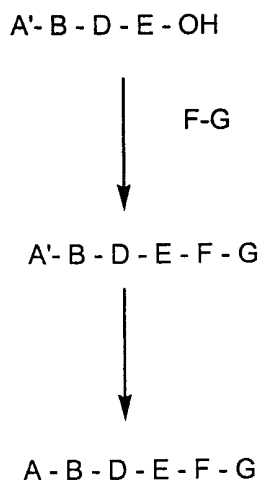
-33-

Scheme I



The tetrapeptide A-B-D-E-OH is coupled with an amino-derivative F-G to give the final compound A-B-D-E-F-G
5 using the methods for peptide coupling as described above.

Scheme II



Here, the N-terminal protected tetrapeptide A'-B-D-E-OH is coupled with an amino-derivative F-G to give an

-34-

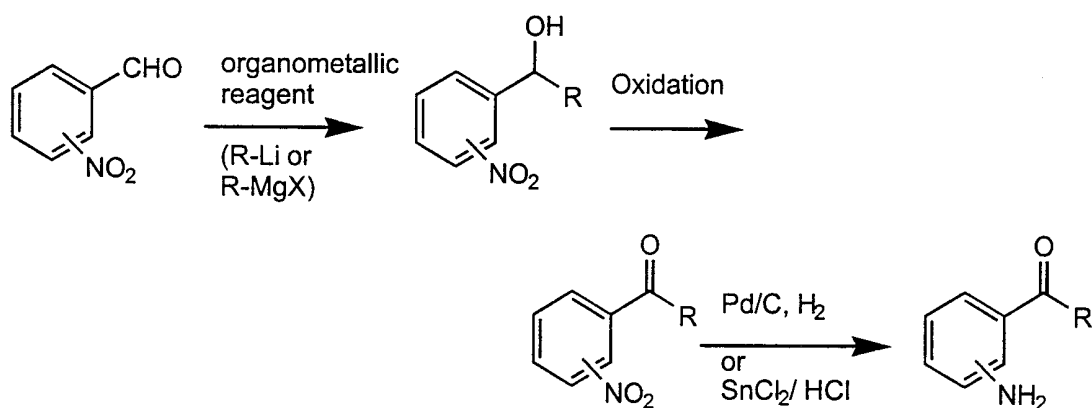
intermediate compound A'-B-D-E-F-G using the methods for peptide coupling as described above. Then, the N-protecting group is removed by conventional methods as described above. The groups R_A and R'_A can then be attached to the amino terminus via reductive alkylation as described above.

Building blocks of use in the synthesis of the claimed compounds (described in scheme I and II as F-G) can be prepared by the following general methods:

a) Synthesis of amino-phenyl-ketones

The following schemes describe synthetic routes to aminophenyl-ketones which are not commercially available.

Scheme III.1

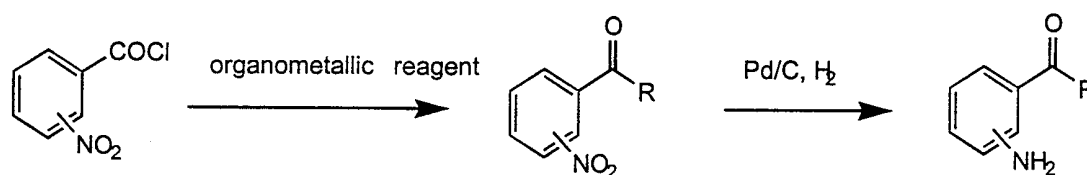


In scheme III.1, the synthesis starts with a nitrobenzaldehyde. Addition of organometallic compounds such as lithium or Grignard reagents led to the corresponding alcohols (Fürstner et al. *Tetrahedron* **52** : 7329-7344 (1996); Fürstner et al., *Tetrahedron* **51**, 773-786

-35-

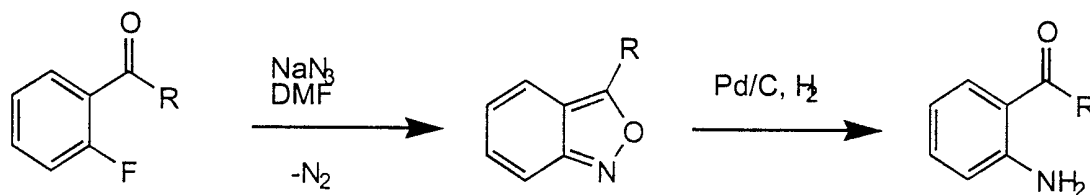
(1995)). These alcohols can be oxidised to the ketones with known oxidation agents, such as chromium(VI) compounds (for example, pyridinium dichromate in dichloromethane, as described by Fürstner *et al.*, *supra*) or the Dess Martin reagent. The nitrophenyl ketones are then reduced to the corresponding amino-phenyl-ketones either by hydrogenation in presence of a palladium catalyst, such as palladium on carbon, or by metal salts in presence of acids such as the combination of tin(II)chloride and hydrochloric acid (Nunn *et al.*, *J. Chem. Soc.* **1952** : 583-588).

Scheme III.2



A more direct route (see scheme III.2) is the reaction of nitrobenzoyl chlorides with an organometallic reagent such as a lithium or Grignard reagent (Fürstner *et al.*, *Tetrahedron* **51**, 773-786 (1995)).

Scheme III.3



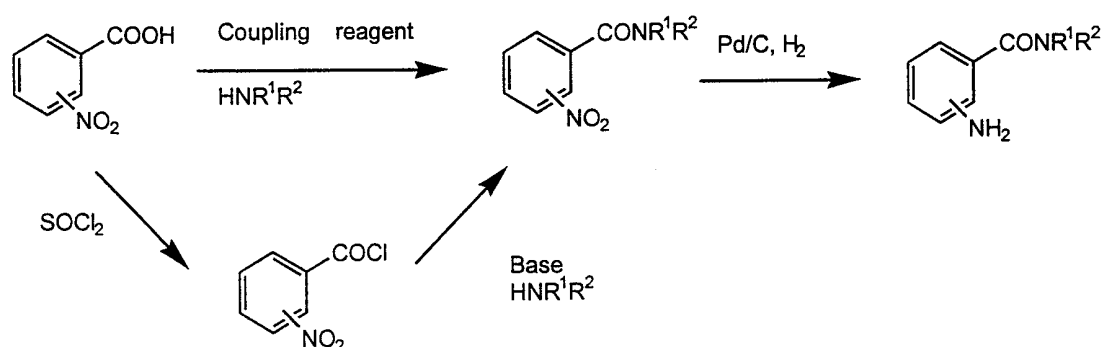
-36-

2-Amino-phenyl ketones can be obtained by reaction of the corresponding 2-fluorophenyl-ketone with sodium azide in a polar solvent, such as N,N-dimethylformamide, and subsequent reduction of the intermediate benzisoxazole (see
5 scheme III.3). For example, the synthesis of 2-aminophenyl-(4-pyridazinyl)-ketone has been described by N. Haider et al. (*Arch. Pharm.* **325** : 119-122 (1992)).

b) synthesis of amino-benzamides

The following schemes describe synthetic routes to
10 aminobenzamides which are not commercially available.

Scheme IV.1



In scheme IV.1, the steps are described starting from nitrobenzoic acids or substituted nitrobenzoic acids. These
15 acids are coupled with primary or secondary amines (HNR^1R^2) by using coupling reagents. Preferred method is the use of coupling reagents such as carboxylic acid activators,

-37-

especially dicyclohexylcarbodiimide (DCC),
diisopropylcarbodiimide (DIC),
1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ),
pivaloylchloride,
5 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
(EDCI), n-propane-phosphonic anhydride (PPA),
N,N-bis(2-oxo-3 oxazolidinyl)-imidophosphoryl chloride
(BOP-Cl), bromo-tris-pyrrolidinophosphonium
hexafluorophosphate (PyBrop), diphenylphosphoryl azide
10 (DPPA), Castro's reagent (BOP, PyBop),
O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU),
diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl
2,3-dihydro-3-oxo-4-hydroxythiophene dioxide (Steglich's
reagent; HOTDO) and 1,1'-carbonyldiimidazole (CDI). The
15 coupling reagents can be employed alone or in combination
with additives such as N,N-dimethyl-4-aminopyridine (DMAP),
N-hydroxy-benzotriazole (HOBT), N-hydroxybenzotriazine
(HOOBT), azabenzotriazole, N-hydroxysuccinimide (HOSu) or
2-hydroxypyridine.

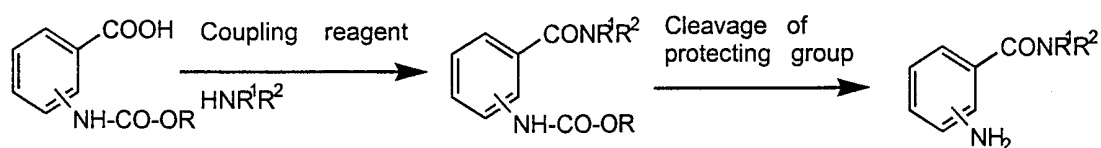
20 In place of the acids, the corresponding nitro-benzoyl
chloride can be used. These are either commercially
available or could be synthesized from the corresponding
acids with thionyl chloride. The amines react with the
nitrobenzoylchlorides in the presence of a base such as
25 pyridine, which can also be used as the solvent (N.S. Cho
et al., *J. Heterocycl. Chem.* **33**, 1201-1206 (1996)). The
nitro-benzamides are then reduced to the corresponding
amino-benzamides by reducing agents such as metal salts in
presence of hydrochloride acids or by metal-catalysed

-38-

hydrogenation using palladium on a solid such as palladium on charcoal as catalyst. This route is described in Example 1.

Another method involves transforming the amine to the trifluoroacetamide by treatment with trifluoroacetic anhydride. The amide is deprotonated with a base such as sodium hydride or potassium t-butanolate and then treated with the corresponding alkyl halide such as methyl iodide, ethyl iodide or isopropyl iodide. The trifluoroacetamide is easily cleaved in basic alcoholic solution such as potassium carbonate in methanol.

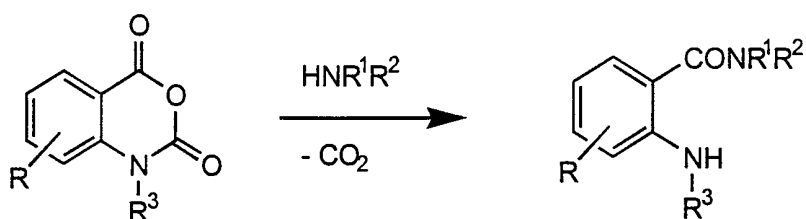
Scheme IV.2



In scheme IV.2. the starting materials for the synthesis of amino-benzamides are the N-protected aminobenzoic acids. Different protecting groups for the nitrogen are compatible such as the above mentioned Z-, Boc- or Fmoc-protecting groups. The N-protected amino-benzoic acids are coupled with amines as described above for the nitro-benzoic acids using the above mentioned coupling conditions. This route is exemplified in Example 2.

Scheme IV.3

-39-



A route for the preparation of 2-aminobenzamides is described in scheme IV.3. Opening of isatoic anhydride (substituted or unsubstituted at the nitrogen) by amines
 5 with evolution of carbon dioxide led to the corresponding 2-amino-benzamides, as described by Clark et al., *J. Org. Chem.* **9** : 55 -64 (1944).

c) Amino-cyclopentane- or aminocyclohexane-carboxamides

Different routes have been described to the synthesis
 10 of cis-2-amino-cyclopentylcarboxylic acid (cispentacin) in racemic form or as pure enantiomer. Using an intramolecular nitron-olefin cycloaddition cis-2-(t-butoxycarbonylamino)cyclopentane-1- carboxylic acid could be prepared in a few synthetic steps (Konosu et al., *Chem.*
 15 *Pharm. Bull.* **41** :1012 (1993)). Another route to enantiomerically pure cis-(1R, 2S)-2-amino-cyclopentylcarboxylic acid is the addition of chiral lithium (S)-(-methylbenzyl)benzylamide to t-butyl-1-cyclopentene-1-carboxylate with subsequent removal of the
 20 benzyl groups by hydrogenation and removal of the t-butyl group by acid treatment (Davies et al., *Synlett* 1993, p. 461). The corresponding trans-epimer could be obtained by isomerisation with a base such as potassium t-butoxide. By

-40-

using the lithium (R)-(-methylbenzyl)benzylamide in the Michael addition (1S, 2R)-2-amino-cyclopentylcarboxylic acid and (1S, 2S)-2-amino-cyclopentylcarboxylic acid can be obtained. This method is also applicable to the synthesis
5 of cis-and trans-aminocyclohexane-1-carboxylic acid.

Resolution of racemic Boc-protected
cis-2-aminocyclopentane carboxylic acid (Bernath et al.,
Acta Chim. **74** : 479 (1972); Nativ et al., *Isr. J. Chem.*
10 : 55 (1972)) can be achieved with (+)- and (-)-ephedrine
10 in high enantiomeric excess (Nöteberg et al., *Tetrahedron*
53 : 7975 (1997)). In this paper also the synthesis of the
trans-enantiomers of Boc-protected
trans-2-aminocyclopentane carboxylic methyl ester was
described, starting with either
15 trans-(3R,4R)-bis(methoxycarbonyl)cyclopentanone or
trans(3S,4S)-bis(methoxycarbonyl)-cyclopentanone.

Amides of Boc-protected 2-aminocyclopentylcarboxylic
acid can be obtained by coupling the acid with the
corresponding amine using the standard procedures as
20 described above for the coupling of nitrobenzoic acid with
amines or as described in D. Nöteberg et al., *Tetrahedron*
53 : 7975 (1997). Deprotection of the amine function can
be achieved by using Lewis acids, for example, a mineral
acid such as hydrochloric acid in ether or dioxane or an
25 organic acid, such as trifluoroacetic acid in methylene
chloride.

Methods of Use of the Claimed Compounds

In another embodiment, the present invention comprises

-41-

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
5 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 agent may be administered alone or in a
10 pharmaceutical composition comprising the agent and an acceptable carrier or diluent. Administration may be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means such as subcutaneously, intravenously,
15 intramuscularly and intraperitoneally, nasally or rectally. The compounds may be administered alone or in the form of pharmaceutical compositions containing a compound of Formula I together with a pharmaceutically accepted carrier appropriate for the desired route of administration. Such
20 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
25 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

-42-

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;
5 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 5 to about 250 milligrams per
10 kilogram of body weight by oral administration and from about 1 to about 100 milligrams per kilogram of body weight by parenteral administration.

The compounds of the present invention can be administered in conventional solid or liquid pharmaceutical
15 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
20 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. Sucker et al.: *Pharmazeutische Technologie*,
25 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 following examples are intended to illustrate the invention but are not to be considered limitations of the
30 invention.

EXAMPLES

The proteinogenous amino acids are abbreviated in the examples using the known three-letter code. Other
5 abbreviations employed are: TFA = trifluoroacetic acid, Ac = acetic acid, DCM = dichloromethane, DMSO = dimethylsulfoxide, Bu = butyl, Et = ethyl, Me = methyl, Bn = benzyl. In the compounds listed, all proteinogenous amino acids are L-amino acids unless otherwise noted.

10

General materials and methods

The compounds of the present invention are synthesized by classical solution synthesis using standard Z- and Boc-methodology as discussed above or by standard methods
15 of solid-phase synthesis on a model 431A synthesizer supplied by APPLIED BIOSYSTEMS. This apparatus uses different synthetic cycles for the Boc and Fmoc protective group techniques, as described below.

20 Synthetic cycle for the Boc protecting group technique

1. 30% trifluoroacetic acid in DCM 1 x 3 min
2. 50% trifluoroacetic acid in DCM 1 x 1 min
3. DCM washing 5 x 1 min
4. 5% diisopropylethylamine in DCM 1 x 1 min
- 25 5. 5% diisopropylethylamine in NMP 1 x 1 min
6. NMP washing 5 x 1 min
7. Addition of preactivated
protected amino acid
(activation with 1 equivalent of
30 DCC and 1 equivalent of HOBt in
NMP/DCM);

- Peptide coupling (1st part) 1 x 30 min
8. Addition of DMSO to the reaction mixture until it contains 20% DMSO by volume
- 5 9. Peptide coupling (2nd part) 1 x 16 min
10. Addition of 3.8 equivalents of diisopropylethylamine to the reaction mixture
11. Peptide coupling (3rd part) 1 x 7 min
- 10 12. DCM washing 3 x 1 min
13. if conversion is incomplete, repetition of coupling (back to step 5)
14. 10% acetic anhydride, 5% diisopropylethylamine in DCM 1 x 2 min
- 15 15. 10% acetic anhydride in DCM 1 x 4 min
16. DCM washing 4 x 1 min
17. back to step 1.

BOP-Cl and PyBrop were used as reagents for coupling an amino acid to an N-methylamino acid. The reaction times were correspondingly increased. In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert-butylloxycarbonyl-amino acid-N-carboxy-anhydrides) or Z-protected amino acid NCAs (N-benzyloxycarbonyl-amino acid-N-carboxy-anhydrides) respectively is most preferable for this type of coupling.

Synthetic cycle for the Fmoc protective group technique

1. DMF washing 1 x 1 min
- 30 2. 20% piperidine in DMF 1 x 4 min

3. 20% piperidine in DMF 1 x 16 min
4. DMF washing 5 x 1 min
5. Addition of the preactivated
5 protected amino acid (activation
by 1 equivalent of TBTU and
1.5 equivalent of DIPEA in DMF);
Peptide coupling 1 x 61 min
6. DMF washing 3 x 1 min
- 10 7. If conversion is incomplete,
repetition of coupling (back to 5.)
8. 10% acetic anhydride in DMF 1 x 8 min
9. DMF washing 3 x 1 min
10. back to 2.

15

BOP-Cl and PyBrop were used as reagents for coupling an amino acid to an N-methylamino acid. The reaction times were correspondingly increased.

20 Reductive alkylation of the N terminus

The peptide-resin prepared as described above 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 NaCNBH₃. After
25 reaction was complete (negative Kaiser test), the resin was washed several times with water, isopropanol, DMF and dichloromethane.

Workup of the peptide-resins

30 The peptide-resin obtained via the Boc protecting

group technique was dried under reduced pressure and transferred into a reaction vessel of a TEFLON HF apparatus (supplied by PENINSULA). A scavenger, usually anisole (1 mL/g of resin), was then added and additionally, in the case of tryptophan-containing peptides, a thiol (0.5 mL/g of resin), preferably ethanedithiol, to remove the indolic formyl group. This was followed by condensing in hydrogen fluoride (10 mL/g of resin) in a bath of liquid N₂. The mixture was allowed to warm to 0°C and stirred at this temperature for 45 min. The hydrogen fluoride was then stripped off under reduced pressure, and the residue was washed with ethyl acetate to remove any remaining scavenger. The peptide was extracted with 30% acetic acid and filtered, and the filtrate was lyophilized.

The peptide-resin formed by the Fmoc protecting group method was dried under reduced pressure and then subjected to one of the following cleavage procedures, depending upon the amino-acid composition (Wade, Tregear, Howard Florey Fmoc Workshop Manual, Melbourne 1985). The suspension of the peptide-resin in the suitable TFA mixture was stirred at room temperature for the stated time and then the resin was filtered off and washed with TFA and DCM. The filtrate and the washings were concentrated, and the peptide was precipitated by addition of diethyl ether. After cooling in an ice bath, the precipitate was filtered off, taken up in 30% acetic acid and lyophilized.

When an o-chlorotrityl-resin (supplied by Biohellas) was used, the suspension of the peptide-resin in an acetic acid/trifluoroethanol/dichloromethane mixture (1:1:3) was stirred at room temperature for 1 h. The suspension was

then filtered with suction and the peptide-resin was thoroughly washed with the cleavage solution. The combined filtrates were concentrated in vacuo and treated with water. The precipitated solid was removed by filtration or
5 centrifugation, washed with diethyl ether and dried under reduced pressure.

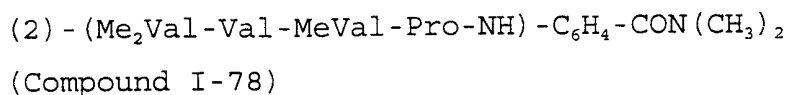
Purification and characterization of the peptides

Purification was carried out by gel chromatography
10 (SEPHADEX G-10, G-15/10% HOAc, SEPHADEX LH20/MeOH) with or without subsequent medium pressure chromatography (stationary phase: HD-SIL C-18, 20-45 m, 100 Å; mobile phase: gradient with A = 0.1% TFA/MeOH, B = 0.1% TFA/H₂O). The purity of the resulting products was determined by
15 analytical HPLC (stationary phase: 100 2.1 mm VYDAC C-18, 5 l, 300 Å; mobile phase: CH₃CN/H₂O gradient, buffered with 0.1% TFA, 40°C).

The polypeptides were characterized by amino-acid analysis and fast atom bombardment mass spectroscopy.

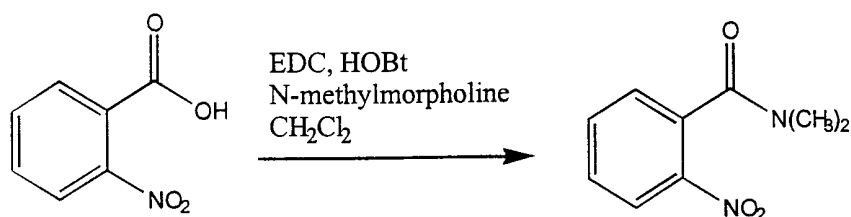
20

Example 1 Synthesis of



25 Me₂Val-Val-MeVal-Pro-OH and Z-Val-Val-MeVal-Pro-OH were prepared by the method disclosed in patent applications DE 4415998 and DE 19527575, the contents of which are incorporated herein by reference.

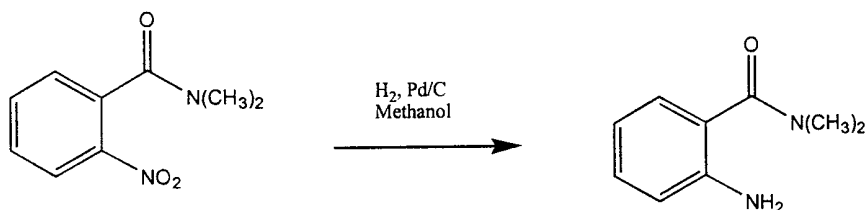
30 a) Synthesis of N,N-dimethyl-2-nitrobenzamide



To a solution of 2.0 g 2-nitrobenzoic acid and 0.98 g dimethylammonium chloride in dichloromethane at 0°C were added 2.29 g 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1.62 g N-hydroxy-benzotriazole and 6.05 g N-methyl-morpholine. The resulting mixture was stirred at room temperature overnight. The reaction mixture was then washed sequentially with saturated sodium hydrogen carbonate, a 5% aqueous solution of citric acid and brine. The organic phase was dried over sodium sulfate. After filtration the solvent was removed *in vacuo* yielding N,N-dimethyl-2-nitrobenzamide (2.13 g).

¹H-NMR (DMSO, 270 MHz) δ = 2.7 (s, 3 H), 3.0 (s, 3 H), 7.5 (d, 1 H), 7.7 (dd, 1 H), 7.85 (dd, 1 H), 8.15 (d, 1 H) ppm

b) Synthesis of N,N-dimethyl-2-aminobenzamide



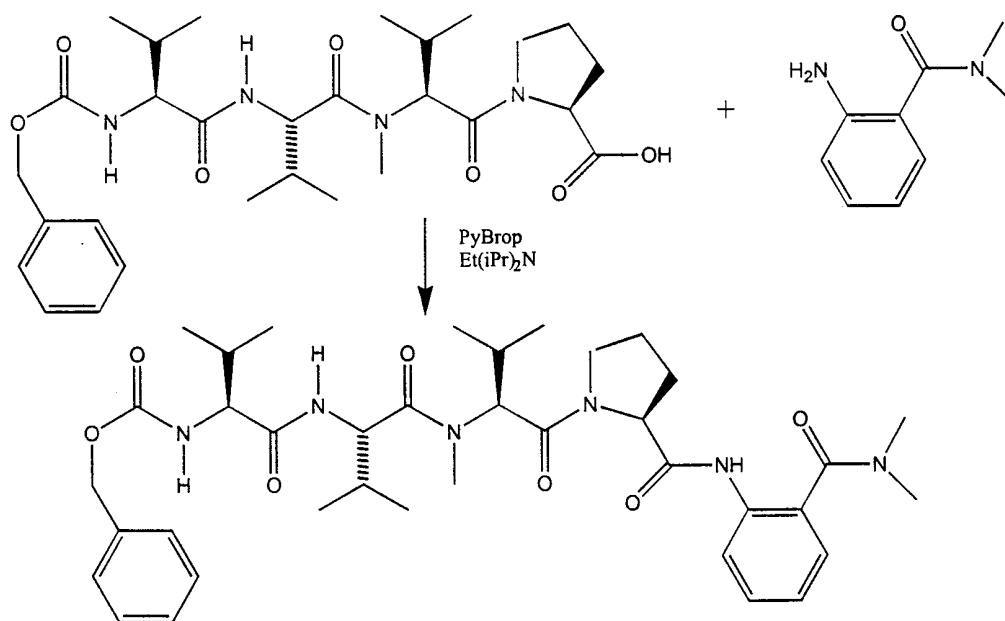
Palladium on charcoal (0.54 g, 10% Pd by weight) was added to a solution of 2.1 g N,N-dimethyl-2-nitrobenzamide

in 150 mL methanol. The resulting suspension was hydrogenated at room temperature at atmospheric pressure for three hours. After filtration of the catalyst, the solvent was removed *in vacuo* affording N,N-dimethyl-2-aminobenzamide (1.8 g).

$^1\text{H-NMR}$ (DMSO, 270 MHz) δ = 2.9 (s, 6 H), 5.1 (s, 2 H), 6.5 (dd, 1 H), 6.65 (d, 1 H), 7.95 (d, 1 H), 7.0 (dd, 1 H) ppm

c) Synthesis of (2)-(Z-Val-Val-MeVal-Pro-NH)-C₆H₄-CON(CH₃)₂

10

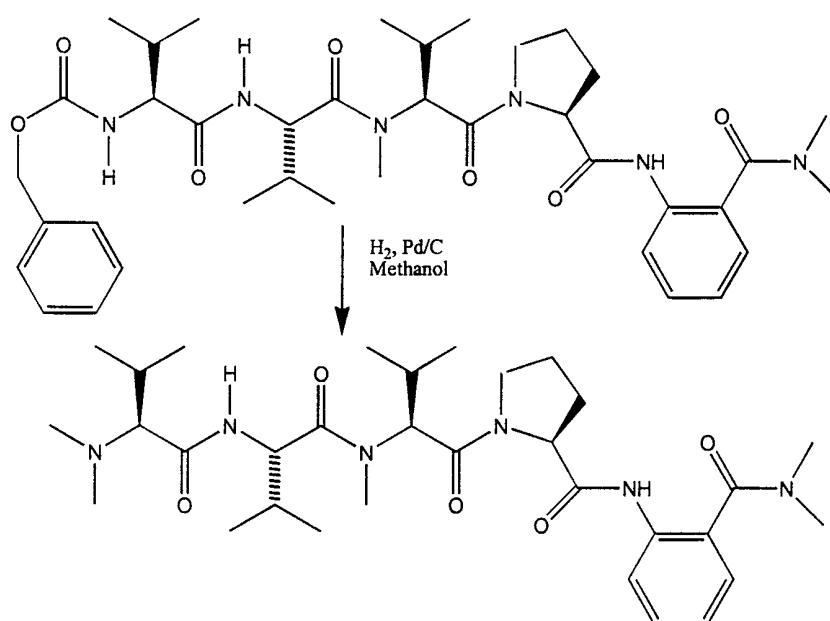


15 To a solution of 2.0 g Z-Val-Val-MeVal-Pro-OH and 0.53 g N,N-dimethyl-2-amino-benzamide in dichloromethane was added 1.66 g bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrop) and 0.77 g N-ethyldiisopropylamine at 0°C. The mixture was stirred at room temperature

20 overnight, and then washed sequentially with saturated sodium hydrogen carbonate, a 5% aqueous solution of citric

acid, and brine. The organic phase was dried over sodium sulfate. After filtration, the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (1:3 dichloromethane:ethyl acetate) to provide
 5 (2)-(Z-Val-Val-MeVal-Pro-NH)-C₆H₄-CON(CH₃)₂ (1.8 g).
 FAB-MS 707.0 (M + H⁺)

d) Synthesis of 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CON(CH₃)₂



10

Palladium on charcoal (58 mg, 10% Pd by weight) was
 15 added to a solution of 1.8 g 2-(Z-Val-Val-MeVal-Pro-NH)-
 C₆H₄-CON(CH₃)₂ in 150 mL methanol. The resulting suspen-
 sion was hydrogenated at room temperature at atmospheric
 pressure for three hours, then 1.5 mL of an aqueous
 formaldehyde solution (37% formaldehyde by weight) and 341
 20 mg of palladium on charcoal were added. The mixture was
 hydrogenated at room temperature at atmospheric pressure

overnight. After filtration over celite the solvent was removed *in vacuo* to give 1.30 g 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CON(CH₃)₂. FAB-MS: 601.0 (M + H⁺)

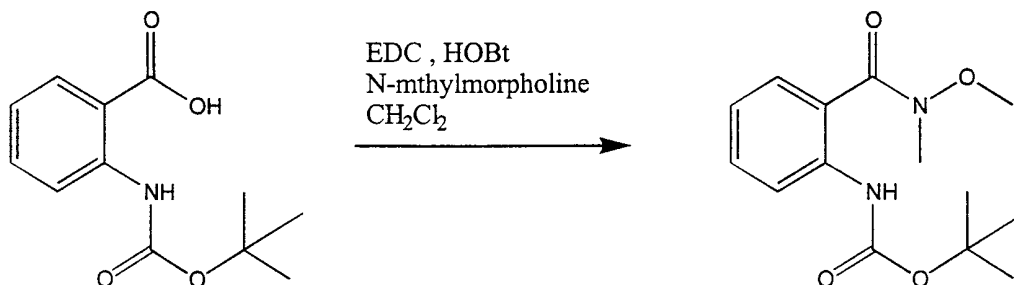
¹H-NMR (DMSO, 270 MHz) δ = 0.7 (s, 6 H), 0.8 - 1.0 (m, 12 H), 1.75 (m, 1 H), 1.8 - 2.2 (m, 6 H), 2.2 (s, 6 H), 2.6 (d, 1 H), 2.8 (s, 3 H), 2.9 (s, 3 H), 3.05 (s, 3 H), 3.55, 3.7 (m, 2 H), 4.4 (m, 1 H), 4.5 (m, 1 H), 5.0 (d, 1 H), 7.2 (dd, 1 H), 7.25 (d, 1 H), 7.4, dd, 1 H, 7.6 (dd, 1 H), 8.0 (d, 1 H), 9.6 (s, 1H)

10

Example 2 Synthesis of

(2) - (Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CON(CH₃) (OCH₃)
(Compound I-60)

15 a) Synthesis of N,O-dimethyl-(2-N-tert.
butoxycarbonyl-amino)benzohydroxylamide

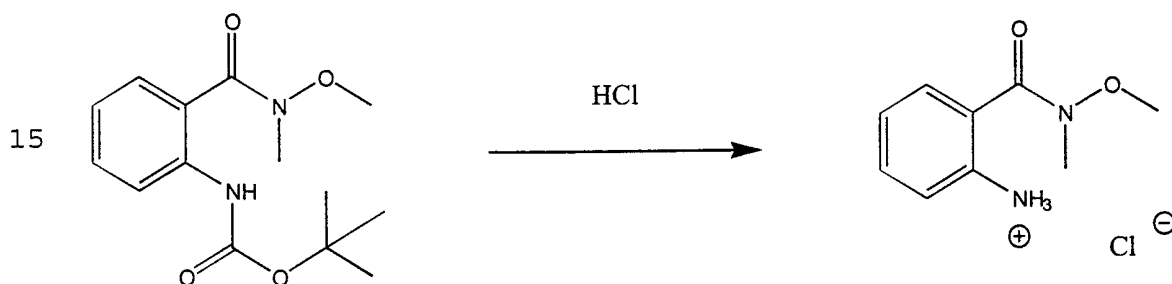


To a solution of 1.5 g 2-N-t-butoxy-carbonyl
20 anthranilic acid and 0.68 g N,O-dimethylhydroxylamine
hydrochloride in dichloromethane at 0°C, 1.33 g 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 0.94 g N-hydroxybenzotriazol and 3.20 g N-methylmorpholine were added. The mixture was stirred at room temperature

overnight. The reaction mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate, a 5% aqueous solution of citric acid and brine. The organic phase was dried over sodium sulfate. After filtration the solvent was removed *in vacuo*. Flash chromatography (silica gel, heptane:ethyl acetate 10:1) afforded N, O-dimethyl-(2-N-tert. Butoxycarbonyl-amino) benzohydroxylamide (1.18 g).

¹H-NMR (CDCl₃, 270 MHz) δ = 1.5 (s, 9 H), 3.4 (s, 3 H), 3.6 (s, 3 H), 7.0 (dd, 1 H), 7.2 -7.4 (m, 2 H), 8.1 (d, 1 H), 8.4 (s, 1 H)

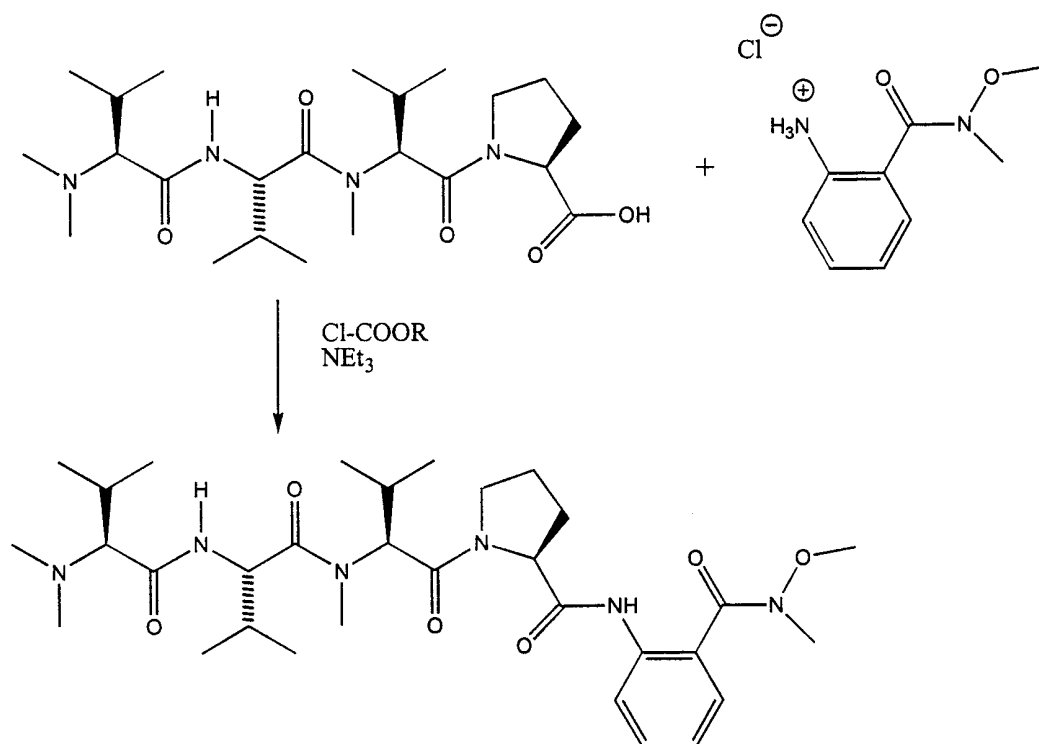
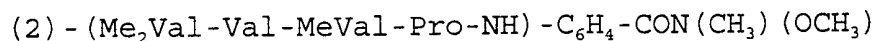
b) Synthesis of N,O-dimethyl-(2-amino)benzohydroxylamide hydrochloride.



To a solution of 0.5 g N,O-dimethyl-(2-N-tert. butoxycarbonyl-amino)benzohydroxylamide in 15 mL dichloromethane at 0°C was added 17 mL of a hydrogen chloride solution in ether and the resulting solution was stirred for 2 hours. The solvent was evaporated to give 0.41 g N,O-dimethyl-(2-amino)benzohydroxylamide hydrochloride.

¹H-NMR (CDCl₃, 270 MHz) δ = 3.4 (s, 3 H), 3.6 (s, 3 H), 7.3 (dd, 1 H), 7.5 (dd, 2 H), 7.6 (d, 1 H), 7.9 (d, 1 H)

c) Synthesis of



5

To a solution of 0.892 g $\text{Me}_2\text{Val}-\text{Val}-\text{MeVal}-\text{Pro}-\text{OH}$ and 0.234 g triethylamine in 10 mL dichloromethane at 0°C was added 0.218 g formate. After stirring the resulting mixture for two hours, 0.41 g N,O-dimethyl-

10 (2-amino)benzohydroxylamide hydrochloride and 0.234 g triethylamine were added and the mixture was stirred overnight at room temperature. The reaction mixture was washed sequentially with saturated sodium hydrogen

15 carbonate solution and brine. The organic phase was dried over sodium sulfate. After filtration the solvent was removed in vacuo. The residue was purified by chromatography (silica gel treated with 1% triethylamine,

solvent: dichloromethane/3% isopropanol) to provide 0.28 g
(2) - (Me₂Val-Val-MeVal- Pro-NH) -C₆H₄-CON(CH₃) (OCH₃) .

FAB-MS: 617.5 (M + H⁺)

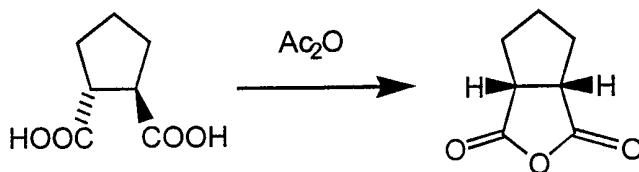
¹H-NMR (DMSO, 270 MHz) δ = 0.7 (s, 6 H), 0.8 -1.0 (m, 12
5 H), 1.7 (m, 1 H), 1.8 - 2.2 (m, 6 H), 2.2 (s, 6 H), 2.6 (d,
1 H), 3.0 (s, 3 H), 3.2 (s, 3 H), 3.5 (s, 3 H), 3.5, 3.7
(m, 2 H), 4.4 (m, 1 H), 4.5 (m, 1 H), 5.0 (d, 1 H), 7.2
(dd, 1 H), 7.3 - 7.5 (m, 2 H), 7.6 (dd, 1 H), 8.0 (d, 1 H),
9.65 (s, 1H)

10

Example 3 Synthesis of

Me₂-Val-Val-MeVal-Pro-[cis-2-aminocyclopentanecar
boxylic acid]-NHBN (Compound VII-2)

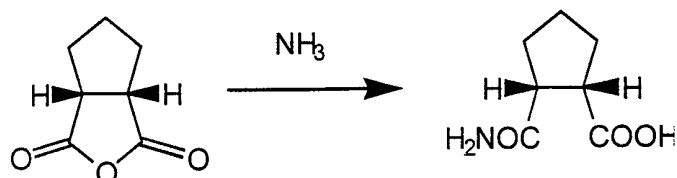
15 d) Synthesis of racemic cyclopentane-cis-1,2-dicarboxylic
acid anhydride



8.4 g (44.3 mmol) of commercially available
20 cyclopentane-trans-1,2-dicarboxylic acid was refluxed for
20h in 75ml of acetic acid anhydride, then evaporated and
the obtained residue distilled in a "Kugelrohr-apparatus"
at 1.0mbar. The fraction boiling at 165° was collected,
yielding 5.8 g of the product as an oil.

25 ¹³C-NMR (400 MHz; DMSO-d₆) δ (ppm): 25.3 (C-4), 30.6
(C-3,5), 45.7 (C-1,2), 175.6 (C-6,7).

- b) Synthesis of racemic
cis-2-carbamoylcyclopentanecarboxylic acid

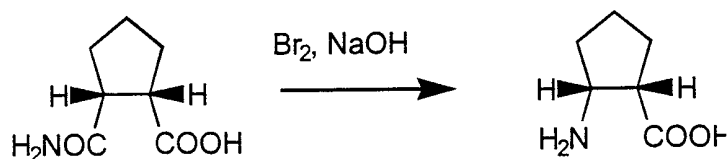


5

1.1 g (7.85 mmol) of cyclopentane-cis-1,2-dicarboxylic acid anhydride were added to 8ml of an aqueous NH_3 -solution and stirred until dissolution of the educt. The excess of ammonia was then evaporated, the remaining solution cooled
10 to 0°C and acidified with conc. HCl . The resulting precipitate was filtered off, washed with cold water and dried, yielding 0.7 g of cis-2-carbamoylcyclopentanecarboxylic acid with a melting point of $132\text{--}133^\circ\text{C}$ (lit.: $126\text{--}128^\circ\text{C}$).

15

- c) Synthesis of racemic cis-2-aminocyclopentanecarboxylic acid



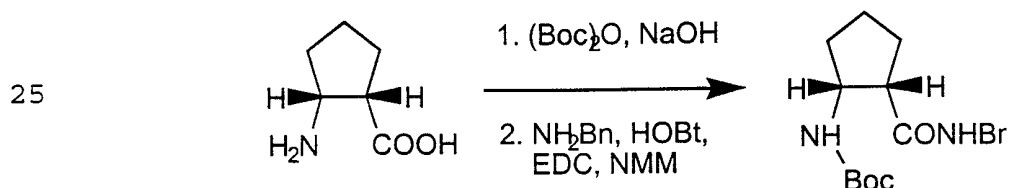
20 Under stirring at 0°C 0.41 g (2.6 mmol) of Br_2 were added to an aqueous solution (1.8 mL) of 0.48 g (12 mmol) NaOH . The mixture was cooled again and then 0.34 g (2.16 mmol) of cis-2-carbamoylcyclopentanecarboxylic acid

added. After stirring for about 10 minutes again 0.35 g (8.65 mmol) NaOH - dissolved in 1.35ml of water- were added, and then the whole mixture warmed to 75°C for about 5 minutes. The mixture then was cooled again, neutralized by addition of conc. HCl, acidified with acetic acid and evaporated to dryness. The residue obtained was extracted five times with refluxing ethanol, and the combined ethanol-fractions evaporated again yielding 1.1 g of a white solid.

Purification was achieved by filtration of this residue over a column with Dowex 50 ion exchange resin. Therefore the column was washed with a solution of the solid in water, and then the product eluted by treatment with solid was dissolved in water and the column, absorbed on by washing the column with aqueous diluted NH_3 . After evaporation of the water the remaining crude product was recrystallized from acetone yielding 0.14 g of pure cis-2-aminocyclopentanecarboxylic acid with a melting point of 200-202°C.

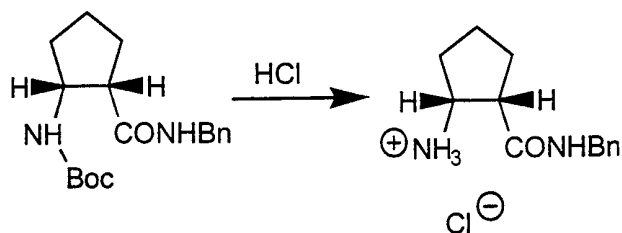
20

d) Synthesis of racemic cis-2-t-butylloxycarbonylaminocyclopentanecarboxylic acid benzylamide



To a solution of 1.5 g (11.6 mmol) of cis-2-aminocyclopentanecarboxylic acid in a mixture of

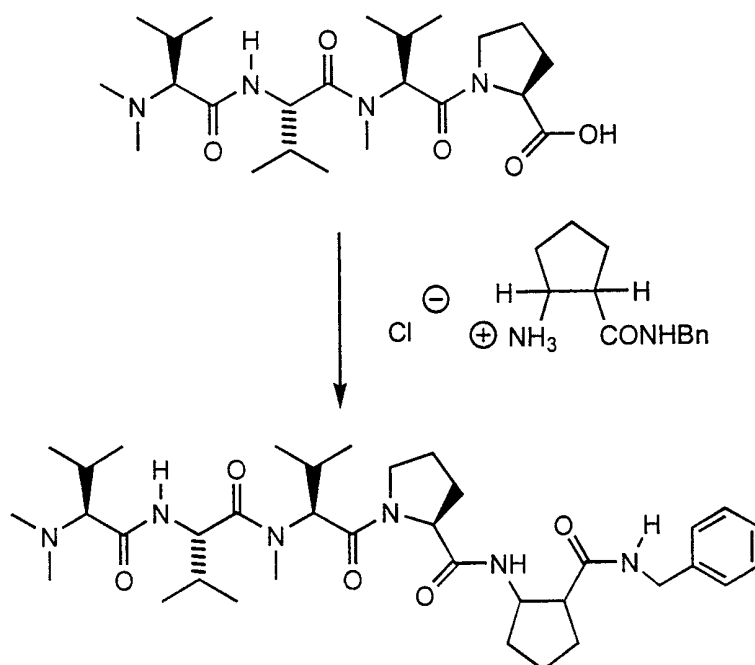
- acetonitrile/water 3:1 were added 3.3g (15.1 mmol) of di^tbutyldicarbonate, 0.5 g (12.2 mmol) of NaOH dissolved in 12 ml of H₂O and 0.1 g (0.82 mmol) of DMAP. The mixture was stirred at ambient temperature for about 3 days, then
- 5 diluted with water, extracted with ethylacetate. The combined organic phases were washed with a saturated aqueous NaCl-solution, dried over MgSO₄ and evaporated to dryness leaving 1.3 g of the Boc-protected compound as an oil. A solution of the crude product and 0.65 g (6.1 mmol)
- 10 benzylamine in a mixture of THF/DMF 10:1 was cooled to -10°C, then were added subsequently 0.9 g (5.86 mmol) of HOBT, 1.12 g (5.86 mmol) of EDC x HCl and 3ml of NMM. The mixture was stirred for 2h at -10°C, for 3h at 0°C and was then allowed to warm up to room temperature. After
- 15 evaporation to dryness the remaining residue was dissolved in ethylacetate, washed with aqueous solutions of 5% citric acid, NaHCO₃ and NaCl and dried over MgSO₄. Evaporation yielded 1.3 g of cis-2-t-butyloxycarbonylamino-cyclopentanecarboxylic acid benzylamide as an oil.
- 20 HPLC (gradient 2): R_t 10.5 min.
(Column: Machery & Nagel Nucleosil C18 PPN, 100 x 2.1, 5m/100A, acetonitrile/H₂O + 0.1% TFA; flow: 0.2 ml/min; temp. 40°C.).
- ¹H-NMR (270 MHz; DMSO-d₆) δ (ppm): 1.35 (s, 9H), 1.35-1.95 (m, 6H), 2.82 (m, 1H), 4.03 (m, 1H), 4.25 (m, 2H), 6.35 (d, NH), 7.1-7.35 (m, 5H), 8.3 (m, 1H).
- 25
- e) Synthesis of racemic cis-2-aminocyclopentanecarboxylic acid benzylamide hydrochloride



To a solution of 0.7 g (2.2 mmol) of of
 cis-2-tert.butyloxycarbonylamino-cyclo-pentanecarboxylic
 5 acid benzylamide in 30ml CH₂Cl₂, were added 25ml of saturated
 HCl in diethylether; the mixture was then stirred for 2h at
 ambient temperature. Evaporation to dryness and
 coevaporation with toluene yielded 0.6 g of the deprotected
 amine as hydrochloride salt.

10

f) Synthesis of
 Me₂-Val-Val-MeVal-Pro-[cis-2-aminocyclopentanecarboxyl
 ic acid]-NHBn (Compound VII-2)



15

To a solution of 0.86 g (1.9 mmol) of the tetrapeptide Me₂Val-Val-MeVal-Pro-OH and 0.56 g (2.2 mmol) aminocyclo-pentanecarboxylic acid benzylamide hydrochloride in 30ml of THF/DMF 5:1 were added subsequently at -10°C

5 0.29 g (1.9 mmol) of HOBT; 0.37 g (1.9 mmol) of EDC x HCl and 1.2ml of NMM. The mixture was stirred for another at -10°C, then for 1-2h at 0°C and then allowed to warm up to ambient temperature. After evaporation the remaining residue was diluted with ethyl acetate, washed with an

10 aqueous solution of NaCl, dried over MgSO₄, and evaporated again. The remaining crude product (1.2 g) was purified by flash chromatography on silica gel (CH₂Cl₂/CH₃OH) yielding 0.37 g of

Me₂Val-Val-MeVal-Pro-[cis-2-aminocyclopentanecarboxylic

15 acid]-NHBn.

FAB-MS: 655 (M+H⁺).

The following compounds can be prepared as outlined in Schemes I-III and according to the above examples.

20

Table 1:

A is Me₂Val, B is Val, D is MeVal, E is Pro, F is of Formula II_F and the group -C(=O)-G is in position 2 relative to the nitrogen atom. G is of Formula II_G or,

25 III_G or IV_G.

No.	R _F	R _F ¹	R _F ²	-C(=O)-G
I-1	H	H	H	-NH-CH ₃
30 I-2	H	H	H	-NH-CH ₂ -C ₆ H ₅
I-3	H	H	H	-NH-isoC ₃ H ₇
I-4	H	H	H	-NH-C ₆ H ₅

	I-5	H	H	H	1,3-Thiazol-2-yl-amide
	I-6	H	4-OCH ₃	5-OCH ₃	-NH-CH ₃
	I-7	H	3-cycloC ₅ H ₉	H	-NH-CH ₃
	I-8	H	H	H	-NH-C ₂ H ₅
5	I-9	H	H	H	-NH-nC ₃ H ₇
	I-10	H	H	H	-NH-nC ₄ H ₉
	I-11	H	H	H	-NH-tertC ₄ H ₉
	I-12	H	H	H	-NH-cycloC ₃ H ₅
	I-13	H	H	H	-NH-cycloC ₄ H ₇
10	I-14	H	H	H	-NH-cycloC ₅ H ₉
	I-15	H	H	H	-NH-cycloC ₆ H ₁₁
	I-16	H	H	H	-NH-cycloC ₇ H ₁₃
	I-17	H	H	H	-NH-CH ₂ -O-CH ₃
	I-18	H	H	H	-NH-CH ₂ -CH ₂ -O-CH ₃
15	I-19	H	H	H	-NH-1-adamantyl
	I-20	H	H	H	-NH-(4-HO-C ₆ H ₅)
	I-21	H	H	H	-NH-(2-CF ₃ -C ₆ H ₄)
	I-22	H	H	H	-NH-(3-CF ₃ -C ₆ H ₄)
	I-23	H	H	H	-NH-(4-CF ₃ -C ₆ H ₄)
20	I-24	H	H	H	-NH-(2-OCH ₃ -C ₆ H ₄)
	I-25	H	H	H	-NH-(3-OCH ₃ -C ₆ H ₄)
	I-26	H	H	H	-NH-(4-OCH ₃ -C ₆ H ₄)
	I-27	H	H	H	-NH-(2-SCH ₃ -C ₆ H ₄)
	I-28	H	H	H	-NH-(3-SCH ₃ -C ₆ H ₄)
25	I-29	H	H	H	-NH-(4-SCH ₃ -C ₆ H ₄)
	I-30	H	H	H	-NH-(2-N(CH ₃) ₂ -C ₆ H ₄)
	I-31	H	H	H	-NH-(3-N(CH ₃) ₂ -C ₆ H ₄)
	I-32	H	H	H	-NH-(4-N(CH ₃) ₂ -C ₆ H ₄)
	I-33	H	H	H	-NH-(4-CN-C ₆ H ₄)
30	I-34	H	H	H	-NH-(4-Cl-C ₆ H ₄)
	I-35	H	H	H	-NH-(4-Br-C ₆ H ₄)
	I-36	H	H	H	-NH-(4-F-C ₆ H ₄)

	I-37	H	H	H	-NH-(4-CH ₃ -C ₆ H ₄)
	I-38	H	H	H	-NH-(2-NO ₂ -C ₆ H ₄)
	I-39	H	H	H	-NH-(3-NO ₂ -C ₆ H ₄)
	I-40	H	H	H	-NH-(4-NO ₂ -C ₆ H ₄)
5	I-41	H	H	H	-NH-(2,4-OCH ₃ -C ₆ H ₃)
	I-42	H	H	H	-NH-(3,4-OCH ₃ -C ₆ H ₃)
	I-43	H	H	H	-NH-(3,4,5-OCH ₃ -C ₆ H ₂)
	I-44	H	H	H	-NH-(3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	I-45	H	H	H	-NH-(2,3-CH ₂ OCH ₂ -C ₆ H ₃)
10	I-46	H	H	H	-NH-2-pyridinyl
	I-47	H	H	H	-NH-2-furanyl
	I-48	H	H	H	-NH-2-thienyl
	I-49	H	H	H	-NH-3-pyridinyl
	I-50	H	H	H	-NH-3-furanyl
15	I-51	H	H	H	-NH-3-thienyl
	I-52	H	H	H	-NH-4-pyridinyl
	I-53	H	H	H	-NH-2-oxazolyl
	I-54	H	H	H	-NH-3-isoxazolyl
	I-55	H	H	H	-NH-4-isoxazolyl
20	I-56	H	H	H	-NH-5-isoxazolyl
	I-57	H	H	H	-NH-2R-(but-2-yl)
	I-58	H	H	H	-NH-2S-(but-2-yl)
	I-59	H	H	H	-NH-O-CH ₃
	I-60	H	H	H	-N(CH ₃)(OCH ₃)
25	I-61	H	H	H	-N(-(CH ₂) ₃ -O-)
	I-62	H	H	H	-NH-O-CH ₂ -C ₆ H ₅
	I-63	H	H	H	-N(CH ₃)(O-CH ₂ -C ₆ H ₅)
	I-64	H	H	H	-N(-(CH ₂) ₂ -CH(C ₆ H ₅)-O-)
	I-65	H	H	H	-NH-O-C ₂ H ₅
30	I-66	H	H	H	-N(C ₂ H ₅)(OC ₂ H ₅)
	I-67	H	H	H	-N(CH ₃)(OC ₂ H ₅)
	I-68	H	H	H	-NH-O-isoC ₃ H ₇

	I-69	H	H	H	-N(CH ₃) (O-isoC ₃ H ₇)
	I-70	H	H	H	-NH-O-nC ₃ H ₇
	I-71	H	H	H	-N(CH ₃) (O-nC ₃ H ₇)
	I-72	H	H	H	-NH-O-nC ₄ H ₉
5	I-73	H	H	H	-N(CH ₃) (O-nC ₄ H ₉)
	I-74	H	H	H	-NH-O-tertC ₄ H ₉
	I-75	H	H	H	-N(CH ₃) (O-tertC ₄ H ₉)
	I-76	H	H	H	-NH-O-C ₆ H ₅
	I-77	H	H	H	-N(CH ₃) (O-C ₆ H ₅)
10	I-78	H	H	H	-N(CH ₃) ₂
	I-79	H	H	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-80	H	H	H	-N(C ₂ H ₅) ₂
	I-81	H	H	H	-N(isoC ₃ H ₇) ₂
	I-82	H	H	H	-N(nC ₃ H ₇) ₂
15	I-83	H	H	H	-N(nC ₄ H ₉) ₂
	I-84	H	H	H	-N(C ₆ H ₅) ₂
	I-85	H	H	H	-NH-CH ₂ -CH ₂ -OH
	I-86	H	H	H	-NH-(CH ₂) ₃ -OH
	I-87	H	H	H	-NH(-(CH ₂) ₂ CH(C ₆ H ₅)OH)
20	I-88	H	H	H	-NH-(CH ₂) ₄ -OH
	I-89	H	H	H	-NH(-CH(CH ₃)-CH ₂ -OH)
	I-90	H	H	H	-NH(-CH ₂ -CH(CH ₃)-OH)
	I-91	H	H	H	-NH(CH(CH ₃)(CH ₂) ₂ OH)
	I-92	H	H	H	-NH(-(CH ₂) ₂ CH(CH ₃)OH)
25	I-93	H	4-CH ₃	H	-NH-CH ₃
	I-94	H	4-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
	I-95	H	4-CH ₃	H	-NH-isoC ₃ H ₇
	I-96	H	4-CH ₃	H	-NH-C ₆ H ₅
	I-97	H	4-CH ₃	H	-NH-C ₂ H ₅
30	I-98	H	4-CH ₃	H	-NH-nC ₃ H ₇
	I-99	H	4-CH ₃	H	-NH-nC ₄ H ₉
	I-100	H	4-CH ₃	H	-NH-tertC ₄ H ₉

	I-101	H	4-CH ₃	H	-NH-cycloC ₃ H ₅
	I-102	H	4-CH ₃	H	-NH-cycloC ₄ H ₇
	I-103	H	4-CH ₃	H	-NH-cycloC ₅ H ₉
	I-104	H	4-CH ₃	H	-NH-cycloC ₆ H ₁₁
5	I-105	H	4-CH ₃	H	-NH-1-adamantyl
	I-106	H	4-CH ₃	H	-NH-2R- (but-2-yl)
	I-107	H	4-CH ₃	H	-NH-2S- (but-2-yl)
	I-108	H	4-CH ₃	H	-NH-O-CH ₃
	I-109	H	4-CH ₃	H	-N(CH ₃)(OCH ₃)
10	I-110	H	4-CH ₃	H	-N(-(CH ₂) ₃ -O-)
	I-111	H	4-CH ₃	H	-N(CH ₃) ₂
	I-112	H	4-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-113	H	4-CH ₃	H	-N(C ₂ H ₅) ₂
	I-114	H	4-CH ₃	H	-N(isoC ₃ H ₇) ₂
15	I-115	H	4-CH ₃	H	-N(nC ₃ H ₇) ₂
	I-116	H	4-CH ₃	H	-N(nC ₄ H ₉) ₂
	I-117	H	4-CH ₃	H	-N(C ₆ H ₅) ₂
	I-118	H	5-CH ₃	H	-NH-CH ₃
	I-119	H	5-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
20	I-120	H	5-CH ₃	H	-NH-isoC ₃ H ₇
	I-121	H	5-CH ₃	H	-NH-C ₆ H ₅
	I-122	H	5-CH ₃	H	-NH-C ₂ H ₅
	I-123	H	5-CH ₃	H	-NH-nC ₃ H ₇
	I-124	H	5-CH ₃	H	-NH-nC ₄ H ₉
25	I-125	H	5-CH ₃	H	-NH-tertC ₄ H ₉
	I-126	H	5-CH ₃	H	-NH-cycloC ₃ H ₅
	I-127	H	5-CH ₃	H	-NH-cycloC ₄ H ₇
	I-128	H	5-CH ₃	H	-NH-cycloC ₅ H ₉
	I-129	H	5-CH ₃	H	-NH-cycloC ₆ H ₁₁
30	I-130	H	5-CH ₃	H	-NH-1-adamantyl
	I-131	H	5-CH ₃	H	-NH-2R- (but-2-yl)
	I-132	H	5-CH ₃	H	-NH-2S- (but-2-yl)

	I-133	H	5-CH ₃	H	-NH-O-CH ₃
	I-134	H	5-CH ₃	H	-N(CH ₃)(OCH ₃)
	I-135	H	5-CH ₃	H	-N(-(CH ₂) ₃ -O-)
	I-136	H	5-CH ₃	H	-N(CH ₃) ₂
5	I-137	H	5-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-138	H	5-CH ₃	H	-N(C ₂ H ₅) ₂
	I-139	H	5-CH ₃	H	-N(isoC ₃ H ₇) ₂
	I-140	H	5-CH ₃	H	-N(nC ₃ H ₇) ₂
	I-141	H	5-CH ₃	H	-N(nC ₄ H ₉) ₂
10	I-142	H	5-CH ₃	H	-N(C ₆ H ₅) ₂
	I-143	CH ₃	H	H	-NH-CH ₃
	I-144	CH ₃	H	H	-NH-CH ₂ -C ₆ H ₅
	I-145	CH ₃	H	H	-NH-isoC ₃ H ₇
	I-146	CH ₃	H	H	-NH-C ₆ H ₅
15	I-147	CH ₃	H	H	-NH-C ₂ H ₅
	I-148	CH ₃	H	H	-NH-nC ₃ H ₇
	I-149	CH ₃	H	H	-NH-nC ₄ H ₉
	I-150	CH ₃	H	H	-NH-tertC ₄ H ₉
	I-151	CH ₃	H	H	-NH-cycloC ₃ H ₅
20	I-152	CH ₃	H	H	-NH-cycloC ₄ H ₇
	I-153	CH ₃	H	H	-NH-cycloC ₅ H ₉
	I-154	CH ₃	H	H	-NH-cycloC ₆ H ₁₁
	I-155	CH ₃	H	H	-NH-1-adamantyl
	I-156	CH ₃	H	H	-NH-2R-(but-2-yl)
25	I-157	CH ₃	H	H	-NH-2S-(but-2-yl)
	I-158	CH ₃	H	H	-NH-O-CH ₃
	I-159	CH ₃	H	H	-N(CH ₃)(OCH ₃)
	I-160	CH ₃	H	H	-N(-(CH ₂) ₃ -O-)
	I-161	CH ₃	H	H	-N(CH ₃) ₂
30	I-162	CH ₃	H	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-163	CH ₃	H	H	-N(C ₂ H ₅) ₂
	I-164	CH ₃	H	H	-N(isoC ₃ H ₇) ₂

	I-165	CH ₃	H	H	-N(nC ₃ H ₇) ₂
	I-166	CH ₃	H	H	-N(nC ₄ H ₉) ₂
	I-167	CH ₃	H	H	-N(C ₆ H ₅) ₂
	I-168	H	4-OCH ₃	H	-NH-CH ₃
5	I-169	H	4-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	I-170	H	4-OCH ₃	H	-NH-isoC ₃ H ₇
	I-171	H	4-OCH ₃	H	-NH-C ₆ H ₅
	I-172	H	4-OCH ₃	H	-NH-C ₂ H ₅
	I-173	H	4-OCH ₃	H	-NH-nC ₃ H ₇
10	I-174	H	4-OCH ₃	H	-NH-nC ₄ H ₉
	I-175	H	4-OCH ₃	H	-NH-tertC ₄ H ₉
	I-176	H	4-OCH ₃	H	-NH-cycloC ₃ H ₅
	I-177	H	4-OCH ₃	H	-NH-cycloC ₄ H ₇
	I-178	H	4-OCH ₃	H	-NH-cycloC ₅ H ₉
15	I-179	H	4-OCH ₃	H	-NH-cycloC ₆ H ₁₁
	I-180	H	4-OCH ₃	H	-NH-1-adamantyl
	I-181	H	4-OCH ₃	H	-NH-2 <i>R</i> -(but-2-yl)
	I-182	H	4-OCH ₃	H	-NH-2 <i>S</i> -(but-2-yl)
	I-183	H	4-OCH ₃	H	-NH-O-CH ₃
20	I-184	H	4-OCH ₃	H	-N(CH ₃)(OCH ₃)
	I-185	H	4-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
	I-186	H	4-OCH ₃	H	-N(CH ₃) ₂
	I-187	H	4-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-188	H	4-OCH ₃	H	-N(C ₂ H ₅) ₂
25	I-189	H	4-OCH ₃	H	-N(isoC ₃ H ₇) ₂
	I-190	H	4-OCH ₃	H	-N(nC ₃ H ₇) ₂
	I-191	H	4-OCH ₃	H	-N(nC ₄ H ₉) ₂
	I-192	H	4-CH ₃	H	-N(C ₆ H ₅) ₂
	I-193	H	5-OCH ₃	H	-NH-CH ₃
30	I-194	H	5-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	I-195	H	5-OCH ₃	H	-NH-isoC ₃ H ₇
	I-196	H	5-OCH ₃	H	-NH-C ₆ H ₅

	I-197	H	5-OCH ₃	H	-NH-C ₂ H ₅
	I-198	H	5-OCH ₃	H	-NH-nC ₃ H ₇
	I-199	H	5-OCH ₃	H	-NH-nC ₄ H ₉
	I-200	H	5-OCH ₃	H	-NH-tertC ₄ H ₉
5	I-201	H	5-OCH ₃	H	-NH-cycloC ₃ H ₅
	I-202	H	5-OCH ₃	H	-NH-cycloC ₄ H ₇
	I-203	H	5-OCH ₃	H	-NH-cycloC ₅ H ₉
	I-204	H	5-OCH ₃	H	-NH-cycloC ₆ H ₁₁
	I-205	H	5-OCH ₃	H	-NH-1-adamantyl
10	I-206	H	5-OCH ₃	H	-NH-2R- (but-2-yl)
	I-207	H	5-OCH ₃	H	-NH-2S- (but-2-yl)
	I-208	H	5-OCH ₃	H	-NH-O-CH ₃
	I-209	H	5-OCH ₃	H	-N(CH ₃)(OCH ₃)
	I-210	H	5-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
15	I-211	H	5-OCH ₃	H	-N(CH ₃) ₂
	I-212	H	5-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	I-213	H	5-OCH ₃	H	-N(C ₂ H ₅) ₂
	I-214	H	5-OCH ₃	H	-N(isoC ₃ H ₇) ₂
	I-215	H	5-OCH ₃	H	-N(nC ₃ H ₇) ₂
20	I-216	H	5-OCH ₃	H	-N(nC ₄ H ₉) ₂
	I-217	H	5-OCH ₃	H	-N(C ₆ H ₅) ₂

Table 2:

A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of
 25 Formula II_f, the group -C(O)-G is in position 3 relative to
 the nitrogen atom and G is of Formula II_g, III_g or IV_g.

No.	R _F	R ¹ F	R ² F	-G
30	II-1	H	H	-NH-CH ₃
	II-2	H	H	-NH-CH ₂ -C ₆ H ₅
	II-3	H	H	-NH-isoC ₃ H ₇

	II-4	H	H	H	-NH-C ₆ H ₅
	II-5	H	H	H	1,3-Thiazol-2-yl-amide
	II-6	H	4-OCH ₃	5-OCH ₃	-NH-CH ₃
	II-7	H	4-cyclo-C ₅ H ₉	H	-NH-CH ₃
5	II-8	H	H	H	-NH-C ₂ H ₅
	II-9	H	H	H	-NH-nC ₃ H ₇
	II-10	H	H	H	-NH-nC ₄ H ₉
	II-11	H	H	H	-NH-tertC ₄ H ₉
	II-12	H	H	H	-NH-cycloC ₃ H ₅
10	II-13	H	H	H	-NH-cycloC ₄ H ₇
	II-14	H	H	H	-NH-cycloC ₅ H ₉
	II-15	H	H	H	-NH-cycloC ₆ H ₁₁
	II-16	H	H	H	-NH-cycloC ₇ H ₁₃
	II-17	H	H	H	-NH-CH ₂ -O-CH ₃
15	II-18	H	H	H	-NH-CH ₂ -CH ₂ -O-CH ₃
	II-19	H	H	H	-NH-1-adamantyl
	II-20	H	H	H	-NH-(4-HO-C ₆ H ₅)
	II-21	H	H	H	-NH-(2-CF ₃ -C ₆ H ₄)
	II-22	H	H	H	-NH-(3-CF ₃ -C ₆ H ₄)
20	II-23	H	H	H	-NH-(4-CF ₃ -C ₆ H ₄)
	II-24	H	H	H	-NH-(2-OCH ₃ -C ₆ H ₄)
	II-25	H	H	H	-NH-(3-OCH ₃ -C ₆ H ₄)
	II-26	H	H	H	-NH-(4-OCH ₃ -C ₆ H ₄)
	II-27	H	H	H	-NH-(2-SCH ₃ -C ₆ H ₄)
25	II-28	H	H	H	-NH-(3-SCH ₃ -C ₆ H ₄)
	II-29	H	H	H	-NH-(4-SCH ₃ -C ₆ H ₄)
	II-30	H	H	H	-NH-(2-N(CH ₃) ₂ -C ₆ H ₄)
	II-31	H	H	H	-NH-(3-N(CH ₃) ₂ -C ₆ H ₄)
	II-32	H	H	H	-NH-(4-N(CH ₃) ₂ -C ₆ H ₄)
30	II-33	H	H	H	-NH-(4-CN-C ₆ H ₄)
	II-34	H	H	H	-NH-(4-Cl-C ₆ H ₄)
	II-35	H	H	H	-NH-(4-Br-C ₆ H ₄)

	II-36	H	H	H	-NH-(4-F-C ₆ H ₄)
	II-37	H	H	H	-NH-(4-CH ₃ -C ₆ H ₄)
	II-38	H	H	H	-NH-(2-NO ₂ -C ₆ H ₄)
	II-39	H	H	H	-NH-(3-NO ₂ -C ₆ H ₄)
5	II-40	H	H	H	-NH-(4-NO ₂ -C ₆ H ₄)
	II-41	H	H	H	-NH-(2,4-OCH ₃ -C ₆ H ₃)
	II-42	H	H	H	-NH-(3,4-OCH ₃ -C ₆ H ₃)
	II-43	H	H	H	-NH-(3,4,5-OCH ₃ -C ₆ H ₂)
	II-44	H	H	H	-NH-(3,4-CH ₂ OCH ₂ -C ₆ H ₃)
10	II-45	H	H	H	-NH-(2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	II-46	H	H	H	-NH-2-pyridinyl
	II-47	H	H	H	-NH-2-furanyl
	II-48	H	H	H	-NH-2-thienyl
	II-49	H	H	H	-NH-3-pyridinyl
15	II-50	H	H	H	-NH-3-furanyl
	II-51	H	H	H	-NH-3-thienyl
	II-52	H	H	H	-NH-4-pyridinyl
	II-53	H	H	H	-NH-2-oxazolyl
	II-54	H	H	H	-NH-3-isoxazolyl
20	II-55	H	H	H	-NH-4-isoxazolyl
	II-56	H	H	H	-NH-5-isoxazolyl
	II-57	H	H	H	-NH-2 <i>R</i> -(but-2-yl)
	II-58	H	H	H	-NH-2 <i>S</i> -(but-2-yl)
	II-59	H	H	H	-NH-O-CH ₃
25	II-60	H	H	H	-N(CH ₃)(OCH ₃)
	II-61	H	H	H	-N(-(CH ₂) ₃ -O-)
	II-62	H	H	H	-NH-O-CH ₂ -C ₆ H ₅
	II-63	H	H	H	-N(CH ₃)(O-CH ₂ -C ₆ H ₅)
	II-64	H	H	H	-N(-(CH ₂) ₂ -CH(C ₆ H ₅)-O-)
30	II-65	H	H	H	-NH-O-C ₂ H ₅
	II-66	H	H	H	-N(C ₂ H ₅)(OC ₂ H ₅)
	II-67	H	H	H	-N(CH ₃)(OC ₂ H ₅)

	II-68	H	H	H	-NH-O-isoC ₃ H ₇ ,
	II-69	H	H	H	-N(CH ₃) (O-isoC ₃ H ₇)
	II-70	H	H	H	-NH-O-nC ₃ H ₇ ,
	II-71	H	H	H	-N(CH ₃) (O-nC ₃ H ₇)
5	II-72	H	H	H	-NH-O-nC ₄ H ₉ ,
	II-73	H	H	H	-N(CH ₃) (O-nC ₄ H ₉)
	II-74	H	H	H	-NH-O-tertC ₄ H ₉ ,
	II-75	H	H	H	-N(CH ₃) (O-tertC ₄ H ₉)
	II-76	H	H	H	-NH-O-C ₆ H ₅
10	II-77	H	H	H	-N(CH ₃) (O-C ₆ H ₅)
	II-78	H	H	H	-N(CH ₃) ₂
	II-79	H	H	H	-N(CH ₂ -C ₆ H ₅) ₂
	II-80	H	H	H	-N(C ₂ H ₅) ₂
	II-81	H	H	H	-N(isoC ₃ H ₇) ₂
15	II-82	H	H	H	-N(nC ₃ H ₇) ₂
	II-83	H	H	H	-N(nC ₄ H ₉) ₂
	II-84	H	H	H	-N(C ₆ H ₅) ₂
	II-85	H	H	H	-NH-CH ₂ -CH ₂ -OH
	II-86	H	H	H	-NH-(CH ₂) ₃ -OH
20	II-87	H	H	H	-NH(-(CH ₂) ₂ -CH(C ₆ H ₅)-OH)
	II-88	H	H	H	-NH-(CH ₂) ₄ -OH
	II-89	H	H	H	-NH(-CH(CH ₃)-CH ₂ -OH)
	II-90	H	H	H	-NH(-CH ₂ -CH(CH ₃)-OH)
	II-91	H	H	H	-NH(-CH(CH ₃)-(CH ₂) ₂ -OH)
25	II-92	H	H	H	-NH(-(CH ₂) ₂ -CH(CH ₃)-OH)
	II-93	H	4-CH ₃	H	-NH-CH ₃
	II-94	H	4-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
	II-95	H	4-CH ₃	H	-NH-isoC ₃ H ₇
	II-96	H	4-CH ₃	H	-NH-C ₆ H ₅
30	II-97	H	4-CH ₃	H	-NH-C ₂ H ₅
	II-98	H	4-CH ₃	H	-NH-nC ₃ H ₇
	II-99	H	4-CH ₃	H	-NH-nC ₄ H ₉

	II-100	H	4-CH ₃	H	-NH-tertC ₄ H ₉
	II-101	H	4-CH ₃	H	-NH-cycloC ₃ H ₅
	II-102	H	4-CH ₃	H	-NH-cycloC ₄ H ₇
	II-103	H	4-CH ₃	H	-NH-cycloC ₅ H ₉
5	II-104	H	4-CH ₃	H	-NH-cycloC ₆ H ₁₁
	II-105	H	4-CH ₃	H	-NH-1-adamantyl
	II-106	H	4-CH ₃	H	-NH-2R- (but-2-yl)
	II-107	H	4-CH ₃	H	-NH-2S- (but-2-yl)
	II-108	H	4-CH ₃	H	-NH-O-CH ₃
10	II-109	H	4-CH ₃	H	-N(CH ₃) (OCH ₃)
	II-110	H	4-CH ₃	H	-N(- (CH ₂) ₃ -O-)
	II-111	H	4-CH ₃	H	-N(CH ₃) ₂
	II-112	H	4-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	II-113	H	4-CH ₃	H	-N(C ₂ H ₅) ₂
15	II-114	H	4-CH ₃	H	-N(isoC ₃ H ₇) ₂
	II-115	H	4-CH ₃	H	-N(nC ₃ H ₇) ₂
	II-116	H	4-CH ₃	H	-N(nC ₄ H ₉) ₂
	II-117	H	4-CH ₃	H	-N(C ₆ H ₅) ₂
	II-118	H	5-CH ₃	H	-NH-CH ₃
20	II-119	H	5-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
	II-120	H	5-CH ₃	H	-NH-isoC ₃ H ₇
	II-121	H	5-CH ₃	H	-NH-C ₆ H ₅
	II-122	H	5-CH ₃	H	-NH-C ₂ H ₅
	II-123	H	5-CH ₃	H	-NH-nC ₃ H ₇
25	II-124	H	5-CH ₃	H	-NH-nC ₄ H ₉
	II-125	H	5-CH ₃	H	-NH-tertC ₄ H ₉
	II-126	H	5-CH ₃	H	-NH-cycloC ₃ H ₅
	II-127	H	5-CH ₃	H	-NH-cycloC ₄ H ₇
	II-128	H	5-CH ₃	H	-NH-cycloC ₅ H ₉
30	II-129	H	5-CH ₃	H	-NH-cycloC ₆ H ₁₁
	II-130	H	5-CH ₃	H	-NH-1-adamantyl
	II-131	H	5-CH ₃	H	-NH-2R- (but-2-yl)

	II-132	H	5-CH ₃	H	-NH-2 <i>S</i> -(but-2-yl)
	II-133	H	5-CH ₃	H	-NH-O-CH ₃
	II-134	H	5-CH ₃	H	-N(CH ₃)(OCH ₃)
	II-135	H	5-CH ₃	H	-N(-(CH ₂) ₃ -O-)
5	II-136	H	5-CH ₃	H	-N(CH ₃) ₂
	II-137	H	5-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	II-138	H	5-CH ₃	H	-N(C ₂ H ₅) ₂
	II-139	H	5-CH ₃	H	-N(isoC ₃ H ₇) ₂
	II-140	H	5-CH ₃	H	-N(nC ₃ H ₇) ₂
10	II-141	H	5-CH ₃	H	-N(nC ₄ H ₉) ₂
	II-142	H	5-CH ₃	H	-N(C ₆ H ₅) ₂
	II-143	CH ₃	H	H	-NH-CH ₃
	II-144	CH ₃	H	H	-NH-CH ₂ -C ₆ H ₅
	II-145	CH ₃	H	H	-NH-isoC ₃ H ₇
15	II-146	CH ₃	H	H	-NH-C ₆ H ₅
	II-147	CH ₃	H	H	-NH-C ₂ H ₅
	II-148	CH ₃	H	H	-NH-nC ₃ H ₇
	II-149	CH ₃	H	H	-NH-nC ₄ H ₉
	II-150	CH ₃	H	H	-NH-tertC ₄ H ₉
20	II-151	CH ₃	H	H	-NH-cycloC ₃ H ₅
	II-152	CH ₃	H	H	-NH-cycloC ₄ H ₇
	II-153	CH ₃	H	H	-NH-cycloC ₅ H ₉
	II-154	CH ₃	H	H	-NH-cycloC ₆ H ₁₁
	II-155	CH ₃	H	H	-NH-1-adamantyl
25	II-156	CH ₃	H	H	-NH-2 <i>R</i> -(but-2-yl)
	II-157	CH ₃	H	H	-NH-2 <i>S</i> -(but-2-yl)
	II-158	CH ₃	H	H	-NH-O-CH ₃
	II-159	CH ₃	H	H	-N(CH ₃)(OCH ₃)
	II-160	CH ₃	H	H	-N(-(CH ₂) ₃ -O-)
30	II-161	CH ₃	H	H	-N(CH ₃) ₂
	II-162	CH ₃	H	H	-N(CH ₂ -C ₆ H ₅) ₂
	II-163	CH ₃	H	H	-N(C ₂ H ₅) ₂

	II-164	CH ₃	H	H	-N(isoC ₃ H ₇) ₂
	II-165	CH ₃	H	H	-N(nC ₃ H ₇) ₂
	II-166	CH ₃	H	H	-N(nC ₄ H ₉) ₂
	II-167	CH ₃	H	H	-N(C ₆ H ₅) ₂
5	II-168	H	4-OCH ₃	H	-NH-CH ₃
	II-169	H	4-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	II-170	H	4-OCH ₃	H	-NH-isoC ₃ H ₇
	II-171	H	4-OCH ₃	H	-NH-C ₆ H ₅
	II-172	H	4-OCH ₃	H	-NH-C ₂ H ₅
10	II-173	H	4-OCH ₃	H	-NH-nC ₃ H ₇
	II-174	H	4-OCH ₃	H	-NH-nC ₄ H ₉
	II-175	H	4-OCH ₃	H	-NH-tertC ₄ H ₉
	II-176	H	4-OCH ₃	H	-NH-cycloC ₃ H ₅
	II-177	H	4-OCH ₃	H	-NH-cycloC ₄ H ₇
15	II-178	H	4-OCH ₃	H	-NH-cycloC ₅ H ₉
	II-179	H	4-OCH ₃	H	-NH-cycloC ₆ H ₁₁
	II-180	H	4-OCH ₃	H	-NH-1-adamantyl
	II-181	H	4-OCH ₃	H	-NH-2R-(but-2-yl)
	II-182	H	4-OCH ₃	H	-NH-2S-(but-2-yl)
20	II-183	H	4-OCH ₃	H	-NH-O-CH ₃
	II-184	H	4-OCH ₃	H	-N(CH ₃)(OCH ₃)
	II-185	H	4-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
	II-186	H	4-OCH ₃	H	-N(CH ₃) ₂
	II-187	H	4-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
25	II-188	H	4-OCH ₃	H	-N(C ₂ H ₅) ₂
	II-189	H	4-OCH ₃	H	-N(isoC ₃ H ₇) ₂
	II-190	H	4-OCH ₃	H	-N(nC ₃ H ₇) ₂
	II-191	H	4-OCH ₃	H	-N(nC ₄ H ₉) ₂
	II-192	H	4-OCH ₃	H	-N(C ₆ H ₅) ₂
30	II-193	H	5-OCH ₃	H	-NH-CH ₃
	II-194	H	5-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	II-195	H	5-OCH ₃	H	-NH-isoC ₃ H ₇

- 73 -

	II-196	H	5-OCH ₃	H	-NH-C ₆ H ₅
	II-197	H	5-OCH ₃	H	-NH-C ₂ H ₅
	II-198	H	5-OCH ₃	H	-NH-nC ₃ H ₇
	II-199	H	5-OCH ₃	H	-NH-nC ₄ H ₉
5	II-200	H	5-OCH ₃	H	-NH-tertC ₄ H ₉
	II-201	H	5-OCH ₃	H	-NH-cycloC ₃ H ₅
	II-202	H	5-OCH ₃	H	-NH-cycloC ₄ H ₇
	II-203	H	5-OCH ₃	H	-NH-cycloC ₅ H ₉
	II-204	H	5-OCH ₃	H	-NH-cycloC ₆ H ₁₁
10	II-205	H	5-OCH ₃	H	-NH-1-adamantyl
	II-206	H	5-OCH ₃	H	-NH-2R- (but-2-yl)
	II-207	H	5-OCH ₃	H	-NH-2S- (but-2-yl)
	II-208	H	5-OCH ₃	H	-NH-O-CH ₃
	II-209	H	5-OCH ₃	H	-N(CH ₃)(OCH ₃)
15	II-210	H	5-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
	II-211	H	5-OCH ₃	H	-N(CH ₃) ₂
	II-212	H	5-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	II-213	H	5-OCH ₃	H	-N(C ₂ H ₅) ₂
	II-214	H	5-OCH ₃	H	-N(isoC ₃ H ₇) ₂
20	II-215	H	5-OCH ₃	H	-N(nC ₃ H ₇) ₂
	II-216	H	5-OCH ₃	H	-N(nC ₄ H ₉) ₂
	II-217	H	5-OCH ₃	H	-N(C ₆ H ₅) ₂

25 Table 3:

A is Me₂Val, B is Val, D is MeVal, E is Pro, F is of Formula II_i, the substituent -(C=O)-G is in position 4 relative to the nitrogen. G is of Formula II_g, III_g or IV_g.

30	No.	R _F	R ¹ F	R ² F	-G
	III-1	H	H	H	-NH-CH ₃

	III-2	H	H	H	-NH-CH ₂ -C ₆ H ₅
	III-3	H	H	H	-NH-isoC ₃ H ₇
	III-4	H	H	H	-NH-C ₆ H ₅
	III-5	H	H	H	1,3-Thiazol-2-yl-amide
5	III-6	H	3-OCH ₃	5-OCH ₃	-NH-CH ₃
	III-7	H	3-cyclo-C ₅ H ₉	H	-NH-CH ₃
	III-8	H	H	H	-NH-C ₂ H ₅
	III-9	H	H	H	-NH-nC ₃ H ₇
	III-10	H	H	H	-NH-nC ₄ H ₉
10	III-11	H	H	H	-NH-tertC ₄ H ₉
	III-12	H	H	H	-NH-cycloC ₃ H ₅
	III-13	H	H	H	-NH-cycloC ₄ H ₇
	III-14	H	H	H	-NH-cycloC ₅ H ₉
	III-15	H	H	H	-NH-cycloC ₆ H ₁₁
15	III-16	H	H	H	-NH-cycloC ₇ H ₁₃
	III-17	H	H	H	-NH-CH ₂ -O-CH ₃
	III-18	H	H	H	-NH-CH ₂ -CH ₂ -O-CH ₃
	III-19	H	H	H	-NH-1-adamantyl
	III-20	H	H	H	-NH-(4-HO-C ₆ H ₅)
20	III-21	H	H	H	-NH-(2-CF ₃ -C ₆ H ₄)
	III-22	H	H	H	-NH-(3-CF ₃ -C ₆ H ₄)
	III-23	H	H	H	-NH-(4-CF ₃ -C ₆ H ₄)
	III-24	H	H	H	-NH-(2-OCH ₃ -C ₆ H ₄)
	III-25	H	H	H	-NH-(3-OCH ₃ -C ₆ H ₄)
25	III-26	H	H	H	-NH-(4-OCH ₃ -C ₆ H ₄)
	III-27	H	H	H	-NH-(2-SCH ₃ -C ₆ H ₄)
	III-28	H	H	H	-NH-(3-SCH ₃ -C ₆ H ₄)
	III-29	H	H	H	-NH-(4-SCH ₃ -C ₆ H ₄)
	III-30	H	H	H	-NH-(2-N(CH ₃) ₂ -C ₆ H ₄)
30	III-31	H	H	H	-NH-(3-N(CH ₃) ₂ -C ₆ H ₄)
	III-32	H	H	H	-NH-(4-N(CH ₃) ₂ -C ₆ H ₄)
	III-33	H	H	H	-NH-(4-CN-C ₆ H ₄)

	III-34	H	H	H	-NH- (4-Cl-C ₆ H ₄)
	III-35	H	H	H	-NH- (4-Br-C ₆ H ₄)
	III-36	H	H	H	-NH- (4-F-C ₆ H ₄)
	III-37	H	H	H	-NH- (4-CH ₃ -C ₆ H ₄)
5	III-38	H	H	H	-NH- (2-NO ₂ -C ₆ H ₄)
	III-39	H	H	H	-NH- (3-NO ₂ -C ₆ H ₄)
	III-40	H	H	H	-NH- (4-NO ₂ -C ₆ H ₄)
	III-41	H	H	H	-NH- (2,4-OCH ₃ -C ₆ H ₃)
	III-42	H	H	H	-NH- (3,4-OCH ₃ -C ₆ H ₃)
10	III-43	H	H	H	-NH- (3,4,5-OCH ₃ -C ₆ H ₂)
	III-44	H	H	H	-NH- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	III-45	H	H	H	-NH- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	III-46	H	H	H	-NH-2-pyridinyl
	III-47	H	H	H	-NH-2-furanyl
15	III-48	H	H	H	-NH-2-thienyl
	III-49	H	H	H	-NH-3-pyridinyl
	III-50	H	H	H	-NH-3-furanyl
	III-51	H	H	H	-NH-3-thienyl
	III-52	H	H	H	-NH-4-pyridinyl
20	III-53	H	H	H	-NH-2-oxazolyl
	III-54	H	H	H	-NH-3-isoxazolyl
	III-55	H	H	H	-NH-4-isoxazolyl
	III-56	H	H	H	-NH-5-isoxazolyl
	III-57	H	H	H	-NH-2 <i>R</i> -(but-2-yl)
25	III-58	H	H	H	-NH-2 <i>S</i> -(but-2-yl)
	III-59	H	H	H	-NH-O-CH ₃
	III-60	H	H	H	-N(CH ₃)(OCH ₃)
	III-61	H	H	H	-N(-(CH ₂) ₃ -O-)
	III-62	H	H	H	-NH-O-CH ₂ -C ₆ H ₅
30	III-63	H	H	H	-N(CH ₃)(O-CH ₂ -C ₆ H ₅)
	III-64	H	H	H	-N(-(CH ₂) ₂ -CH(C ₆ H ₅)-O-)
	III-65	H	H	H	-NH-O-C ₂ H ₅

	III-66	H	H	H	-N(C ₂ H ₅)(OC ₂ H ₅)
	III-67	H	H	H	-N(CH ₃)(OC ₂ H ₅)
	III-68	H	H	H	-NH-O-isoC ₃ H ₇
	III-69	H	H	H	-N(CH ₃)(O-isoC ₃ H ₇)
5	III-70	H	H	H	-NH-O-nC ₃ H ₇
	III-71	H	H	H	-N(CH ₃)(O-nC ₃ H ₇)
	III-72	H	H	H	-NH-O-nC ₄ H ₉
	III-73	H	H	H	-N(CH ₃)(O-nC ₄ H ₉)
	III-74	H	H	H	-NH-O-tertC ₄ H ₉
10	III-75	H	H	H	-N(CH ₃)(O-tertC ₄ H ₉)
	III-76	H	H	H	-NH-O-C ₆ H ₅
	III-77	H	H	H	-N(CH ₃)(O-C ₆ H ₅)
	III-78	H	H	H	-N(CH ₃) ₂
	III-79	H	H	H	-N(CH ₂ -C ₆ H ₅) ₂
15	III-80	H	H	H	-N(C ₂ H ₅) ₂
	III-81	H	H	H	-N(isoC ₃ H ₇) ₂
	III-82	H	H	H	-N(nC ₃ H ₇) ₂
	III-83	H	H	H	-N(nC ₄ H ₉) ₂
	III-84	H	H	H	-N(C ₆ H ₅) ₂
20	III-85	H	H	H	-NH-CH ₂ -CH ₂ -OH
	III-86	H	H	H	-NH-(CH ₂) ₃ -OH
	III-87	H	H	H	-NH(-(CH ₂) ₂ -CH(C ₆ H ₅)-OH)
	III-88	H	H	H	-NH-(CH ₂) ₄ -OH
	III-89	H	H	H	-NH(-CH(CH ₃)-CH ₂ -OH)
25	III-90	H	H	H	-NH(-CH ₂ -CH(CH ₃)-OH)
	III-91	H	H	H	-NH(-CH(CH ₃)-(CH ₂) ₂ -OH)
	III-92	H	H	H	-NH(-(CH ₂) ₂ -CH(CH ₃)-OH)
	III-93	H	2-CH ₃	H	-NH-CH ₃
	III-94	H	2-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
30	III-95	H	2-CH ₃	H	-NH-isoC ₃ H ₇
	III-96	H	2-CH ₃	H	-NH-C ₆ H ₅
	III-97	H	2-CH ₃	H	-NH-C ₂ H ₅

	III-98	H	2-CH ₃	H	-NH-nC ₃ H ₇
	III-99	H	2-CH ₃	H	-NH-nC ₄ H ₉
	III-100	H	2-CH ₃	H	-NH-tertC ₄ H ₉
	III-101	H	2-CH ₃	H	-NH-cycloC ₃ H ₅
5	III-102	H	2-CH ₃	H	-NH-cycloC ₄ H ₇
	III-103	H	2-CH ₃	H	-NH-cycloC ₅ H ₉
	III-104	H	2-CH ₃	H	-NH-cycloC ₆ H ₁₁
	III-105	H	2-CH ₃	H	-NH-1-adamantyl
	III-106	H	2-CH ₃	H	-NH-2R- (but-2-yl)
10	III-107	H	2-CH ₃	H	-NH-2S- (but-2-yl)
	III-108	H	2-CH ₃	H	-NH-O-CH ₃
	III-109	H	2-CH ₃	H	-N(CH ₃)(OCH ₃)
	III-110	H	2-CH ₃	H	-N(-(CH ₂) ₃ -O-)
	III-111	H	2-CH ₃	H	-N(CH ₃) ₂
15	III-112	H	2-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	III-113	H	2-CH ₃	H	-N(C ₂ H ₅) ₂
	III-114	H	2-CH ₃	H	-N(isoC ₃ H ₇) ₂
	III-115	H	2-CH ₃	H	-N(nC ₃ H ₇) ₂
	III-116	H	2-CH ₃	H	-N(nC ₄ H ₉) ₂
20	III-117	H	2-CH ₃	H	-N(C ₆ H ₅) ₂
	III-118	H	3-CH ₃	H	-NH-CH ₃
	III-119	H	3-CH ₃	H	-NH-CH ₂ -C ₆ H ₅
	III-120	H	3-CH ₃	H	-NH-isoC ₃ H ₇
	III-121	H	3-CH ₃	H	-NH-C ₆ H ₅
25	III-122	H	3-CH ₃	H	-NH-C ₂ H ₅
	III-123	H	3-CH ₃	H	-NH-nC ₃ H ₇
	III-124	H	3-CH ₃	H	-NH-nC ₄ H ₉
	III-125	H	3-CH ₃	H	-NH-tertC ₄ H ₉
	III-126	H	3-CH ₃	H	-NH-cycloC ₃ H ₅
30	III-127	H	3-CH ₃	H	-NH-cycloC ₄ H ₇
	III-128	H	3-CH ₃	H	-NH-cycloC ₅ H ₉
	III-129	H	3-CH ₃	H	-NH-cycloC ₆ H ₁₁

	III-130	H	3-CH ₃	H	-NH-1-adamantyl
	III-131	H	3-CH ₃	H	-NH-2R- (but-2-yl)
	III-132	H	3-CH ₃	H	-NH-2S- (but-2-yl)
	III-133	H	3-CH ₃	H	-NH-O-CH ₃
5	III-134	H	3-CH ₃	H	-N(CH ₃) (OCH ₃)
	III-135	H	3-CH ₃	H	-N(- (CH ₂) ₃ -O-)
	III-136	H	3-CH ₃	H	-N(CH ₃) ₂
	III-137	H	3-CH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	III-138	H	3-CH ₃	H	-N(C ₂ H ₅) ₂
10	III-139	H	3-CH ₃	H	-N(isoC ₃ H ₇) ₂
	III-140	H	3-CH ₃	H	-N(nC ₃ H ₇) ₂
	III-141	H	3-CH ₃	H	-N(nC ₄ H ₉) ₂
	III-142	H	3-CH ₃	H	-N(C ₆ H ₅) ₂
	III-143	CH ₃	H	H	-NH-CH ₃
15	III-144	CH ₃	H	H	-NH-CH ₂ -C ₆ H ₅
	III-145	CH ₃	H	H	-NH-isoC ₃ H ₇
	III-146	CH ₃	H	H	-NH-C ₆ H ₅
	III-147	CH ₃	H	H	-NH-C ₂ H ₅
	III-148	CH ₃	H	H	-NH-nC ₃ H ₇
20	III-149	CH ₃	H	H	-NH-nC ₄ H ₉
	III-150	CH ₃	H	H	-NH-tertC ₄ H ₉
	III-151	CH ₃	H	H	-NH-cycloC ₃ H ₅
	III-152	CH ₃	H	H	-NH-cycloC ₄ H ₇
	III-153	CH ₃	H	H	-NH-cycloC ₅ H ₉
25	III-154	CH ₃	H	H	-NH-cycloC ₆ H ₁₁
	III-155	CH ₃	H	H	-NH-1-adamantyl
	III-156	CH ₃	H	H	-NH-2R- (but-2-yl)
	III-157	CH ₃	H	H	-NH-2S- (but-2-yl)
	III-158	CH ₃	H	H	-NH-O-CH ₃
30	III-159	CH ₃	H	H	-N(CH ₃) (OCH ₃)
	III-160	CH ₃	H	H	-N(- (CH ₂) ₃ -O-)
	III-161	CH ₃	H	H	-N(CH ₃) ₂

	III-162	CH ₃	H	H	-N(CH ₂ -C ₆ H ₅) ₂
	III-163	CH ₃	H	H	-N(C ₂ H ₅) ₂
	III-164	CH ₃	H	H	-N(isoC ₃ H ₇) ₂
	III-165	CH ₃	H	H	-N(nC ₃ H ₇) ₂
5	III-166	CH ₃	H	H	-N(nC ₄ H ₉) ₂
	III-167	CH ₃	H	H	-N(C ₆ H ₅) ₂
	III-168	H	2-OCH ₃	H	-NH-CH ₃
	III-169	H	2-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	III-170	H	2-OCH ₃	H	-NH-isoC ₃ H ₇
10	III-171	H	2-OCH ₃	H	-NH-C ₆ H ₅
	III-172	H	2-OCH ₃	H	-NH-C ₂ H ₅
	III-173	H	2-OCH ₃	H	-NH-nC ₃ H ₇
	III-174	H	2-OCH ₃	H	-NH-nC ₄ H ₉
	III-175	H	2-OCH ₃	H	-NH-tertC ₄ H ₉
15	III-176	H	2-OCH ₃	H	-NH-cycloC ₃ H ₅
	III-177	H	2-OCH ₃	H	-NH-cycloC ₄ H ₇
	III-178	H	2-OCH ₃	H	-NH-cycloC ₅ H ₉
	III-179	H	2-OCH ₃	H	-NH-cycloC ₆ H ₁₁
	III-180	H	2-OCH ₃	H	-NH-1-adamantyl
20	III-181	H	2-OCH ₃	H	-NH-2R- (but-2-yl)
	III-182	H	2-OCH ₃	H	-NH-2S- (but-2-yl)
	III-183	H	2-OCH ₃	H	-NH-O-CH ₃
	III-184	H	2-OCH ₃	H	-N(CH ₃)(OCH ₃)
	III-185	H	2-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
25	III-186	H	2-OCH ₃	H	-N(CH ₃) ₂
	III-187	H	2-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
	III-188	H	2-OCH ₃	H	-N(C ₂ H ₅) ₂
	III-189	H	2-OCH ₃	H	-N(isoC ₃ H ₇) ₂
	III-190	H	2-OCH ₃	H	-N(nC ₃ H ₇) ₂
30	III-191	H	2-OCH ₃	H	-N(nC ₄ H ₉) ₂
	III-192	H	2-OCH ₃	H	-N(C ₆ H ₅) ₂
	III-193	H	3-OCH ₃	H	-NH-CH ₃

- 80 -

	III-194	H	3-OCH ₃	H	-NH-CH ₂ -C ₆ H ₅
	III-195	H	3-OCH ₃	H	-NH-isoC ₃ H ₇
	III-196	H	3-OCH ₃	H	-NH-C ₆ H ₅
	III-197	H	3-OCH ₃	H	-NH-C ₂ H ₅
5	III-198	H	3-OCH ₃	H	-NH-nC ₃ H ₇
	III-199	H	3-OCH ₃	H	-NH-nC ₄ H ₉
	III-200	H	3-OCH ₃	H	-NH-tertC ₄ H ₉
	III-201	H	3-OCH ₃	H	-NH-cycloC ₃ H ₅
	III-202	H	3-OCH ₃	H	-NH-cycloC ₄ H ₇
10	III-203	H	3-OCH ₃	H	-NH-cycloC ₅ H ₉
	III-204	H	3-OCH ₃	H	-NH-cycloC ₆ H ₁₁
	III-205	H	3-OCH ₃	H	-NH-1-adamantyl
	III-206	H	3-OCH ₃	H	-NH-2R- (but-2-yl)
	III-207	H	3-OCH ₃	H	-NH-2S- (but-2-yl)
15	III-208	H	3-OCH ₃	H	-NH-O-CH ₃
	III-209	H	3-OCH ₃	H	-N(CH ₃)(OCH ₃)
	III-210	H	3-OCH ₃	H	-N(-(CH ₂) ₃ -O-)
	III-211	H	3-OCH ₃	H	-N(CH ₃) ₂
	III-212	H	3-OCH ₃	H	-N(CH ₂ -C ₆ H ₅) ₂
20	III-213	H	3-OCH ₃	H	-N(C ₂ H ₅) ₂
	III-214	H	3-OCH ₃	H	-N(isoC ₃ H ₇) ₂
	III-215	H	3-OCH ₃	H	-N(nC ₃ H ₇) ₂
	III-216	H	3-OCH ₃	H	-N(nC ₄ H ₉) ₂
	III-217	H	3-OCH ₃	H	-N(C ₆ H ₅) ₂

25

Table 4:

A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of
 Formula II₁, the substituent -(C=O)-G is in position 2
 30 relative to the nitrogen. G is of Formula V₉, VI₉, VII₉,
 VIII₉ or IX₉.

-81-

	No.	R _F	R ¹ F	R ² F	-G
	IV-1	H	H	H	-CH ₃
	IV-2	H	H	H	-C ₂ H ₅
5	IV-3	H	H	H	-nC ₃ H ₇
	IV-4	H	H	H	-isoC ₃ H ₇
	IV-5	H	H	H	-nC ₄ H ₉
	IV-6	H	H	H	-tertC ₄ H ₉
	IV-7	H	H	H	-cycloC ₃ H ₅
10	IV-8	H	H	H	-cycloC ₄ H ₇
	IV-9	H	H	H	-cycloC ₅ H ₉
	IV-10	H	H	H	-cycloC ₆ H ₁₁
	IV-11	H	H	H	-cycloC ₇ H ₁₂
	IV-12	H	H	H	-CH ₂ -O-CH ₃
15	IV-13	H	H	H	-CH ₂ -CH ₂ -O-CH ₃
	IV-14	H	H	H	-CH ₂ -C ₆ H ₅
	IV-15	H	H	H	-C ₆ H ₅
	IV-16	H	H	H	-(4-HO-C ₆ H ₅)
	IV-17	H	H	H	-(2-CF ₃ -C ₆ H ₄)
20	IV-18	H	H	H	-(3-CF ₃ -C ₆ H ₄)
	IV-19	H	H	H	-(4-CF ₃ -C ₆ H ₄)
	IV-20	H	H	H	-(2-OCH ₃ -C ₆ H ₄)
	IV-21	H	H	H	-(3-OCH ₃ -C ₆ H ₄)
	IV-22	H	H	H	-(4-OCH ₃ -C ₆ H ₄)
25	IV-23	H	H	H	-(2-SCH ₃ -C ₆ H ₄)
	IV-24	H	H	H	-(3-SCH ₃ -C ₆ H ₄)
	IV-25	H	H	H	-(4-SCH ₃ -C ₆ H ₄)
	IV-26	H	H	H	-(2-N(CH ₃) ₂ -C ₆ H ₄)
	IV-27	H	H	H	-(3-N(CH ₃) ₂ -C ₆ H ₄)
30	IV-28	H	H	H	-(4-N(CH ₃) ₂ -C ₆ H ₄)
	IV-29	H	H	H	-(4-CN-C ₆ H ₄)
	IV-30	H	H	H	-(4-Cl-C ₆ H ₄)

	IV-31	H	H	H	- (4-Br-C ₆ H ₄)
	IV-32	H	H	H	- (4-F-C ₆ H ₄)
	IV-33	H	H	H	- (4-CH ₃ -C ₆ H ₄)
	IV-34	H	H	H	- (2-NO ₂ -C ₆ H ₄)
5	IV-35	H	H	H	- (3-NO ₂ -C ₆ H ₄)
	IV-36	H	H	H	- (4-NO ₂ -C ₆ H ₄)
	IV-37	H	H	H	- (2,4-OCH ₃ -C ₆ H ₃)
	IV-38	H	H	H	- (3,4-OCH ₃ -C ₆ H ₃)
	IV-39	H	H	H	- (3,4,5-OCH ₃ -C ₆ H ₂)
10	IV-40	H	H	H	- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	IV-41	H	H	H	- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	IV-42	H	H	H	-2-pyridinyl
	IV-43	H	H	H	-2-furanyl
	IV-44	H	H	H	-2-thienyl
15	IV-45	H	H	H	-3-pyridinyl
	IV-46	H	H	H	-3-furanyl
	IV-47	H	H	H	-3-thienyl
	IV-48	H	H	H	-4-pyridinyl
	IV-49	H	H	H	-2-thiazolyl
20	IV-50	H	H	H	-2-oxazolyl
	IV-51	H	H	H	-3-isoxazolyl
	IV-52	H	H	H	-4-isoxazolyl
	IV-53	H	H	H	-5-isoxazolyl
	IV-54	H	H	H	-CF ₃
25	IV-55	H	H	H	-C ₂ F ₅
	IV-56	H	H	H	-CH ₃
	IV-57	H	H	H	-C ₂ H ₅
	IV-58	H	H	H	-nC ₃ H ₇
	IV-59	H	H	H	-tertC ₄ H ₉
30	IV-60	H	H	H	-CH ₂ -C ₆ H ₅
	IV-61	H	H	H	-C ₆ H ₅
	IV-62	H	H	H	-CH ₂ -COOCH ₃

	IV-63	H	H	H	$-\text{CH}_2-\text{COOC}_2\text{H}_5$
	IV-64	H	H	H	$-\text{CF}_2-\text{COOCH}_3$
	IV-65	H	H	H	$-\text{CF}_2-\text{COOC}_2\text{H}_5$
	IV-66	H	H	H	$-\text{CH}_2-\text{CONH}_2$
5	IV-67	H	H	H	$-\text{CH}_2-\text{CONHCH}_3$
	IV-68	H	H	H	$-\text{CH}_2-\text{CON}(\text{CH}_3)_2$
	IV-69	H	H	H	$-\text{CH}_2-\text{CONH}-\text{CH}_2-\text{C}_6\text{H}_5$
	IV-70	H	H	H	$-\text{CH}_2-\text{CONH}-\text{C}_6\text{H}_5$
	IV-71	H	H	H	$-\text{CH}_2-\text{CONH}(\text{CH}_2-\text{C}_6\text{H}_5)_2$
10	IV-72	H	H	H	$-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	IV-73	H	H	H	$-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	IV-74	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COOCH}_3$
	IV-75	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COOC}_2\text{H}_5$
	IV-76	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}_2$
15	IV-77	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONHCH}_3$
	IV-78	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(\text{CH}_3)_2$
	IV-79	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}-\text{CH}_2-\text{C}_6\text{H}_5$
	IV-80	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}-\text{C}_6\text{H}_5$
	IV-81	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}(\text{CH}_2-\text{C}_6\text{H}_5)_2$
20	IV-82	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	IV-83	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-(\text{CH}_2)_3-\text{CH}_2-)$
	IV-84	H	H	H	$-\text{CH}_2-\text{COCH}_3$
	IV-85	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COCH}_3$
	IV-86	H	H	H	$-\text{CH}_2-\text{COC}_2\text{H}_5$
25	IV-87	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COC}_2\text{H}_5$
	IV-88	H	H	H	$-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
	IV-89	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
	IV-90	H	H	H	$-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
	IV-91	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
30	IV-92	H	H	H	$-\text{CH}_2-\text{SOC}_6\text{H}_5$
	IV-93	H	H	H	$-\text{CH}_2-\text{SOCH}_3$
	IV-94	H	H	H	$-\text{CH}_2-\text{SO}(4-\text{CH}_3-\text{C}_6\text{H}_4)$

	IV-95	H	H	H	-CH ₂ -SO ₂ C ₆ H ₅
	IV-96	H	H	H	-CH ₂ -SO ₂ CH ₃
	IV-97	H	H	H	-CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
	IV-98	H	H	H	-CH ₂ -CH ₂ -SOC ₆ H ₅
5	IV-99	H	H	H	-CH ₂ -CH ₂ -SOCH ₃
	IV-100	H	H	H	-CH ₂ -CH ₂ -SO(4-CH ₃ -C ₆ H ₄)
	IV-101	H	H	H	-CH ₂ -CH ₂ -SO ₂ C ₆ H ₅
	IV-102	H	H	H	-CH ₂ -CH ₂ -SO ₂ CH ₃
	IV-103	H	H	H	-CH ₂ -CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
10	IV-104	CH ₃	H	H	-CH ₃
	IV-105	CH ₃	H	H	-C ₂ H ₅
	IV-106	CH ₃	H	H	-nC ₃ H ₇
	IV-107	CH ₃	H	H	-isoC ₃ H ₇
	IV-108	CH ₃	H	H	-nC ₄ H ₉
15	IV-109	CH ₃	H	H	-tertC ₄ H ₉
	IV-110	CH ₃	H	H	-cycloC ₃ H ₅
	IV-111	CH ₃	H	H	-cycloC ₄ H ₇
	IV-112	CH ₃	H	H	-cycloC ₅ H ₉
	IV-113	CH ₃	H	H	-cycloC ₆ H ₁₁
20	IV-114	CH ₃	H	H	-cycloC ₇ H ₁₂
	IV-115	CH ₃	H	H	-CH ₂ -O-CH ₃
	IV-116	CH ₃	H	H	-CH ₂ -CH ₂ -O-CH ₃
	IV-117	CH ₃	H	H	-CH ₂ -C ₆ H ₅
	IV-118	CH ₃	H	H	-C ₆ H ₅
25	IV-119	CH ₃	H	H	-(4-HO-C ₆ H ₅)
	IV-120	CH ₃	H	H	-(2-CF ₃ -C ₆ H ₄)
	IV-121	CH ₃	H	H	-(3-CF ₃ -C ₆ H ₄)
	IV-122	CH ₃	H	H	-(4-CF ₃ -C ₆ H ₄)
	IV-123	CH ₃	H	H	-(2-OCH ₃ -C ₆ H ₄)
30	IV-124	CH ₃	H	H	-(3-OCH ₃ -C ₆ H ₄)
	IV-125	CH ₃	H	H	-(4-OCH ₃ -C ₆ H ₄)
	IV-126	CH ₃	H	H	-(2-SCH ₃ -C ₆ H ₄)

	IV-127	CH ₃	H	H	- (3-SCH ₃ -C ₆ H ₄)
	IV-128	CH ₃	H	H	- (4-SCH ₃ -C ₆ H ₄)
	IV-129	CH ₃	H	H	- (2-N(CH ₃) ₂ -C ₆ H ₄)
	IV-130	CH ₃	H	H	- (3-N(CH ₃) ₂ -C ₆ H ₄)
5	IV-131	CH ₃	H	H	- (4-N(CH ₃) ₂ -C ₆ H ₄)
	IV-132	CH ₃	H	H	- (4-CN-C ₆ H ₄)
	IV-133	CH ₃	H	H	- (4-Cl-C ₆ H ₄)
	IV-134	CH ₃	H	H	- (4-Br-C ₆ H ₄)
	IV-135	CH ₃	H	H	- (4-F-C ₆ H ₄)
10	IV-136	CH ₃	H	H	- (4-CH ₃ -C ₆ H ₄)
	IV-137	CH ₃	H	H	- (2-NO ₂ -C ₆ H ₄)
	IV-138	CH ₃	H	H	- (3-NO ₂ -C ₆ H ₄)
	IV-139	CH ₃	H	H	- (4-NO ₂ -C ₆ H ₄)
	IV-140	CH ₃	H	H	- (2,4-OCH ₃ -C ₆ H ₃)
15	IV-141	CH ₃	H	H	- (3,4-OCH ₃ -C ₆ H ₃)
	IV-142	CH ₃	H	H	- (3,4,5-OCH ₃ -C ₆ H ₂)
	IV-143	CH ₃	H	H	- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	IV-144	CH ₃	H	H	- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	IV-145	CH ₃	H	H	-2-pyridinyl
20	IV-146	CH ₃	H	H	-2-furanyl
	IV-147	CH ₃	H	H	-2-thienyl
	IV-148	CH ₃	H	H	-3-pyridinyl
	IV-149	CH ₃	H	H	-3-furanyl
	IV-150	CH ₃	H	H	-3-thienyl
25	IV-151	CH ₃	H	H	-4-pyridinyl
	IV-152	CH ₃	H	H	-2-thiazolyl
	IV-153	CH ₃	H	H	-2-oxazolyl
	IV-154	CH ₃	H	H	-3-isoxazolyl
	IV-155	CH ₃	H	H	-4-isoxazolyl
30	IV-156	CH ₃	H	H	-5-isoxazolyl
	IV-157	CH ₃	H	H	-CF ₃
	IV-158	CH ₃	H	H	-C ₂ F ₅

	IV-159	CH ₃	H	H	-CH ₃
	IV-160	CH ₃	H	H	-C ₂ H ₅
	IV-161	CH ₃	H	H	-nC ₃ H ₇
	IV-162	CH ₃	H	H	-tertC ₄ H ₉
5	IV-163	CH ₃	H	H	-CH ₂ -C ₆ H ₅
	IV-164	CH ₃	H	H	-C ₆ H ₅
	IV-165	CH ₃	H	H	-CH ₂ -COOCH ₃
	IV-166	CH ₃	H	H	-CH ₂ -COOC ₂ H ₅
	IV-167	CH ₃	H	H	-CF ₂ -COOCH ₃
10	IV-168	CH ₃	H	H	-CF ₂ -COOC ₂ H ₅
	IV-169	CH ₃	H	H	-CH ₂ -CONH ₂
	IV-170	CH ₃	H	H	-CH ₂ -CONHCH ₃
	IV-171	CH ₃	H	H	-CH ₂ -CON(CH ₃) ₂
	IV-172	CH ₃	H	H	-CH ₂ -CONH-CH ₂ -C ₆ H ₅
15	IV-173	CH ₃	H	H	-CH ₂ -CONH-C ₆ H ₅
	IV-174	CH ₃	H	H	-CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
	IV-175	CH ₃	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	IV-176	CH ₃	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	IV-177	CH ₃	H	H	-CH ₂ -CH ₂ -COOCH ₃
20	IV-178	CH ₃	H	H	-CH ₂ -CH ₂ -COOC ₂ H ₅
	IV-179	CH ₃	H	H	-CH ₂ -CH ₂ -CONH ₂
	IV-180	CH ₃	H	H	-CH ₂ -CH ₂ -CONHCH ₃
	IV-181	CH ₃	H	H	-CH ₂ -CH ₂ -CON(CH ₃) ₂
	IV-182	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-CH ₂ -C ₆ H ₅
25	IV-183	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-C ₆ H ₅
	IV-184	CH ₃	H	H	-CH ₂ -CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
	IV-185	CH ₃	H	H	-CH ₂ -CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	IV-186	CH ₃	H	H	-CH ₂ -CH ₂ -CON(-CH ₂ -(CH ₂) ₃ -CH ₂ -)
	IV-187	CH ₃	H	H	-CH ₂ -COCH ₃
30	IV-188	CH ₃	H	H	-CH ₂ -CH ₂ -COCH ₃
	IV-189	CH ₃	H	H	-CH ₂ -COC ₂ H ₅
	IV-190	CH ₃	H	H	-CH ₂ -CH ₂ -COC ₂ H ₅

	IV-191	CH ₃	H	H	-CH ₂ -CO-C ₆ H ₅
	IV-192	CH ₃	H	H	-CH ₂ -CH ₂ -CO-C ₆ H ₅
	IV-193	CH ₃	H	H	-CH ₂ -CO-CH ₂ -C ₆ H ₅
	IV-194	CH ₃	H	H	-CH ₂ -CH ₂ -CO-CH ₂ -C ₆ H ₅
5	IV-195	CH ₃	H	H	-CH ₂ -SOC ₆ H ₅
	IV-196	CH ₃	H	H	-CH ₂ -SOCH ₃
	IV-197	CH ₃	H	H	-CH ₂ -SO (4-CH ₃ -C ₆ H ₄)
	IV-198	CH ₃	H	H	-CH ₂ -SO ₂ C ₆ H ₅
	IV-199	CH ₃	H	H	-CH ₂ -SO ₂ CH ₃
10	IV-200	CH ₃	H	H	-CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
	IV-201	CH ₃	H	H	-CH ₂ -CH ₂ -SOC ₆ H ₅
	IV-202	CH ₃	H	H	-CH ₂ -CH ₂ -SOCH ₃
	IV-203	CH ₃	H	H	-CH ₂ -CH ₂ -SO (4-CH ₃ -C ₆ H ₄)
	IV-204	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ C ₆ H ₅
15	IV-205	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ CH ₃
	IV-206	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)

Table 5:

- 20 A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of Formula II_f, the substituent -(C=O)-G is in position 3 relative to the nitrogen. G is of Formula V_g, VI_g, VII_g, VIII_g or IX_g.

25	No.	R _F	R ¹ F	R ² F	-G
	V-1	H	H	H	-CH ₃
	V-2	H	H	H	-C ₂ H ₅
	V-3	H	H	H	-nC ₃ H ₇
30	V-4	H	H	H	-isoC ₃ H ₇
	V-5	H	H	H	-nC ₄ H ₉
	V-6	H	H	H	-tertC ₄ H ₉

	V-7	H	H	H	-cycloC ₃ H ₅
	V-8	H	H	H	-cycloC ₄ H ₇
	V-9	H	H	H	-cycloC ₅ H ₉
	V-10	H	H	H	-cycloC ₆ H ₁₁
5	V-11	H	H	H	-cycloC ₇ H ₁₂
	V-12	H	H	H	-CH ₂ -O-CH ₃
	V-13	H	H	H	-CH ₂ -CH ₂ -O-CH ₃
	V-14	H	H	H	-CH ₂ -C ₆ H ₅
	V-15	H	H	H	-C ₆ H ₅
10	V-16	H	H	H	-(4-HO-C ₆ H ₅)
	V-17	H	H	H	-(2-CF ₃ -C ₆ H ₄)
	V-18	H	H	H	-(3-CF ₃ -C ₆ H ₄)
	V-19	H	H	H	-(4-CF ₃ -C ₆ H ₄)
	V-20	H	H	H	-(2-OCH ₃ -C ₆ H ₄)
15	V-21	H	H	H	-(3-OCH ₃ -C ₆ H ₄)
	V-22	H	H	H	-(4-OCH ₃ -C ₆ H ₄)
	V-23	H	H	H	-(2-SCH ₃ -C ₆ H ₄)
	V-24	H	H	H	-(3-SCH ₃ -C ₆ H ₄)
	V-25	H	H	H	-(4-SCH ₃ -C ₆ H ₄)
20	V-26	H	H	H	-(2-N(CH ₃) ₂ -C ₆ H ₄)
	V-27	H	H	H	-(3-N(CH ₃) ₂ -C ₆ H ₄)
	V-28	H	H	H	-(4-N(CH ₃) ₂ -C ₆ H ₄)
	V-29	H	H	H	-(4-CN-C ₆ H ₄)
	V-30	H	H	H	-(4-Cl-C ₆ H ₄)
25	V-31	H	H	H	-(4-Br-C ₆ H ₄)
	V-32	H	H	H	-(4-F-C ₆ H ₄)
	V-33	H	H	H	-(4-CH ₃ -C ₆ H ₄)
	V-34	H	H	H	-(2-NO ₂ -C ₆ H ₄)
	V-35	H	H	H	-(3-NO ₂ -C ₆ H ₄)
30	V-36	H	H	H	-(4-NO ₂ -C ₆ H ₄)
	V-37	H	H	H	-(2,4-OCH ₃ -C ₆ H ₃)
	V-38	H	H	H	-(3,4-OCH ₃ -C ₆ H ₃)

	V-39	H	H	H	- (3,4,5-OCH ₃ -C ₆ H ₂)
	V-40	H	H	H	- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	V-41	H	H	H	- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	V-42	H	H	H	-2-pyridinyl
5	V-43	H	H	H	-2-furanyl
	V-44	H	H	H	-2-thienyl
	V-45	H	H	H	-3-pyridinyl
	V-46	H	H	H	-3-furanyl
	V-47	H	H	H	-3-thienyl
10	V-48	H	H	H	-4-pyridinyl
	V-49	H	H	H	-2-thiazolyl
	V-50	H	H	H	-2-oxazolyl
	V-51	H	H	H	-3-isoxazolyl
	V-52	H	H	H	-4-isoxazolyl
15	V-53	H	H	H	-5-isoxazolyl
	V-54	H	H	H	-CF ₃
	V-55	H	H	H	-C ₂ F ₅
	V-56	H	H	H	-CH ₃
	V-57	H	H	H	-C ₂ H ₅
20	V-58	H	H	H	-nC ₃ H ₇
	V-59	H	H	H	-tertC ₄ H ₉
	V-60	H	H	H	-CH ₂ -C ₆ H ₅
	V-61	H	H	H	-C ₆ H ₅
	V-62	H	H	H	-CH ₂ -COOCH ₃
25	V-63	H	H	H	-CH ₂ -COOC ₂ H ₅
	V-64	H	H	H	-CF ₂ -COOCH ₃
	V-65	H	H	H	-CF ₂ -COOC ₂ H ₅
	V-66	H	H	H	-CH ₂ -CONH ₂
	V-67	H	H	H	-CH ₂ -CONHCH ₃
30	V-68	H	H	H	-CH ₂ -CON(CH ₃) ₂
	V-69	H	H	H	-CH ₂ -CONH-CH ₂ -C ₆ H ₅
	V-70	H	H	H	-CH ₂ -CONH-C ₆ H ₅

	V-71	H	H	H	$-\text{CH}_2-\text{CONH}(\text{CH}_2-\text{C}_6\text{H}_5)_2$
	V-72	H	H	H	$-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	V-73	H	H	H	$-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2)$
	V-74	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COOCH}_3$
5	V-75	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COOC}_2\text{H}_5$
	V-76	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}_2$
	V-77	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONHCH}_3$
	V-78	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(\text{CH}_3)_2$
	V-79	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}-\text{CH}_2-\text{C}_6\text{H}_5$
10	V-80	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}-\text{C}_6\text{H}_5$
	V-81	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}(\text{CH}_2-\text{C}_6\text{H}_5)_2$
	V-82	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	V-83	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-(\text{CH}_2)_3-\text{CH}_2)$
	V-84	H	H	H	$-\text{CH}_2-\text{COCH}_3$
15	V-85	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COCH}_3$
	V-86	H	H	H	$-\text{CH}_2-\text{COC}_2\text{H}_5$
	V-87	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COC}_2\text{H}_5$
	V-88	H	H	H	$-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
	V-89	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
20	V-90	H	H	H	$-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
	V-91	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
	V-92	H	H	H	$-\text{CH}_2-\text{SOC}_6\text{H}_5$
	V-93	H	H	H	$-\text{CH}_2-\text{SOCH}_3$
	V-94	H	H	H	$-\text{CH}_2-\text{SO}(4-\text{CH}_3-\text{C}_6\text{H}_4)$
25	V-95	H	H	H	$-\text{CH}_2-\text{SO}_2\text{C}_6\text{H}_5$
	V-96	H	H	H	$-\text{CH}_2-\text{SO}_2\text{CH}_3$
	V-97	H	H	H	$-\text{CH}_2-\text{SO}_2(4-\text{CH}_3-\text{C}_6\text{H}_4)$
	V-98	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SOC}_6\text{H}_5$
	V-99	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SOCH}_3$
30	V-100	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}(4-\text{CH}_3-\text{C}_6\text{H}_4)$
	V-101	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}_2\text{C}_6\text{H}_5$
	V-102	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}_2\text{CH}_3$

	V-103	H	H	H	-CH ₂ -CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
	V-104	CH ₃	H	H	-CH ₃
	V-105	CH ₃	H	H	-C ₂ H ₅
	V-106	CH ₃	H	H	-nC ₃ H ₇
5	V-107	CH ₃	H	H	-isoC ₃ H ₇
	V-108	CH ₃	H	H	-nC ₄ H ₉
	V-109	CH ₃	H	H	-tertC ₄ H ₉
	V-110	CH ₃	H	H	-cycloC ₃ H ₅
	V-111	CH ₃	H	H	-cycloC ₄ H ₇
10	V-112	CH ₃	H	H	-cycloC ₅ H ₉
	V-113	CH ₃	H	H	-cycloC ₆ H ₁₁
	V-114	CH ₃	H	H	-cycloC ₇ H ₁₂
	V-115	CH ₃	H	H	-CH ₂ -O-CH ₃
	V-116	CH ₃	H	H	-CH ₂ -CH ₂ -O-CH ₃
15	V-117	CH ₃	H	H	-CH ₂ -C ₆ H ₅
	V-118	CH ₃	H	H	-C ₆ H ₅
	V-119	CH ₃	H	H	-(4-HO-C ₆ H ₅)
	V-120	CH ₃	H	H	-(2-CF ₃ -C ₆ H ₄)
	V-121	CH ₃	H	H	-(3-CF ₃ -C ₆ H ₄)
20	V-122	CH ₃	H	H	-(4-CF ₃ -C ₆ H ₄)
	V-123	CH ₃	H	H	-(2-OCH ₃ -C ₆ H ₄)
	V-124	CH ₃	H	H	-(3-OCH ₃ -C ₆ H ₄)
	V-125	CH ₃	H	H	-(4-OCH ₃ -C ₆ H ₄)
	V-126	CH ₃	H	H	-(2-SCH ₃ -C ₆ H ₄)
25	V-127	CH ₃	H	H	-(3-SCH ₃ -C ₆ H ₄)
	V-128	CH ₃	H	H	-(4-SCH ₃ -C ₆ H ₄)
	V-129	CH ₃	H	H	-(2-N(CH ₃) ₂ -C ₆ H ₄)
	V-130	CH ₃	H	H	-(3-N(CH ₃) ₂ -C ₆ H ₄)
	V-131	CH ₃	H	H	-(4-N(CH ₃) ₂ -C ₆ H ₄)
30	V-132	CH ₃	H	H	-(4-CN-C ₆ H ₄)
	V-133	CH ₃	H	H	-(4-Cl-C ₆ H ₄)
	V-134	CH ₃	H	H	-(4-Br-C ₆ H ₄)

	V-135	CH ₃	H	H	- (4-F-C ₆ H ₄)
	V-136	CH ₃	H	H	- (4-CH ₃ -C ₆ H ₄)
	V-137	CH ₃	H	H	- (2-NO ₂ -C ₆ H ₄)
	V-138	CH ₃	H	H	- (3-NO ₂ -C ₆ H ₄)
5	V-139	CH ₃	H	H	- (4-NO ₂ -C ₆ H ₄)
	V-140	CH ₃	H	H	- (2,4-OCH ₃ -C ₆ H ₃)
	V-141	CH ₃	H	H	- (3,4-OCH ₃ -C ₆ H ₃)
	V-142	CH ₃	H	H	- (3,4,5-OCH ₃ -C ₆ H ₂)
	V-143	CH ₃	H	H	- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
10	V-144	CH ₃	H	H	- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	V-145	CH ₃	H	H	-2-pyridinyl
	V-146	CH ₃	H	H	-2-furanyl
	V-147	CH ₃	H	H	-2-thienyl
	V-148	CH ₃	H	H	-3-pyridinyl
15	V-149	CH ₃	H	H	-3-furanyl
	V-150	CH ₃	H	H	-3-thienyl
	V-151	CH ₃	H	H	-4-pyridinyl
	V-152	CH ₃	H	H	-2-thiazolyl
	V-153	CH ₃	H	H	-2-oxazolyl
20	V-154	CH ₃	H	H	-3-isoxazolyl
	V-155	CH ₃	H	H	-4-isoxazolyl
	V-156	CH ₃	H	H	-5-isoxazolyl
	V-157	CH ₃	H	H	-CF ₃
	V-158	CH ₃	H	H	-C ₂ F ₅
25	V-159	CH ₃	H	H	-CH ₃
	V-160	CH ₃	H	H	-C ₂ H ₅
	V-161	CH ₃	H	H	-nC ₃ H ₇
	V-162	CH ₃	H	H	-tertC ₄ H ₉
	V-163	CH ₃	H	H	-CH ₂ -C ₆ H ₅
30	V-164	CH ₃	H	H	-C ₆ H ₅
	V-165	CH ₃	H	H	-CH ₂ -COOCH ₃
	V-166	CH ₃	H	H	-CH ₂ -COOC ₂ H ₅

	V-167	CH ₃	H	H	-CF ₂ -COOCH ₃
	V-168	CH ₃	H	H	-CF ₂ -COOC ₂ H ₅
	V-169	CH ₃	H	H	-CH ₂ -CONH ₂
	V-170	CH ₃	H	H	-CH ₂ -CONHCH ₃
5	V-171	CH ₃	H	H	-CH ₂ -CON(CH ₃) ₂
	V-172	CH ₃	H	H	-CH ₂ -CONH-CH ₂ -C ₆ H ₅
	V-173	CH ₃	H	H	-CH ₂ -CONH-C ₆ H ₅
	V-174	CH ₃	H	H	-CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
	V-175	CH ₃	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
10	V-176	CH ₃	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	V-177	CH ₃	H	H	-CH ₂ -CH ₂ -COOCH ₃
	V-178	CH ₃	H	H	-CH ₂ -CH ₂ -COOC ₂ H ₅
	V-179	CH ₃	H	H	-CH ₂ -CH ₂ -CONH ₂
	V-180	CH ₃	H	H	-CH ₂ -CH ₂ -CONHCH ₃
15	V-181	CH ₃	H	H	-CH ₂ -CH ₂ -CON(CH ₃) ₂
	V-182	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-CH ₂ -C ₆ H ₅
	V-183	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-C ₆ H ₅
	V-184	CH ₃	H	H	-CH ₂ -CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
	V-185	CH ₃	H	H	-CH ₂ -CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
20	V-186	CH ₃	H	H	-CH ₂ -CH ₂ -CON(-CH ₂ -(CH ₂) ₃ -CH ₂ -)
	V-187	CH ₃	H	H	-CH ₂ -COCH ₃
	V-188	CH ₃	H	H	-CH ₂ -CH ₂ -COCH ₃
	V-189	CH ₃	H	H	-CH ₂ -COC ₂ H ₅
	V-190	CH ₃	H	H	-CH ₂ -CH ₂ -COC ₂ H ₅
25	V-191	CH ₃	H	H	-CH ₂ -CO-C ₆ H ₅
	V-192	CH ₃	H	H	-CH ₂ -CH ₂ -CO-C ₆ H ₅
	V-193	CH ₃	H	H	-CH ₂ -CO-CH ₂ -C ₆ H ₅
	V-194	CH ₃	H	H	-CH ₂ -CH ₂ -CO-CH ₂ -C ₆ H ₅
	V-195	CH ₃	H	H	-CH ₂ -SOC ₆ H ₅
30	V-196	CH ₃	H	H	-CH ₂ -SOCH ₃
	V-197	CH ₃	H	H	-CH ₂ -SO(4-CH ₃ -C ₆ H ₄)
	V-198	CH ₃	H	H	-CH ₂ -SO ₂ C ₆ H ₅

	V-199	CH ₃	H	H	-CH ₂ -SO ₂ CH ₃
	V-200	CH ₃	H	H	-CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
	V-201	CH ₃	H	H	-CH ₂ -CH ₂ -SOC ₆ H ₅
	V-202	CH ₃	H	H	-CH ₂ -CH ₂ -SOCH ₃
5	V-203	CH ₃	H	H	-CH ₂ -CH ₂ -SO(4-CH ₃ -C ₆ H ₄)
	V-204	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ C ₆ H ₅
	V-205	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ CH ₃
	V-206	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)

10 Table 6:

A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of Formula II_f, the substituent -(C=O)-G is in position 4 relative to the nitrogen. G is of Formula V_g, VI_g, VII_g, VIII_g or IX_g.

15

	No.	R _F	R ¹ F	R ² F	-G
	VI-1	H	H	H	-CH ₃
	VI-2	H	H	H	-C ₂ H ₅
20	VI-3	H	H	H	-nC ₃ H ₇
	VI-4	H	H	H	-isoC ₃ H ₇
	VI-5	H	H	H	-nC ₄ H ₉
	VI-6	H	H	H	-tertC ₄ H ₉
	VI-7	H	H	H	-cycloC ₃ H ₅
25	VI-8	H	H	H	-cycloC ₄ H ₇
	VI-9	H	H	H	-cycloC ₅ H ₉
	VI-10	H	H	H	-cycloC ₆ H ₁₁
	VI-11	H	H	H	-cycloC ₇ H ₁₂
	VI-12	H	H	H	-CH ₂ -O-CH ₃
30	VI-13	H	H	H	-CH ₂ -CH ₂ -O-CH ₃
	VI-14	H	H	H	-CH ₂ -C ₆ H ₅
	VI-15	H	H	H	-C ₆ H ₅

	VI-16	H	H	H	- (4-HO-C ₆ H ₅)
	VI-17	H	H	H	- (2-CF ₃ -C ₆ H ₄)
	VI-18	H	H	H	- (3-CF ₃ -C ₆ H ₄)
	VI-19	H	H	H	- (4-CF ₃ -C ₆ H ₄)
5	VI-20	H	H	H	- (2-OCH ₃ -C ₆ H ₄)
	VI-21	H	H	H	- (3-OCH ₃ -C ₆ H ₄)
	VI-22	H	H	H	- (4-OCH ₃ -C ₆ H ₄)
	VI-23	H	H	H	- (2-SCH ₃ -C ₆ H ₄)
	VI-24	H	H	H	- (3-SCH ₃ -C ₆ H ₄)
10	VI-25	H	H	H	- (4-SCH ₃ -C ₆ H ₄)
	VI-26	H	H	H	- (2-N(CH ₃) ₂ -C ₆ H ₄)
	VI-27	H	H	H	- (3-N(CH ₃) ₂ -C ₆ H ₄)
	VI-28	H	H	H	- (4-N(CH ₃) ₂ -C ₆ H ₄)
	VI-29	H	H	H	- (4-CN-C ₆ H ₄)
15	VI-30	H	H	H	- (4-Cl-C ₆ H ₄)
	VI-31	H	H	H	- (4-Br-C ₆ H ₄)
	VI-32	H	H	H	- (4-F-C ₆ H ₄)
	VI-33	H	H	H	- (4-CH ₃ -C ₆ H ₄)
	VI-34	H	H	H	- (2-NO ₂ -C ₆ H ₄)
20	VI-35	H	H	H	- (3-NO ₂ -C ₆ H ₄)
	VI-36	H	H	H	- (4-NO ₂ -C ₆ H ₄)
	VI-37	H	H	H	- (2,4-OCH ₃ -C ₆ H ₃)
	VI-38	H	H	H	- (3,4-OCH ₃ -C ₆ H ₃)
	VI-39	H	H	H	- (3,4,5-OCH ₃ -C ₆ H ₂)
25	VI-40	H	H	H	- (3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	VI-41	H	H	H	- (2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	VI-42	H	H	H	-2-pyridinyl
	VI-43	H	H	H	-2-furanyl
	VI-44	H	H	H	-2-thienyl
30	VI-45	H	H	H	-3-pyridinyl
	VI-46	H	H	H	-3-furanyl
	VI-47	H	H	H	-3-thienyl

	VI-48	H	H	H	-4-pyridinyl
	VI-49	H	H	H	-2-thiazolyl
	VI-50	H	H	H	-2-oxazolyl
	VI-51	H	H	H	-3-isoxazolyl
5	VI-52	H	H	H	-4-isoxazolyl
	VI-53	H	H	H	-5-isoxazolyl
	VI-54	H	H	H	-CF ₃
	VI-55	H	H	H	-C ₂ F ₅
	VI-56	H	H	H	-CH ₃
10	VI-57	H	H	H	-C ₂ H ₅
	VI-58	H	H	H	-nC ₃ H ₇
	VI-59	H	H	H	-tertC ₄ H ₉
	VI-60	H	H	H	-CH ₂ -C ₆ H ₅
	VI-61	H	H	H	-C ₆ H ₅
15	VI-62	H	H	H	-CH ₂ -COOCH ₃
	VI-63	H	H	H	-CH ₂ -COOC ₂ H ₅
	VI-64	H	H	H	-CF ₂ -COOCH ₃
	VI-65	H	H	H	-CF ₂ -COOC ₂ H ₅
	VI-66	H	H	H	-CH ₂ -CONH ₂
20	VI-67	H	H	H	-CH ₂ -CONHCH ₃
	VI-68	H	H	H	-CH ₂ -CON(CH ₃) ₂
	VI-69	H	H	H	-CH ₂ -CONH-CH ₂ -C ₆ H ₅
	VI-70	H	H	H	-CH ₂ -CONH-C ₆ H ₅
	VI-71	H	H	H	-CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
25	VI-72	H	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	VI-73	H	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	VI-74	H	H	H	-CH ₂ -CH ₂ -COOCH ₃
	VI-75	H	H	H	-CH ₂ -CH ₂ -COOC ₂ H ₅
	VI-76	H	H	H	-CH ₂ -CH ₂ -CONH ₂
30	VI-77	H	H	H	-CH ₂ -CH ₂ -CONHCH ₃
	VI-78	H	H	H	-CH ₂ -CH ₂ -CON(CH ₃) ₂
	VI-79	H	H	H	-CH ₂ -CH ₂ -CONH-CH ₂ -C ₆ H ₅

	VI-80	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}-\text{C}_6\text{H}_5$
	VI-81	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CONH}(\text{CH}_2-\text{C}_6\text{H}_5)_2$
	VI-82	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-)$
	VI-83	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CON}(-\text{CH}_2-(\text{CH}_2)_3-\text{CH}_2)$
5	VI-84	H	H	H	$-\text{CH}_2-\text{COCH}_3$
	VI-85	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COCH}_3$
	VI-86	H	H	H	$-\text{CH}_2-\text{COC}_2\text{H}_5$
	VI-87	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{COC}_2\text{H}_5$
	VI-88	H	H	H	$-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
10	VI-89	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$
	VI-90	H	H	H	$-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
	VI-91	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$
	VI-92	H	H	H	$-\text{CH}_2-\text{SOC}_6\text{H}_5$
	VI-93	H	H	H	$-\text{CH}_2-\text{SOCH}_3$
15	VI-94	H	H	H	$-\text{CH}_2-\text{SO}(4-\text{CH}_3-\text{C}_6\text{H}_4)$
	VI-95	H	H	H	$-\text{CH}_2-\text{SO}_2\text{C}_6\text{H}_5$
	VI-96	H	H	H	$-\text{CH}_2-\text{SO}_2\text{CH}_3$
	VI-97	H	H	H	$-\text{CH}_2-\text{SO}_2(4-\text{CH}_3-\text{C}_6\text{H}_4)$
	VI-98	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SOC}_6\text{H}_5$
20	VI-99	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SOCH}_3$
	VI-100	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}(4-\text{CH}_3-\text{C}_6\text{H}_4)$
	VI-101	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}_2\text{C}_6\text{H}_5$
	VI-102	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}_2\text{CH}_3$
	VI-103	H	H	H	$-\text{CH}_2-\text{CH}_2-\text{SO}_2(4-\text{CH}_3-\text{C}_6\text{H}_4)$
25	VI-104	CH_3	H	H	$-\text{CH}_3$
	VI-105	CH_3	H	H	$-\text{C}_2\text{H}_5$
	VI-106	CH_3	H	H	$-\text{nC}_3\text{H}_7$
	VI-107	CH_3	H	H	$-\text{isoC}_3\text{H}_7$
	VI-108	CH_3	H	H	$-\text{nC}_4\text{H}_9$
30	VI-109	CH_3	H	H	$-\text{tertC}_4\text{H}_9$
	VI-110	CH_3	H	H	$-\text{cycloC}_3\text{H}_5$
	VI-111	CH_3	H	H	$-\text{cycloC}_4\text{H}_7$

	VI-112	CH ₃	H	H	-cycloC ₅ H ₉
	VI-113	CH ₃	H	H	-cycloC ₆ H ₁₁
	VI-114	CH ₃	H	H	-cycloC ₇ H ₁₂
	VI-115	CH ₃	H	H	-CH ₂ -O-CH ₃
5	VI-116	CH ₃	H	H	-CH ₂ -CH ₂ -O-CH ₃
	VI-117	CH ₃	H	H	-CH ₂ -C ₆ H ₅
	VI-118	CH ₃	H	H	-C ₆ H ₅
	VI-119	CH ₃	H	H	-(4-HO-C ₆ H ₅)
	VI-120	CH ₃	H	H	-(2-CF ₃ -C ₆ H ₄)
10	VI-121	CH ₃	H	H	-(3-CF ₃ -C ₆ H ₄)
	VI-122	CH ₃	H	H	-(4-CF ₃ -C ₆ H ₄)
	VI-123	CH ₃	H	H	-(2-OCH ₃ -C ₆ H ₄)
	VI-124	CH ₃	H	H	-(3-OCH ₃ -C ₆ H ₄)
	VI-125	CH ₃	H	H	-(4-OCH ₃ -C ₆ H ₄)
15	VI-126	CH ₃	H	H	-(2-SCH ₃ -C ₆ H ₄)
	VI-127	CH ₃	H	H	-(3-SCH ₃ -C ₆ H ₄)
	VI-128	CH ₃	H	H	-(4-SCH ₃ -C ₆ H ₄)
	VI-129	CH ₃	H	H	-(2-N(CH ₃) ₂ -C ₆ H ₄)
	VI-130	CH ₃	H	H	-(3-N(CH ₃) ₂ -C ₆ H ₄)
20	VI-131	CH ₃	H	H	-(4-N(CH ₃) ₂ -C ₆ H ₄)
	VI-132	CH ₃	H	H	-(4-CN-C ₆ H ₄)
	VI-133	CH ₃	H	H	-(4-Cl-C ₆ H ₄)
	VI-134	CH ₃	H	H	-(4-Br-C ₆ H ₄)
	VI-135	CH ₃	H	H	-(4-F-C ₆ H ₄)
25	VI-136	CH ₃	H	H	-(4-CH ₃ -C ₆ H ₄)
	VI-137	CH ₃	H	H	-(2-NO ₂ -C ₆ H ₄)
	VI-138	CH ₃	H	H	-(3-NO ₂ -C ₆ H ₄)
	VI-139	CH ₃	H	H	-(4-NO ₂ -C ₆ H ₄)
	VI-140	CH ₃	H	H	-(2,4-OCH ₃ -C ₆ H ₃)
30	VI-141	CH ₃	H	H	-(3,4-OCH ₃ -C ₆ H ₃)
	VI-142	CH ₃	H	H	-(3,4,5-OCH ₃ -C ₆ H ₂)
	VI-143	CH ₃	H	H	-(3,4-CH ₂ OCH ₂ -C ₆ H ₃)

	VI-144	CH ₃	H	H	-(2,3-CH ₂ OCH ₂ -C ₆ H ₅)
	VI-145	CH ₃	H	H	-2-pyridinyl
	VI-146	CH ₃	H	H	-2-furanyl
	VI-147	CH ₃	H	H	-2-thienyl
5	VI-148	CH ₃	H	H	-3-pyridinyl
	VI-149	CH ₃	H	H	-3-furanyl
	VI-150	CH ₃	H	H	-3-thienyl
	VI-151	CH ₃	H	H	-4-pyridinyl
	VI-152	CH ₃	H	H	-2-thiazolyl
10	VI-153	CH ₃	H	H	-2-oxazolyl
	VI-154	CH ₃	H	H	-3-isoxazolyl
	VI-155	CH ₃	H	H	-4-isoxazolyl
	VI-156	CH ₃	H	H	-5-isoxazolyl
	VI-157	CH ₃	H	H	-CF ₃
15	VI-158	CH ₃	H	H	-C ₂ F ₅
	VI-159	CH ₃	H	H	-CH ₃
	VI-160	CH ₃	H	H	-C ₂ H ₅
	VI-161	CH ₃	H	H	-nC ₃ H ₇
	VI-162	CH ₃	H	H	-tertC ₄ H ₉
20	VI-163	CH ₃	H	H	-CH ₂ -C ₆ H ₅
	VI-164	CH ₃	H	H	-C ₆ H ₅
	VI-165	CH ₃	H	H	-CH ₂ -COOCH ₃
	VI-166	CH ₃	H	H	-CH ₂ -COOC ₂ H ₅
	VI-167	CH ₃	H	H	-CF ₂ -COOCH ₃
25	VI-168	CH ₃	H	H	-CF ₂ -COOC ₂ H ₅
	VI-169	CH ₃	H	H	-CH ₂ -CONH ₂
	VI-170	CH ₃	H	H	-CH ₂ -CONHCH ₃
	VI-171	CH ₃	H	H	-CH ₂ -CON(CH ₃) ₂
	VI-172	CH ₃	H	H	-CH ₂ -CONH-CH ₂ -C ₆ H ₅
30	VI-173	CH ₃	H	H	-CH ₂ -CONH-C ₆ H ₅
	VI-174	CH ₃	H	H	-CH ₂ -CONH(CH ₂ -C ₆ H ₅) ₂
	VI-175	CH ₃	H	H	-CH ₂ -CON(-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)

	VI-176	CH ₃	H	H	-CH ₂ -CON (-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂)
	VI-177	CH ₃	H	H	-CH ₂ -CH ₂ -COOCH ₃
	VI-178	CH ₃	H	H	-CH ₂ -CH ₂ -COOC ₂ H ₅
	VI-179	CH ₃	H	H	-CH ₂ -CH ₂ -CONH ₂
5	VI-180	CH ₃	H	H	-CH ₂ -CH ₂ -CONHCH ₃
	VI-181	CH ₃	H	H	-CH ₂ -CH ₂ -CON (CH ₃) ₂
	VI-182	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-CH ₂ -C ₆ H ₅
	VI-183	CH ₃	H	H	-CH ₂ -CH ₂ -CONH-C ₆ H ₅
	VI-184	CH ₃	H	H	-CH ₂ -CH ₂ -CONH (CH ₂ -C ₆ H ₅) ₂
10	VI-185	CH ₃	H	H	-CH ₂ -CH ₂ -CON (-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	VI-186	CH ₃	H	H	-CH ₂ -CH ₂ -CON (-CH ₂ - (CH ₂) ₃ -CH ₂)
	VI-187	CH ₃	H	H	-CH ₂ -COCH ₃
	VI-188	CH ₃	H	H	-CH ₂ -CH ₂ -COCH ₃
	VI-189	CH ₃	H	H	-CH ₂ -COC ₂ H ₅
15	VI-190	CH ₃	H	H	-CH ₂ -CH ₂ -COC ₂ H ₅
	VI-191	CH ₃	H	H	-CH ₂ -CO-C ₆ H ₅
	VI-192	CH ₃	H	H	-CH ₂ -CH ₂ -CO-C ₆ H ₅
	VI-193	CH ₃	H	H	-CH ₂ -CO-CH ₂ -C ₆ H ₅
	VI-194	CH ₃	H	H	-CH ₂ -CH ₂ -CO-CH ₂ -C ₆ H ₅
20	VI-195	CH ₃	H	H	-CH ₂ -SOC ₆ H ₅
	VI-196	CH ₃	H	H	-CH ₂ -SOCH ₃
	VI-197	CH ₃	H	H	-CH ₂ -SO (4-CH ₃ -C ₆ H ₄)
	VI-198	CH ₃	H	H	-CH ₂ -SO ₂ C ₆ H ₅
	VI-199	CH ₃	H	H	-CH ₂ -SO ₂ CH ₃
25	VI-200	CH ₃	H	H	-CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)
	VI-201	CH ₃	H	H	-CH ₂ -CH ₂ -SOC ₆ H ₅
	VI-202	CH ₃	H	H	-CH ₂ -CH ₂ -SOCH ₃
	VI-203	CH ₃	H	H	-CH ₂ -CH ₂ -SO (4-CH ₃ -C ₆ H ₄)
	VI-204	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ C ₆ H ₅
30	VI-205	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ CH ₃
	VI-206	CH ₃	H	H	-CH ₂ -CH ₂ -SO ₂ (4-CH ₃ -C ₆ H ₄)

Table 7:

A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of Formula III_f, the substituent -(C=O)-G is in position 2 relative to the nitrogen and a_f is 1. G is of Formula II_g,
 5 or III_g. The compounds are mixtures of diastereomers, configuration in F is *R*, *S* (*cis*) or *S*,*R* (*cis*).

No.	R _f	-G
10	VII-1	H
	VII-2	H
	VII-3	H
	VII-4	H
	VII-5	H
15	VII-6	H
	VII-7	H
	VII-8	H
	VII-9	H
	VII-10	H
20	VII-11	H
	VII-12	H
	VII-13	H
	VII-14	H
	VII-15	H
25	VII-16	H
	VII-17	H
	VII-18	H
	VII-19	H
	VII-20	H
30	VII-21	H
	VII-22	H
	VII-23	H

	VII-24	H	-NH-(2-OCH ₃ -C ₆ H ₄)
	VII-25	H	-NH-(3-OCH ₃ -C ₆ H ₄)
	VII-26	H	-NH-(4-OCH ₃ -C ₆ H ₄)
	VII-27	H	-NH-(2-SCH ₃ -C ₆ H ₄)
5	VII-28	H	-NH-(3-SCH ₃ -C ₆ H ₄)
	VII-29	H	-NH-(4-SCH ₃ -C ₆ H ₄)
	VII-30	H	-NH-(2-N(CH ₃) ₂ -C ₆ H ₄)
	VII-31	H	-NH-(3-N(CH ₃) ₂ -C ₆ H ₄)
	VII-32	H	-NH-(4-N(CH ₃) ₂ -C ₆ H ₄)
10	VII-33	H	-NH-(4-CN-C ₆ H ₄)
	VII-34	H	-NH-(4-Cl-C ₆ H ₄)
	VII-35	H	-NH-(4-Br-C ₆ H ₄)
	VII-36	H	-NH-(4-F-C ₆ H ₄)
	VII-37	H	-NH-(4-CH ₃ -C ₆ H ₄)
15	VII-38	H	-NH-(2-NO ₂ -C ₆ H ₄)
	VII-39	H	-NH-(3-NO ₂ -C ₆ H ₄)
	VII-40	H	-NH-(4-NO ₂ -C ₆ H ₄)
	VII-41	H	-NH-(2,4-OCH ₃ -C ₆ H ₃)
	VII-42	H	-NH-(3,4-OCH ₃ -C ₆ H ₃)
20	VII-43	H	-NH-(3,4,5-OCH ₃ -C ₆ H ₂)
	VII-44	H	-NH-(3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	VII-45	H	-NH-(2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	VII-46	H	-NH-2-pyridinyl
	VII-47	H	-NH-2-furanyl
25	VII-48	H	-NH-2-thienyl
	VII-49	H	-NH-3-pyridinyl
	VII-50	H	-NH-3-furanyl
	VII-51	H	-NH-3-thienyl
	VII-52	H	-NH-4-pyridinyl
30	VII-53	H	-NH-2-oxazolyl
	VII-54	H	-NH-3-isoxazolyl
	VII-55	H	-NH-4-isoxazolyl

	VII-56	H	-NH-5-isoxazoyl
	VII-57	H	-NH-2R- (but-2-yl)
	VII-58	H	-NH-2S- (but-2-yl)
	VII-59	H	-NH-O-CH ₃
5	VII-60	H	-N(CH ₃) (OCH ₃)
	VII-61	H	-N(- (CH ₂) ₃ -O-)
	VII-62	H	-NH-O-CH ₂ -C ₆ H ₅
	VII-63	H	-N(CH ₃) (O-CH ₂ -C ₆ H ₅)
	VII-64	H	-N(- (CH ₂) ₂ -CH(C ₆ H ₅)-O-)
10	VII-65	H	-NH-O-C ₂ H ₅
	VII-66	H	-N(C ₂ H ₅) (OC ₂ H ₅)
	VII-67	H	-N(CH ₃) (OC ₂ H ₅)
	VII-68	H	-NH-O-isoC ₃ H ₇
	VII-69	H	-N(CH ₃) (O-isoC ₃ H ₇)
15	VII-70	H	-NH-O-nC ₃ H ₇
	VII-71	H	-N(CH ₃) (O-nC ₃ H ₇)
	VII-72	H	-NH-O-nC ₄ H ₉
	VII-73	H	-N(CH ₃) (O-nC ₄ H ₉)
	VII-74	H	-NH-O-tertC ₄ H ₉
20	VII-75	H	-N(CH ₃) (O-tertC ₄ H ₉)
	VII-76	H	-NH-O-C ₆ H ₅
	VII-77	H	-N(CH ₃) (O-C ₆ H ₅)
	VII-78	H	-N(CH ₃) ₂
	VII-79	H	-N(CH ₂ -C ₆ H ₅) ₂
25	VII-80	H	-N(C ₂ H ₅) ₂
	VII-81	H	-N(isoC ₃ H ₇) ₂
	VII-82	H	-N(nC ₃ H ₇) ₂
	VII-83	H	-N(nC ₄ H ₉) ₂
	VII-84	H	-N(C ₆ H ₅) ₂
30	VII-85	H	-NH-CH ₂ -CH ₂ -OH
	VII-86	H	-NH-(CH ₂) ₃ -OH
	VII-87	H	-NH(- (CH ₂) ₂ -CH(C ₆ H ₅)-OH)

	VII-88	H	-NH-(CH ₂) ₄ -OH
	VII-89	H	-NH(-CH(CH ₃)-CH ₂ -OH)
	VII-90	H	-NH(-CH ₂ -CH(CH ₃)-OH)
	VII-91	H	-NH(-CH(CH ₃)-(CH ₂) ₂ -OH)
5	VII-92	H	-NH(-(CH ₂) ₂ -CH(CH ₃)-OH)
	VII-93	CH ₃	-NH-CH ₃
	VII-94	CH ₃	-NH-CH ₂ -C ₆ H ₅
	VII-95	CH ₃	-NH-isoC ₃ H ₇
	VII-96	CH ₃	-NH-C ₆ H ₅
10	VII-97	CH ₃	-NH-C ₂ H ₅
	VII-98	CH ₃	-NH-nC ₃ H ₇
	VII-99	CH ₃	-NH-nC ₄ H ₉
	VII-100	CH ₃	-NH-tertC ₄ H ₉
	VII-101	CH ₃	-NH-cycloC ₃ H ₅
15	VII-102	CH ₃	-NH-cycloC ₄ H ₇
	VII-103	CH ₃	-NH-cycloC ₅ H ₉
	VII-104	CH ₃	-NH-cycloC ₆ H ₁₁
	VII-105	CH ₃	-NH-1-adamantyl
	VII-106	CH ₃	-NH-2R-(but-2-yl)
20	VII-107	CH ₃	-NH-2S-(but-2-yl)
	VII-108	CH ₃	-NH-O-CH ₃
	VII-109	CH ₃	-N(CH ₃)(OCH ₃)
	VII-110	CH ₃	-N(-(CH ₂) ₃ -O-)
	VII-111	CH ₃	-N(CH ₃) ₂
25	VII-112	CH ₃	-N(CH ₂ -C ₆ H ₅) ₂
	VII-113	CH ₃	-N(C ₂ H ₅) ₂
	VII-114	CH ₃	-N(isoC ₃ H ₇) ₂
	VII-115	CH ₃	-N(nC ₃ H ₇) ₂
	VII-116	CH ₃	-N(nC ₄ H ₉) ₂
30	VII-117	CH ₃	-N(C ₆ H ₅) ₂

Table 8:

A is Me₂Val, B is Val, D is MeVal, E is Pro and F is of Formula III_f, the substituent -(C=O)-G is in position 2 relative to the nitrogen and a_f is 1. G is of Formula II_g or III_g.

The compounds are mixtures of diastereomers, configuration in F is either R, R (trans) or S, S (trans).

No.	R _f	-G
10		
VIII-1	H	-NH-CH ₃
VIII-2	H	-NH-CH ₂ -C ₆ H ₅
VIII-3	H	-NH-isoC ₃ H ₇
VIII-4	H	-NH-C ₆ H ₅
15	VIII-5	H 1,3-Thiazol-2-yl-amide
VIII-6	H	-NH-CH ₃
VIII-7	H	-NH-CH ₃
VIII-8	H	-NH-C ₂ H ₅
VIII-9	H	-NH-nC ₃ H ₇
20	VIII-10	H -NH-nC ₄ H ₉
VIII-11	H	-NH-tertC ₄ H ₉
VIII-12	H	-NH-cycloC ₃ H ₅
VIII-13	H	-NH-cycloC ₄ H ₇
VIII-14	H	-NH-cycloC ₅ H ₉
25	VIII-15	H -NH-cycloC ₆ H ₁₁
VIII-16	H	-NH-cycloC ₇ H ₁₃
VIII-17	H	-NH-CH ₂ -O-CH ₃
VIII-18	H	-NH-CH ₂ -CH ₂ -O-CH ₃
VIII-19	H	-NH-1-adamantyl
30	VIII-20	H -NH-(4-HO-C ₆ H ₅)
VIII-21	H	-NH-(2-CF ₃ -C ₆ H ₄)
VIII-22	H	-NH-(3-CF ₃ -C ₆ H ₄)

	VIII-23	H	-NH-(4-CF ₃ -C ₆ H ₄)
	VIII-24	H	-NH-(2-OCH ₃ -C ₆ H ₄)
	VIII-25	H	-NH-(3-OCH ₃ -C ₆ H ₄)
	VIII-26	H	-NH-(4-OCH ₃ -C ₆ H ₄)
5	VIII-27	H	-NH-(2-SCH ₃ -C ₆ H ₄)
	VIII-28	H	-NH-(3-SCH ₃ -C ₆ H ₄)
	VIII-29	H	-NH-(4-SCH ₃ -C ₆ H ₄)
	VIII-30	H	-NH-(2-N(CH ₃) ₂ -C ₆ H ₄)
	VIII-31	H	-NH-(3-N(CH ₃) ₂ -C ₆ H ₄)
10	VIII-32	H	-NH-(4-N(CH ₃) ₂ -C ₆ H ₄)
	VIII-33	H	-NH-(4-CN-C ₆ H ₄)
	VIII-34	H	-NH-(4-Cl-C ₆ H ₄)
	VIII-35	H	-NH-(4-Br-C ₆ H ₄)
	VIII-36	H	-NH-(4-F-C ₆ H ₄)
15	VIII-37	H	-NH-(4-CH ₃ -C ₆ H ₄)
	VIII-38	H	-NH-(2-NO ₂ -C ₆ H ₄)
	VIII-39	H	-NH-(3-NO ₂ -C ₆ H ₄)
	VIII-40	H	-NH-(4-NO ₂ -C ₆ H ₄)
	VIII-41	H	-NH-(2,4-OCH ₃ -C ₆ H ₃)
20	VIII-42	H	-NH-(3,4-OCH ₃ -C ₆ H ₃)
	VIII-43	H	-NH-(3,4,5-OCH ₃ -C ₆ H ₂)
	VIII-44	H	-NH-(3,4-CH ₂ OCH ₂ -C ₆ H ₃)
	VIII-45	H	-NH-(2,3-CH ₂ OCH ₂ -C ₆ H ₃)
	VIII-46	H	-NH-2-pyridinyl
25	VIII-47	H	-NH-2-furanyl
	VIII-48	H	-NH-2-thienyl
	VIII-49	H	-NH-3-pyridinyl
	VIII-50	H	-NH-3-furanyl
	VIII-51	H	-NH-3-thienyl
30	VIII-52	H	-NH-4-pyridinyl
	VIII-53	H	-NH-2-oxazolyl
	VIII-54	H	-NH-3-isoxazolyl

	VIII-55	H	-NH-4-isoxazolyl
	VIII-56	H	-NH-5-isoxazolyl
	VIII-57	H	-NH-2 <i>R</i> -(but-2-yl)
	VIII-58	H	-NH-2 <i>S</i> -(but-2-yl)
5	VIII-59	H	-NH-O-CH ₃
	VIII-60	H	-N(CH ₃)(OCH ₃)
	VIII-61	H	-N(-(CH ₂) ₃ -O-)
	VIII-62	H	-NH-O-CH ₂ -C ₆ H ₅
	VIII-63	H	-N(CH ₃)(O-CH ₂ -C ₆ H ₅)
10	VIII-64	H	-N(-(CH ₂) ₂ -CH(C ₆ H ₅)-O-)
	VIII-65	H	-NH-O-C ₂ H ₅
	VIII-66	H	-N(C ₂ H ₅)(OC ₂ H ₅)
	VIII-67	H	-N(CH ₃)(OC ₂ H ₅)
	VIII-68	H	-NH-O-isoC ₃ H ₇
15	VIII-69	H	-N(CH ₃)(O-isoC ₃ H ₇)
	VIII-70	H	-NH-O-nC ₃ H ₇
	VIII-71	H	-N(CH ₃)(O-nC ₃ H ₇)
	VIII-72	H	-NH-O-nC ₄ H ₉
	VIII-73	H	-N(CH ₃)(O-nC ₄ H ₉)
20	VIII-74	H	-NH-O-tertC ₄ H ₉
	VIII-75	H	-N(CH ₃)(O-tertC ₄ H ₉)
	VIII-76	H	-NH-O-C ₆ H ₅
	VIII-77	H	-N(CH ₃)(O-C ₆ H ₅)
	VIII-78	H	-N(CH ₃) ₂
25	VIII-79	H	-N(CH ₂ -C ₆ H ₅) ₂
	VIII-80	H	-N(C ₂ H ₅) ₂
	VIII-81	H	-N(isoC ₃ H ₇) ₂
	VIII-82	H	-N(nC ₃ H ₇) ₂
	VIII-83	H	-N(nC ₄ H ₉) ₂
30	VIII-84	H	-N(C ₆ H ₅) ₂
	VIII-85	H	-NH-CH ₂ -CH ₂ -OH
	VIII-86	H	-NH-(CH ₂) ₃ -OH

	VIII-87	H	-NH(- (CH ₂) ₂ -CH (C ₆ H ₅) -OH)
	VIII-88	H	-NH- (CH ₂) ₄ -OH
	VIII-89	H	-NH(-CH (CH ₃) -CH ₂ -OH)
	VIII-90	H	-NH(-CH ₂ -CH (CH ₃) -OH)
5	VIII-91	H	-NH(-CH (CH ₃) - (CH ₂) ₂ -OH)
	VIII-92	H	-NH(- (CH ₂) ₂ -CH (CH ₃) -OH)
	VIII-93	CH ₃	-NH-CH ₃
	VIII-94	CH ₃	-NH-CH ₂ -C ₆ H ₅
	VIII-95	CH ₃	-NH-isoC ₃ H ₇
10	VIII-96	CH ₃	-NH-C ₆ H ₅
	VIII-97	CH ₃	-NH-C ₂ H ₅
	VIII-98	CH ₃	-NH-nC ₃ H ₇
	VIII-99	CH ₃	-NH-nC ₄ H ₉
	VIII-100	CH ₃	-NH-tertC ₄ H ₉
15	VIII-101	CH ₃	-NH-cycloC ₃ H ₅
	VIII-102	CH ₃	-NH-cycloC ₄ H ₇
	VIII-103	CH ₃	-NH-cycloC ₅ H ₉
	VIII-104	CH ₃	-NH-cycloC ₆ H ₁₁
	VIII-105	CH ₃	-NH-1-adamantyl
20	VIII-106	CH ₃	-NH-2R- (but-2-yl)
	VIII-107	CH ₃	-NH-2S- (but-2-yl)
	VIII-108	CH ₃	-NH-O-CH ₃
	VIII-109	CH ₃	-N(CH ₃) (OCH ₃)
	VIII-110	CH ₃	-N(- (CH ₂) ₃ -O-)
25	VIII-111	CH ₃	-N(CH ₃) ₂
	VIII-112	CH ₃	-N(CH ₂ -C ₆ H ₅) ₂
	VIII-113	CH ₃	-N(C ₂ H ₅) ₂
	VIII-114	CH ₃	-N(isoC ₃ H ₇) ₂
	VIII-115	CH ₃	-N(nC ₃ H ₇) ₂
30	VIII-116	CH ₃	-N(nC ₄ H ₉) ₂
	VIII-117	CH ₃	-N(C ₆ H ₅) ₂

Mass spectrometry data of selected examples :

- I-1 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄C(O)NHCH₃
 FAB-MS: 588 (M + H⁺)
- 5
- I-2 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄C(O)NHCH₂C₆H₅
 FAB-MS: 664 (M + H⁺)
- I-3 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄C(O)NHCH(CH₃)₂
 10 FAB-MS: 616 (M + H⁺)
- I-4 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄C(O)NHC₆H₅
 FAB-MS: 650 (M + H⁺)
- 15 I-5 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄C(O)NH(thiazol-2-yl)
 FAB-MS: 657 (M + H⁺)
- I-6 2(Me₂Val-Val-MeVal-ProNH)-4,5-bis(methoxy)C₆H₂C(O)NHCH₃
 FAB-MS: 649 (M + H⁺)
- 20 I-7 2-(Me₂ValVal-MeVal-ProNH)-3-cyclopentanyl-C₆H₃C(O)NHCH₃
 FAB-MS: 656 (M + H⁺)
- I-64 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CO-N(-(CH₂)₂-CH(C₆H₅)O-)
 25 (mix. of diastereomers) FAB-MS: 706 (M + H⁺)
- I-79 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CO-N(CH₂C₆H₅)₂
 FAB-MS: 754 (M + H⁺)
- 30 I-86 2-(Me₂Val-Val-MeVal-Pro-NH)-C₆H₄-CO-NH(-(CH₂)₃-OH)
 FAB-MS: 632 (M + H⁺)

- I-87 2 - (Me₂Val-Val-MeVal-Pro-NH) - C₆H₄C(O)NH((CH₂)₂CH(C₆H₅)OH)
FAB-MS: 708 (M + H⁺)
- I-143 2 - (Me₂Val-Val-MeVal-Pro-N(CH₃)) - C₆H₄-CONHCH₃
5 FAB-MS: 601 (M + H⁺)
- II-1 3 - (Me₂Val-Val-MeVal-Pro-NH) - C₆H₄-CO-NHCH₃
FAB-MS: 588 (M + H⁺)
- 10 II-2 3 - (Me₂Val-Val-MeVal-Pro-NH) - C₆H₄-CO-NH CH₂C₆H₅
FAB-MS: 664 (M + H⁺)
- IV-1 2 - (Me₂Val-Val-MeVal-Pro-NH) - C₆H₄-CO-CH₃
FAB-MS: 609 (M + H⁺)
- 15
- IV-15 2 - (Me₂Val-Val-MeVal-Pro-NH) - C₆H₄-CO-C₆H₅
FAB-MS: 635 (M + H⁺)

Evaluation of biological activity

20

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 tumor cells such as the HT-29 colon carcinoma or LX-1 lung tumor 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

25

30

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 IC₅₀.

	Compound No.	IC ₅₀ (mol/l)
15	I-1	4×10^{-7}
	I-2	$> 10^{-6}$
	I-3	5×10^{-7}
	I-4	4×10^{-7}
	I-5	1.5×10^{-7}
20	I-6	2×10^{-7}
	I-7	4×10^{-7}
	I-60	4×10^{-7}
	I-64	2.5×10^{-7}
	I-86	6×10^{-7}
25	I-87	2×10^{-7}
	II-1	$> 10^{-6}$
	II-2	$> 10^{-6}$
	IV-1	$> 10^{-6}$
	IV-15	7×10^{-8}
30	VII-2	$> 10^{-6}$

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 which have been grown in athymic nude mice are 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 calculated for each treatment group, and T/C values determined for each group relative to the untreated control tumors.

The novel compounds of the present invention show good *in vitro* activity in the above-mentioned assay system.

EQUIVALENTS

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that
5 various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the
10 specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the claims.

CLAIMS

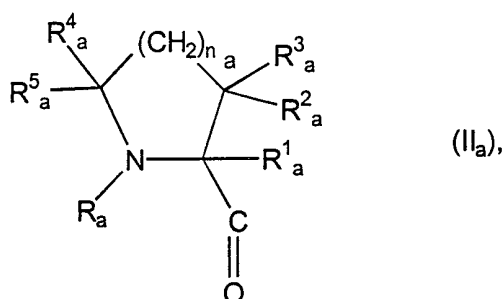
We claim:

5 1. A compound of the formula

A-B-D-E-F-G,

or a salt thereof with a pharmaceutically acceptable acid, wherein

10 A is a proline derivative of Formula II_a,

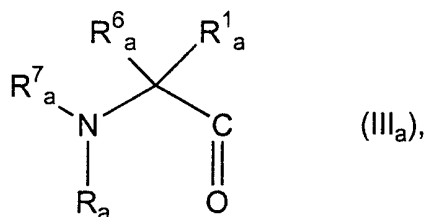


wherein n_a is 0 to 3; R_a is hydrogen, or unsubstituted or fluorine-substituted n_a

15 branched or cyclic C₁-C₃-alkyl; R¹_a is hydrogen, C₁-
C₃-alkyl, phenyl, or substituted phenyl; or R_a and
R¹_a together form a propylene bridge; and R²_a, R³_a,
R⁴_a and R⁵_a are each, independently, hydrogen or
alkyl; or

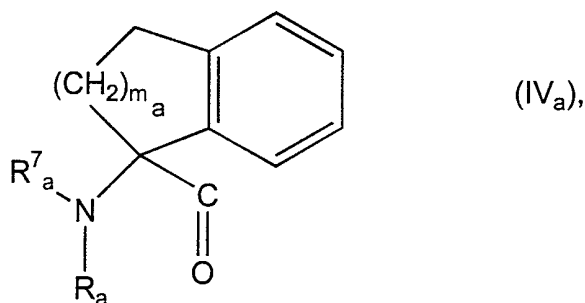
20

an α -amino acid derivative of Formula III_a,



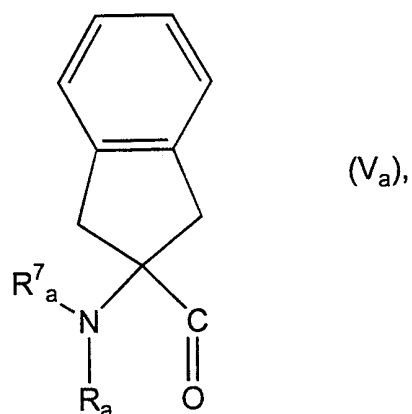
wherein R_a is hydrogen or unsubstituted or
 fluorine-substituted C₁-C₃-alkyl; R¹_a is hydrogen or
 C₁-C₄-alkyl; R⁶_a is alkyl, substituted alkyl,
 5 alkenyl, phenyl or substituted phenyl; or R¹_a is an
 alkyl group and R⁶_a is C₁-C₆-alkyl, cycloalkylmethyl,
 benzyl or substituted benzyl; and R⁷_a is hydrogen or
 alkyl; or

10 an α-amino acid derivative of Formula IV_a,



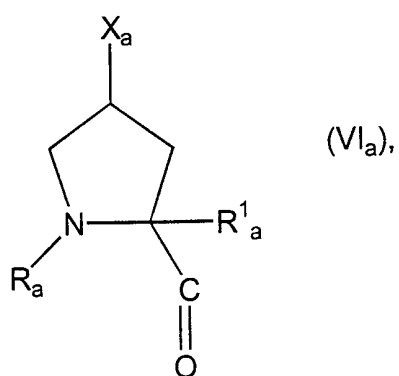
wherein m_a is 1 or 2; R⁷_a is hydrogen or alkyl; R_a is
 hydrogen, or unsubstituted or fluorine-substituted
 15 alkyl; or

an α-amino acid derivative of Formula V_a,



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

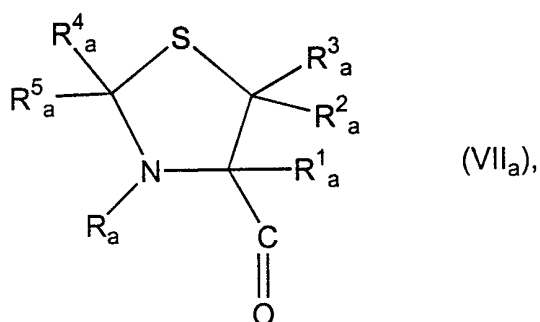
5 an α -amino acid of Formula VI_a,



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

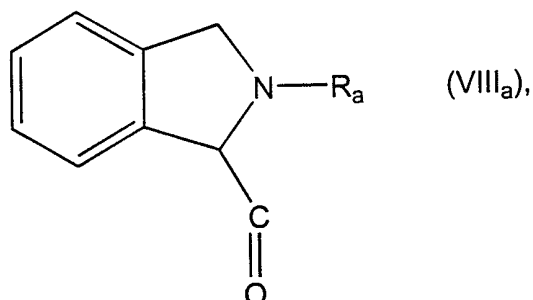
phenyl, or substituted phenyl; or R_a and R^1_a together form a propylene bridge; and X_a is hydroxy, alkoxy or fluorine; or

5 an α -amino acid of Formula VII_a,



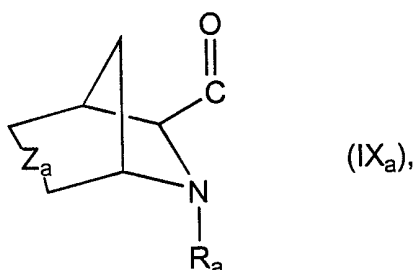
wherein R_a is hydrogen, or unsubstituted or fluorine-substituted alkyl; R^1_a is hydrogen, alkyl, phenyl, or substituted phenyl; or R_a and R^1_a together form a propylene bridge; and R^2_a , R^3_a , R^4_a and R^5_a are each, independently, hydrogen or alkyl; or

15 an α -amino acid residue of Formula VIII_a,



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

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

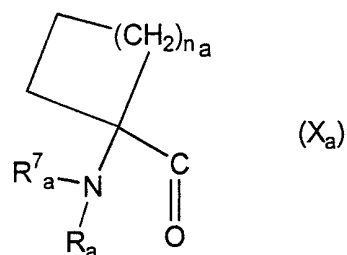


10 wherein the 3-carbonyl moiety is in the endo or exo
position, Z_a is a single bond or a double bond, and
 R_a is hydrogen or unsubstituted or fluorine-
substituted alkyl; or

an α -amino acid residue of Formula X_a,

15

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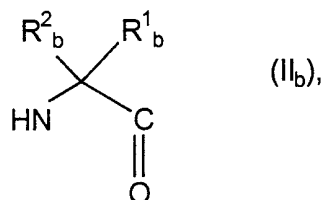
wherein n_a is 1, 2 or 3, and R^7_a is hydrogen or alkyl and R_a is hydrogen, unsubstituted alkyl or fluorine-substituted alkyl;

5

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,

10

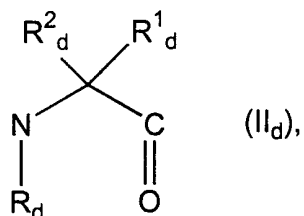


wherein R^1_b is hydrogen, and R^2_b is alkyl or alkenyl; or R^1_b and R^2_b together form an isopropylidene group;

15

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

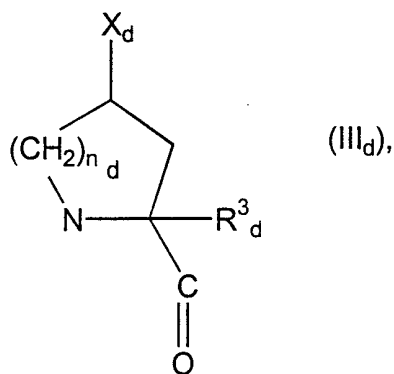
an α -amino acid residue of Formula II_d,



5 wherein R_d is hydrogen, or unsubstituted or
 fluorine-substituted alkyl; R¹_d is hydrogen; and R²_d
 is alkyl, substituted alkyl or alkenyl; or R¹_d and
 R²_d together form an isopropylidene group; or

an α -amino acid residue of Formula III_d,

10

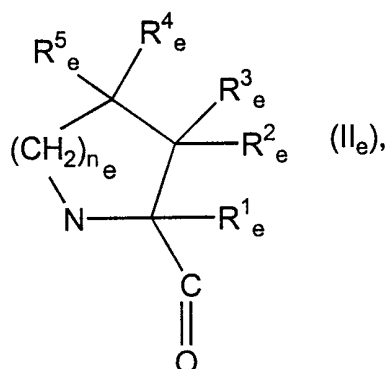


15 wherein n_d is 1 or 2; R³_d is hydrogen, alkyl or
 fluorine-substituted alkyl; and X_d is hydrogen; or
 n_d is 1 and X_d is fluorine, hydroxy, methoxy, or
 ethoxy;

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

an α -amino acid residue of Formula II_e,

5

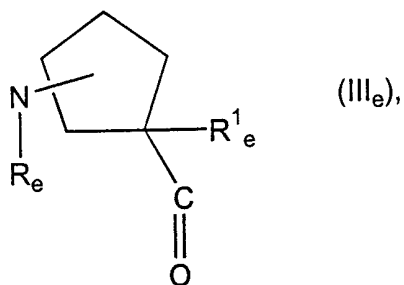


wherein n_e is 0, 1 or 2, R^1_e is hydrogen, or
unsubstituted or fluorine-substituted alkyl; R^2_e and
 R^3_e are each, independently, hydrogen or alkyl; R^4_e
is hydrogen, hydroxy or alkoxy; and R^5_e is hydrogen
or fluorine; or n_e is 1 and R^3_e and R^4_e together form
a double bond; or n_e is 1 and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

10

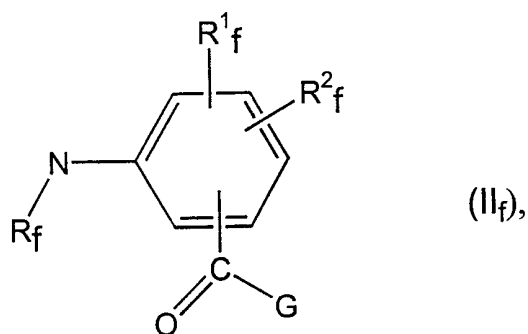
15

an aminocyclopentanecarboxylic acid residue of
Formula III_e,



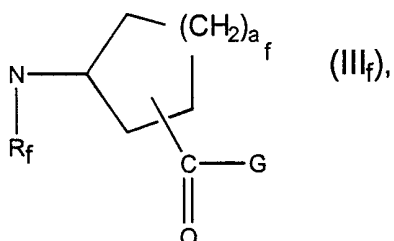
wherein R_e is alkyl and R¹_e is hydrogen, or
unsubstituted or fluorine-substituted alkyl;

5 F is an aminobenzoyl derivative of Formula II_f,



10 wherein R_f is a hydrogen atom or an alkyl group;
the carbonyl group is ortho, meta, or para to the
nitrogen atom; R¹_f and R²_f are each, independently,
a hydrogen atom; a halogen atom; a C₁-C₄-alkyl
group; a methoxy, ethoxy, trifluoromethyl, nitro,
cyano, amino or dimethylamino group; or R¹_f and R²_f
can together form a dioxymethylene group; or

F is an aminocycloalkanecarboxylic acid residue of Formula III_f,

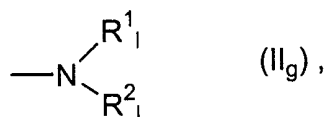


- 5 wherein R_f is a hydrogen atom or an alkyl group;
 a_f is 0, 1 or 2; and the carbonyl group is in
 position 2 or position 3 of the cycloalkane ring
 relative to the nitrogen atom; and
- 10 G is a substituted or unsubstituted amino, hydrazido,
 aminoxy, oximato, arylalkyl, heteroarylalkyl, aryl,
 heteroaryl, alkoxycarbonylalkyl,
 aryloxycarbonylalkyl, alkoxycarbonyl,
 aryloxycarbonyl, aminocarbonylalkyl, aminocarbonyl,
 15 alkylcarbonylalkyl, alkylcarbonyl,
 arylcarbonylalkyl, arylcarbonyl,
 alkylsulfinylalkyl, alkylsulfinyl,
 arylsulfinylalkyl, arylsulfinyl,
 alkylsulfonylalkyl, alkylsulfonyl,
 20 arylsulfonylalkyl or arylsulfonyl group.

2. The compound of Claim 1 wherein the pharmaceutically acceptable acid is 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
 5 acid, oxalic acid, ascorbic acid or acetylglycine.

3. The compound of Claim 1 wherein G is a monovalent
 radical of Formula II_g,



10

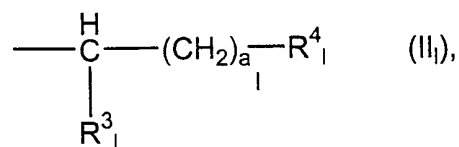
wherein

R¹₁ is a hydrogen atom, a normal or branched,
 saturated or unsaturated C₁-C₁₈-alkoxy group, a
 substituted or unsubstituted aryloxy group, a
 15 substituted or unsubstituted aryl-C₁-C₆-alkoxy
 group, a substituted or unsubstituted
 aryloxy-C₁-C₆-alkoxy group, wherein the aryl
 substituents comprise one or more halogen atoms
 or one or more C₁-C₄-alkyl, methoxy, ethoxy,
 20 trifluoromethyl, nitro or dioxymethylene groups;
 or a heteroaryl-C₁-C₆-alkoxy group, wherein the
 heteroaryl group is derived from imidazole,
 isoxazole, isothiazole, thiazole, oxazole,
 pyrazole, thiophene, furan, pyrrole, 1,2,4- or
 25 1,2,3-triazole, pyrazine, indole, benzofuran,
 benzothiophene, indole, isoindole, indazole,
 quinoline, pyridazine, pyrimidine, benzimidazole,

benzopyran, benzothiazole, oxadiazole,
thiadiazole or pyridine; and

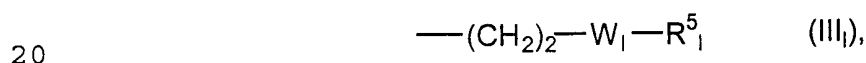
R^2_1 is a hydrogen atom, a normal or branched
C₁-C₁₈-alkyl group, a normal C₁-C₁₈ alkenyl group,
5 a C₃-C₁₀-cycloalkyl group, an aryl group, or a
substituted aryl group, wherein the aryl
substituents comprise one or more halogen atoms,
or one or more alkyl, alkoxy, dioxymethylene,
trifluoromethyl or nitro groups; or a heteroaryl
10 or 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, isoindole, indazole,
15 quinoline, pyridazine, pyrimidine, benzimidazole,
benzopyran, benzothiazole, oxadiazole,
thiadiazole or pyridine and the heteroaryl
substituents comprise one or more C₁-C₆-alkyl,
hydroxyl or phenyl groups; or

20 a monovalent radical of Formula II₁,



wherein a_1 is 0, 1, 2, 3, 4, or 5; R^3_1 is a methyl,
25 ethyl, normal propyl or isopropyl group; R^4_1 is a
saturated or partially unsaturated carbocyclic

system which contains from 3 to 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 alkoxy, dioxymethylene, trifluoromethyl, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; or a substituted or unsubstituted heteroaryl group 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 group substituents comprise one or more C₁-C₆-alkyl, hydroxyl or phenyl groups; or a monovalent radical of Formula III₁,

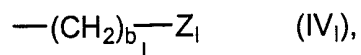


wherein W₁ is an NR₁⁶ group, an oxygen atom or a sulfur atom, R₁⁵ and R₁⁶ are each, independently, a hydrogen atom or a C₁-C₄-alkyl, C₃-C₇-cycloalkyl, aryl, arylmethyl or substituted aryl or arylmethyl group, wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, dioxymethylene, trifluoromethyl, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or

C₁-C₇-dialkylamino groups; or R⁶₁ is a C₁-C₁₈-alkanoyl or benzoyl group; or

a monovalent radical of Formula IV₁,

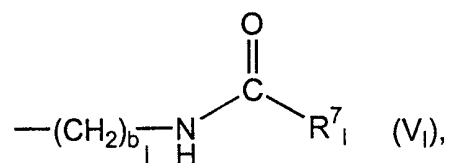
5



b₁ is 2, 3, or 4 and Z₁ is a formyl, aminocarbonyl, hydrazinocarbonyl, cyclic acetal, cyclic thioacetal, acyclic acetal or acyclic thioacetal group; or

10

a monovalent radical of Formula V₁,

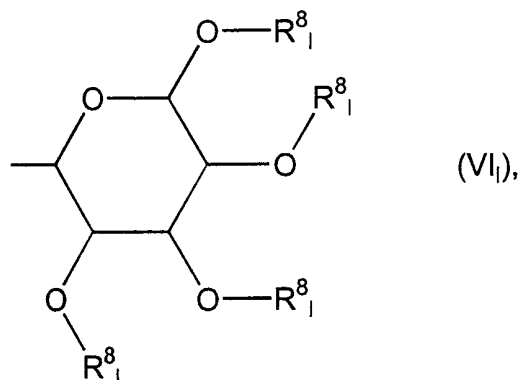


15

b₁ is 2, 3, or 4; R⁷₁ is a polyglycol group of the formula -O-(CH₂-CH₂-O)_{d₁}-CH₃; and d₁ is between about 2 and about 4, or between about 40 and about 90; or

20

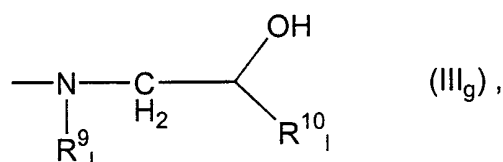
a monovalent radical of Formula VI₁,



wherein R^8_1 is a hydrogen atom, or a C_1 - C_4 alkanoyl, C_1 - C_4 alkyl, benzoyl, or benzyl group.

5

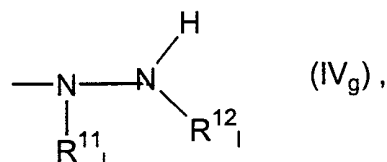
4. The compound of Claim 1 wherein G is a β -hydroxy amino group of Formula III_g,



10 R^9_1 is a hydrogen atom, or a C_1 - C_6 -alkyl, aryl or substituted aryl group wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C_1 - C_7 -alkoxycarbonyl, C_1 - C_7 -alkylsulfonyl, amino, or C_1 - C_7 -dialkylamino groups; and R^{10}_1 is a

15 hydrogen atom, a methyl group or a phenyl group.

5. The compound of Claim 1 wherein G is a hydrazido group of Formula IV_g,



- 5 wherein R¹¹₁ is a hydrogen atom and R¹²₁ is a hydrogen atom, a normal or branched C₁-C₈-alkyl group, a C₃-C₈-cycloalkyl group, a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group, an aryl-C₁-C₄-alkyl group, an aryl group, a substituted aryl group, wherein the aryl substituents
- 10 comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; or a heteroaryl group, a heteroaryl-C₁-C₄-alkyl group or a substituted
- 15 heteroaryl group 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,
- 20 benzimidazole, benzothiazole, benzopyran, indole, isoindole, indazole or quinoline and the heteroaryl substituents comprise one or more C₁-C₆-alkyl, hydroxyl or phenyl groups.
- 25 6. The compound of Claim 1 wherein G is a monovalent radical of the formula -O-R¹³₁ or of the formula

-S-R¹³₁, and R¹³₁ is a C₃-C₁₀-cycloalkyl, straight-chain or branched C₂-C₁₆-alkenylmethyl, C₁-C₁₆-alkyl or halogen-substituted C₁-C₁₆-alkyl group; R¹³₁ is a monovalent radical of the formula -(CH₂)_{e1}-R¹⁴₁, e₁ is 1, 2, or 3, and R¹⁴₁ is a saturated or partially unsaturated C₃-C₁₀ carbocyclic group; R¹³₁ is a monovalent radical of the formula -[CH₂-CH=C(CH₃)-CH₂]_{f1}-H, and f₁ is 1, 2, 3, or 4; R¹³₁ is a monovalent radical of the formula -[CH₂-CH₂-O]_{g1}-CH₃, and g₁ is between about 2 and about 4, or between about 40 and about 90; R¹³₁ is a monovalent radical of the formula -(CH₂)_{h1}-X, h₁ is 0, 1, 2, or 3; and X is an aryl or substituted aryl group wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; or a heteroaryl or substituted heteroaryl group 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 C₁-C₆-alkyl, hydroxyl or phenyl groups; R¹³₁ is a monovalent radical of the formula -(CH₂)_{b1}-W₁-R⁵₁, b₁ is 2, 3, or 4, W₁ is an oxygen atom, a sulfur atom or an NR⁶₁ group; R⁵₁ is a

saturated carbocyclic system which contains from about 3 to about 10 carbon atoms, a partially unsaturated carbocyclic system containing 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 alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; a heteroaryl or substituted heteroaryl group 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 C₁-C₆-alkyl, hydroxyl or phenyl groups; and R⁶₁ is a hydrogen atom, or a C₁-C₄ alkyl, C₃-C₇ cycloalkyl, C₁-C₁₈-alkanoyl, benzoyl, arylmethyl, aryl or substituted aryl or arylmethyl group, wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups.

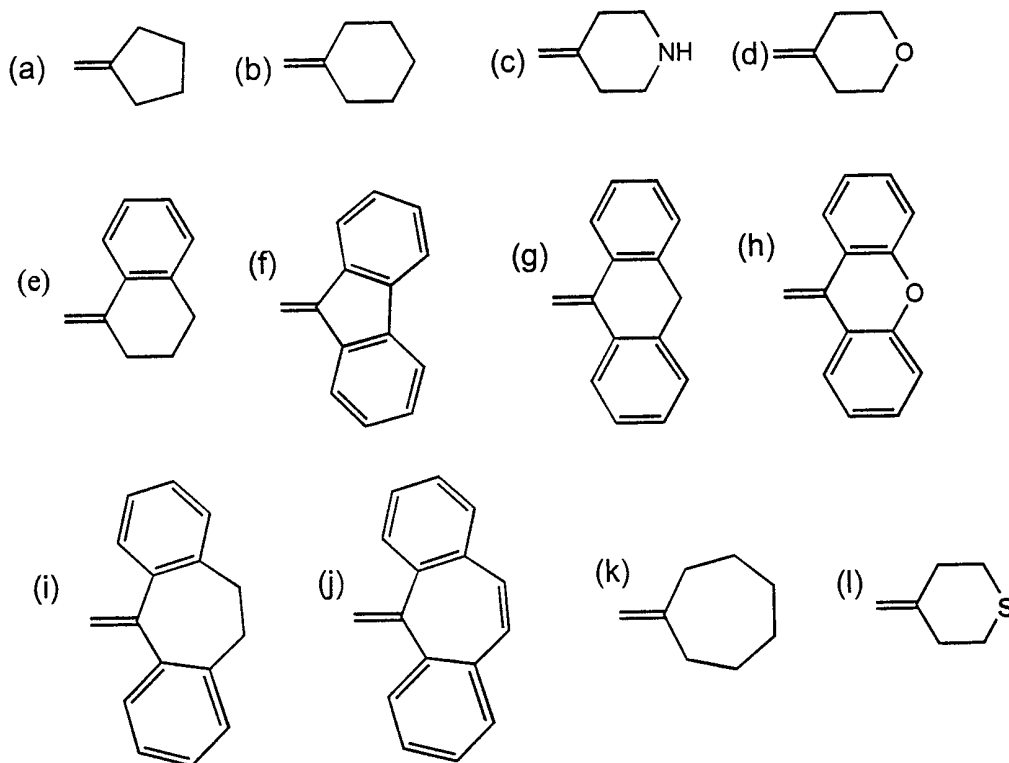
7. The compound of Claim 1 wherein G is an aminoxy group of the formula -O-N(R¹⁶₁)(R¹⁵₁), wherein R¹⁵₁ and R¹⁶₁ are each, independently, a hydrogen atom, a normal or branched C₁-C₈ alkyl group, a halogen-

substituted normal or branched C₁-C₈-alkyl group, a C₃-C₈- cycloalkyl group, a C₃-C₈-cycloalkyl-C₁-C₄ alkyl group, an aryl-C₁-C₄-alkyl group, an aryl group or a substituted aryl-C₁-C₄-alkyl or aryl group, wherein
5 the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; a heteroaryl or substituted heteroaryl group
10 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,
15 indazole or quinoline and the heteroaryl substituents comprise one or more C₁-C₆-alkyl, hydroxyl or phenyl groups; or
R¹⁵₁ and R¹⁶₁ together with the nitrogen atom form a
20 heterocyclic ring structure comprising 5, 6, or 7 atoms.

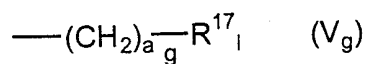
8. The compound of Claim 1 wherein G is a oximato group of the formula -O-N=C(R¹⁵₁)(R¹⁶₁), wherein
25 R¹⁵₁ and R¹⁶₁ are each, independently, a hydrogen atom, a normal or branched C₁-C₈ alkyl group, a halogen-substituted normal or branched C₁-C₈-alkyl group, a C₃-C₈-cycloalkyl group, a C₃-C₈-cycloalkyl-C₁-C₄ alkyl group, an aryl-C₁-C₄-alkyl group, an aryl group or a
30 substituted aryl-C₁-C₄-alkyl or aryl group, wherein

the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; a heteroaryl or substituted heteroaryl group 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 C₁-C₆-alkyl, hydroxyl or phenyl groups; or

R¹⁵₁ and R¹⁶₁, together with the carbon atom, form a cyclic system, a cyclic system fused to an aromatic ring system or a cyclic system selected from the group consisting of:



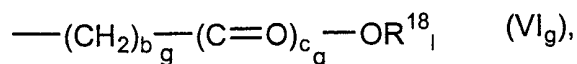
9. The compound of Claim 1 wherein G is a hydrogen atom,
 5 a normal or branched C₁-C₈-alkyl group, a halogen-substituted normal or branched C₁-C₈-alkyl group, a C₃-C₈ cycloalkyl group, or a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group.
- 10 10. The compound of Claim 1 wherein G is a monovalent radical of Formula V_g,



- 15 a_g is 0, 1, or 2, and R¹⁷₁ is an aryl group or a substituted aryl group wherein the aryl substituents comprise one or more halogen atoms or

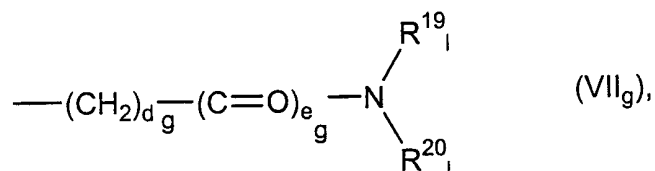
one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups; or a heteroaryl or substituted heteroaryl group derived from imidazole, pyrrole, thiophene, furan, thiazole, oxazole, pyrazole, 1,2,4- or 1,2,3-triazole, 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 C₁-C₆-alkyl, hydroxyl or phenyl groups

11. The compound of Claim 1 wherein G is a monovalent radical of Formula VI_g,



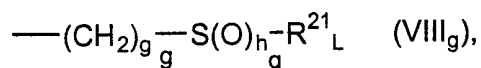
b_g is 0, 1, 2, or 3; e_g is 0 or 1; R¹⁸₁ is a hydrogen atom, a normal or branched C₁-C₈-alkyl group, a halogen substituted normal or branched C₁-C₈-alkyl group, a C₃-C₈-cycloalkyl group, a C₃-C₈-cycloalkyl-C₁-C₄-alkyl group, an aryl group or a substituted aryl group wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C₁-C₇-alkoxycarbonyl, C₁-C₇-alkylsulfonyl, amino, or C₁-C₇-dialkylamino groups.

12. The compound of Claim 1 wherein G is a monovalent radical of Formula VII_g,



- 5 d_g is 0, 1, 2, or 3; e_g is 0 or 1; R^{19}_1 and R^{20}_1 are, independently, a hydrogen atom, a normal or branched C_1 - C_8 -alkyl group, a halogen-substituted 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 or a
10 substituted aryl group wherein the aryl substituents comprise one or more halogen atoms or one or more alkoxy, trifluoromethyl, dioxymethylene, nitro, cyano, C_1 - C_7 -alkoxycarbonyl, C_1 - C_7 -alkylsulfonyl, amino, or C_1 - C_7 -dialkylamino
15 groups; a heteroaryl or substituted heteroaryl group derived from imidazole, pyrrole, thiophene, furan, thiazole, oxazole, pyrazole, 1,2,4- or 1,2,3-triazole, oxadiazole, thiadiazole, isoxazole, isothiazole, pyrazine, pyridazine, pyrimidine,
20 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; or R^{19}_1 , R^{20}_1 and the
25 nitrogen atom form a ring system comprising 6 or fewer carbon atoms.

13. The compound of Claim 1 wherein G is an alkylene sulfoxide or an alkylene sulfone of Formula VIII_g,

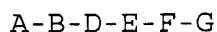


5

g_g is 1 or 2, h_g is 1 or 2, and R^{21}_L is a methyl, trifluoromethyl, ethyl or phenyl group.

14. A compound of the formula

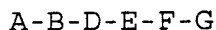
10



wherein A is N,N-dimethylvalyl, B is tertiary-leucyl, D is N-methylvalyl, E is prolyl, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue and G is a monovalent radical.

15

15. A compound of the formula

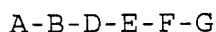


wherein A is N,N-dimethylvalyl, B is valyl, D is N-methyl-tertiaryleucyl, E is prolyl, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue and G is a monovalent radical.

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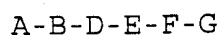
16. A compound of the formula

25



wherein A is N-methyl-d-prolyl, B is valyl, D is N-methylvalyl, E is prolyl, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue and G is a monovalent radical.

17. A compound of the formula



wherein A is N-methylhomopropyl, B is valyl, D is N-methylvalyl, E is propyl, F is an aminobenzoic acid residue or an aminocycloalkanecarboxylic acid residue and G is a monovalent radical.

18. A compound of the formula $\text{Me}_2\text{Val-Val-MeVal-Pro-F-G}$, wherein F is of Formula II_f and R_f is a hydrogen atom or a methyl group, R¹_f and R²_f are each a hydrogen atom, an alkyl group or an alkoxy group, and G is an amino group, an N-substituted amino group, a hydrazido, an alkyl, cycloalkyl, aryl, or alkylaryl, an alkylene ester, an alkylene amide, an alkylene sulfoxide or an alkylene sulfone group or a monovalent radical of the formula $-\text{O-R}^{13}_1$ or $-\text{S-R}^{13}_1$, and R¹³₁ is an alkyl, aryl or alkylaryl group.

19. A compound of the formula $\text{Me}_2\text{Val-Val-MeVal-Pro-F-G}$, wherein F is of Formula III_f, R_f is a hydrogen atom or a methyl group, a_f is 1 or 2, and G is an amino group, an N-substituted amino group, a hydrazido, an alkyl, cycloalkyl, aryl, or alkylaryl, an alkylene ester, an alkylene amide, an alkylene sulfoxide or an alkylene sulfone group or a monovalent radical of the formula $-\text{O-R}^{13}_1$ or $-\text{S-R}^{13}_1$, and R¹³₁ is an alkyl, aryl or alkylaryl group.

20. A method for treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.
- 5 21. The method of Claim 45 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

Internat. Application No.
PCT/US 99/14099

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K7/02 C07K5/103 C07K5/117 A61K38/07 A61K38/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 17364 A (BASF AG ;KLING ANDREAS (DE); JANSSEN BERND (DE); AMBERG WILHELM (D) 15 May 1997 (1997-05-15) The whole document; see especially page 14, lin 30 to page 15, line 16 ---	1-17, 19-21
A	WO 97 22621 A (BASF AG ;AMBERG WILHELM (DE); BARLOZZARI TERESA (US); BERNARD HARA) 26 June 1997 (1997-06-26) the whole document ---	1-21
A	WO 93 23424 A (BASF AG ;HAUPT ANDREAS (DE); EMLING FRANZ (DE); ROMERDAHL CYNTHIA) 25 November 1993 (1993-11-25) the whole document -----	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 October 1999

Date of mailing of the international search report

28/10/1999

Name and mailing address of the ISA

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Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 14099

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-13,20,21(partial)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 99 /14099

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-17,20,21 (all partially), 18 (complete)

Compounds according to the formula of claim 1 wherein F is formula II_f and their use.

2. Claims: 1-17,20,21 (all partially), 19 (complete)

Compounds according to the formula of claim 1 wherein F is formula III_f and their use.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /14099

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13,20,21(all partially)

The scope of the claims 1-13 is very broad and speculative. A formula consisting virtually of variables which are moreover in at least part of the claims ill-defined (e.g. the use of "(substituted) alkyl", "aryl" and "heteroaryl") cannot be considered to be a clear and concise definition of patentable subject-matter (Art.6 PCT).

Furthermore the available experimental data actually only comprise a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area. Therefore the claims can also not be considered to represent a permissible generalisation which is fairly based on experimental evidence, that is, they are also not adequately supported by the description (Art.6 PCT).

Therefore a meaningful search could not encompass the complete subject-matter of the claims. Consequently the search had been limited to the actually synthesised examples and (closely) related analogs, that is the compounds encompassed by the claims 14-19 and the examples and also the claims 20 and 21 as far as relating to said compounds (Art.17(2)(a)(ii) and (b) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 99/14099

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