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(71) Applicant: F.HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basel (CH).

(72) Inventors: **FUJII, Toshihiko**; 6-1-29-203 Kounandai, Kounan-Ward, Yokohama-shi, Kanagawa-ken 234-0054 (JP). **OKADA, Takehiro**; 4-17-17-102, Fujigatani, Kugenuma-Fujigaya, Fujisawa-shi, Kanagawa-ken, 252-0804 (JP). **TANIGUCHI, Mikio**; 2-24-8 Shonandai, Fujisawa-shi, Kanagawa-ken 252-0804 (JP). **WATANABE, Fumio**; Saitoh Apartment 202, 356 Ueki, Kamakura-shi, Kanagawa-ken, 247-0073 (JP).

(74) Agent: **WITTE, Hubert**; 124 Grenzacherstrasse, CH-4070 Basle (CH).

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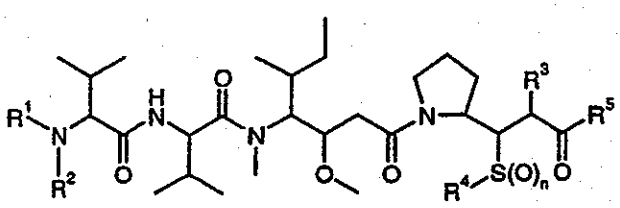
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(54) Title: DOLASTATIN 10 DERIVATIVES



(I)

process for the preparation of compounds (I).

(57) Abstract: The present invention relates to new compounds of formula I, having an anti-tumor activity, wherein R^1, R^2, R^3, R^4, R^5 and n are as defined in the description and the claims and pharmaceutical acceptable salts thereof. The present invention concerns also pharmaceutical composition comprising compounds of formula (I), the use of compounds of formula (I) for the preparation of medicaments and

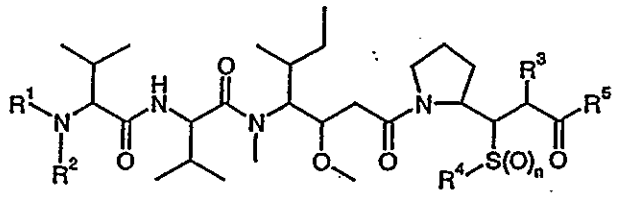
DOLASTATIN 10 DERIVATIVES

The present invention relates to novel compounds having an anti-tumor activity, the use of these compounds in the medical therapy, pharmaceutical compositions containing those compounds as well as to process and intermediates for the preparation of those compounds.

Microtubules are known to be the main component of spindles in a mitotic apparatus of eucaryotic cells, and are also involved in many other basic and essential cell functions. Tubulin, a component of microtubules, has attracted our attention for many years as a good molecular target for anticancer therapy (*Exp. Opin. Ther. Patents 1999, 9(8): 1069-1081*). In fact, tubulin inhibitors such as taxanes and vinca alkaloids are currently used as important anticancer drugs for the treatment of various solid tumors. However, their efficacy is limited and their toxicity such as myelotoxicity is severe because they lack tumor selective activity. Dolastatin 10 is known to be a potent antimitotic peptide, isolated from the marine mollusk *Dolabella auricularia*, which inhibits tubulin polymerization and is a different chemical class from taxanes and vincas (*Curr. Pharm. Des. 1999, 5: 139-162*). Preclinical studies of dolastatin 10 have demonstrated activities against a variety of murine and human tumors in cell cultures and animal models. Dolastatin 10 and two synthetic dolastatin derivatives, Cemadotin and TZT-1027 (*Drugs of the future 1999, 24(4): 404-409*) are currently in Phase I and II clinical trials. This new class of anti-tumor agents would provide a new chemical entity for clinical treatment in the near future, however, these agents still have drawbacks in safety, such as myelotoxicity, neurotoxicity and some other adverse events.

Surprisingly it has been found that certain dolastatin 10 derivatives having various thio-groups at the dolaproine part show significantly improved anti-tumor activity and therapeutic index in human cancer xenograft models.

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



(I)

wherein

R^1, R^2 and R^3 are each independently hydrogen or (C_1-C_4)-alkyl;

R^4 is hydrogen;

alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, carboxy, alkoxycarbonyl, carbamoyloxy, alkylcarbonyloxy, carbamoyl or halogen;

alkenyl;

alkinyl;

(C_3-C_7)-cycloalkyl;

aryl optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, carbamoyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl; or

heterocyclylalkyl;

R^5 is (C_1-C_6)-alkylamino;

hydroxy;

(C_3-C_7)-cycloalkylamino optionally substituted by phenyl or benzyl;

arylamino;

aralkylamino having (C_1-C_4)-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, carbamoyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

(C_1-C_4)-alkoxy;

benzhydrazino;

heterocyclyl optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, mono- or di-alkylamino, acylamino, alkoxycarbonylamino, phenyl or halogen;

heterocyclylamino;

heterocycloalkylamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen;

aralkyloxy and aralkyl, both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl;

and

n is an integer of 0, 1 or 2;

and pharmaceutical acceptable salts thereof.

These compounds have an anti-tumor activity and are useful for the treatment of malignant diseases, particularly of colorectal cancer, lung cancer, breast cancer, stomach cancer, cervical cancer and bladder cancer.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to described the invention herein.

The term "alkyl" as used herein, alone or in combination, means a straight-chain or branched-chain hydrocarbon group containing a maximum of 12, preferably a maximum of 6, carbon atoms, e.g., methyl, ethyl, n-propyl, 2-methylpropyl (iso-butyl), 1-methylethyl (iso-propyl), n-butyl, and 1,1-dimethylethyl (t-butyl), and more preferably a maximum of 4 carbon atoms. The alkyl group may be unsubstituted or may be substituted with one or more substituents, preferably with one to three substituents, most preferably with one substituent. The substituents are selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, alkoxycarbonyl, carbamoyloxy, carbamoyl or halogen.

The term "alkenyl" as used therein, alone or in combination, refers to a hydrocarbon chain as defined for alkyl having at least one olefinic double bond (including for example, vinyl, allyl and butenyl) and having the general formula C_mH_{2m-1} wherein m is an integer greater than 2, preferably m is an integer of 2 to 7.

The term "alkynyl" refers to a hydrocarbon chain as defined for alkyl having at least one triple bond (including for example propynyl, butyn-(1)-yl, etc) and having the general formula C_mH_{2m-2} wherein m is an integer greater than 2, preferably m is an integer of 2 to 7.

The term "(C_3-C_7)-cycloalkyl" signifies a saturated, cyclic hydrocarbon group with 3-7 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and the like. The cycloalkyl group may be unsubstituted or substituted with one or more substituents, preferably with one to three substituents, most preferably with one substituent.. The

substituents are selected from alkyl, phenyl, amino, hydroxy or halogen, preferably is phenyl.

The term "alkylene" refers to a biradical branched or unbranched hydrocarbon chain containing 1 to 4 carbon atoms, such as methylene (-CH_2-), ethylene, propylene, isopropylene and butylene.

The term "aryl" refers to an aromatic carbocyclic radical, i.e. a 6 or 10 membered aromatic or partially aromatic ring, e.g. phenyl (i.e. "Ph"), naphthyl or tetrahydro-naphthyl, preferably phenyl or naphthyl, and most preferably phenyl. The aryl moiety is optionally substituted with one or more subsituents, preferably with one to three, most preferably one, selected from the group consisting of halogen, preferably fluorine, chlorine, alkoxycarbonyl, (e.g. methoxycarbonyl), alkylcarbonyloxy (e.g., acetoxy), cyano, alkyl, alkoxy, phenyl, phenoxy, trifluormethyl, trifluormethoxy, alkylthio, hydroxy, carbamoyloxy, alkylcarbonylamino, heterocyclyl, sulfamoyl (i.e. H_2NSO_2-), amino, 1,3-dioxolyl, or 1,4-dioxolyl. Especially preferred substituents are alkyl, alkoxy, hydroxy, halogen, amino, alkylamino, dialkylamino, alkylthio, sulfamoyl, benzyl or heterocyclyl.

The term "aralkyl" refers to an aryl group as defined above attached to an alkylene group as defined above. The aryl group of the aralkyl may be substituted with one or more substituents, preferably one to three, more preferably with one to two and most preferably with one substituent selected from the group consisting of halogen, preferably fluorine, chlorine, alkoxycarbonyl, (e.g. methoxycarbonyl), alkylcarbonyloxy (e.g., acetoxy), cyano, alkyl, alkoxy, phenyl, phenoxy, trifluormethyl, trifluormethoxy, alkylthio, hydroxy, carbamoyloxy, alkylcarbonylamino, heterocyclyl, sulfamoyl, amino, 1,3-dioxolyl, or 1,4-dioxolyl. Especially preferred substituents aralkyl, alkoxy, hydroxy, halogen, amino, mono- or di-alkylamino or alkylthio.

The term "heterocyclyl" refers to a saturated, unsaturated or aromatic monovalent cyclic radical having at one to 3 hetero atoms selected from nitrogen, oxygen or sulfur or a combination thereof, examples of such heterocycles are; furyl, piperidine (preferably piperidin-1-yl, piperidin-4-yl), piperazine (preferably piperazine-1-yl), pyridine, thiophene, thiadiazole, thiazole, benzthiazol, imidazole, tetrahydroisoquinoline and the like. The heterocyclyl may be substituted with one or more substituents, preferably one to

three, more preferably with one to two and most preferably with one substituent selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkyl-carbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen.

The term "heterocyclyl-amino" refers to a heterocyclic group as defined above attached via an amino radical, i.e., heterocyclyl-NH-.

The term "heterocyclyl-alkyl-amino" refers to a heterocyclic group as defined above attached via an alkylene group as defined above to the amino radical, i.e. heterocyclyl-alkylene-NH-. The heterocyclylamino may be substituted with one or more substituents, preferably one to three, more preferably with one to two and most preferably with one substituent selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, mono- or di-alkylamino, acylamino, alkoxycarbonyl-amino or halogen. Especially preferred substituents are alkyl, hydroxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkylcarbonylamino or halogen.

The term "amino" refers to the group $-NH_2$ and includes amino groups which are further substituted by lower alkyl group(s), or protected by a group known in the art such as a benzoxycarbonyl group, acetyl group, alkoxycarbonyl group or benzyl group and the like.

The term "cycloalkylamino" refers to cycloalkyl group as defined above attached to a structure via an amino radical, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and the like. The cycloalkylamino group may be unsubstituted or substituted with one or more substituents, preferably one to three, more preferably with one to two and most preferably with one substituent. The substituents are preferably phenyl or benzyl.

The term "arylamino" refers to an aryl group as defined above attached to a parent structure via an amino radical, i.e., aryl-NH-.

The term "aralkylamino" refers to an aryl group as defined above attached to a parent structure via an alkylene-amino radical, i.e., aralkyl-NH-. The aralkylamino group

may be optionally substituted with a lower alkyl group, preferably a methyl group, i.e., aralkyl-NCH_3.

The term "acetoxy" refers to the group –O-OC-CH_3.

The term "carbamoyl" refers to the group –CO-NH_2 and the carbamoyloxy to the group –O – CO – NH.

The term "alkylcarbamoyloxy" refers to an alkyl group as defined above attached to a parent structure via a carbymoyloxy radical, i.e.,–O-CO- NH-alkyl.

The term "alkylcarbonyloxy" refers to an alkyl group as defined above attached to a parent structure via a carbonyloxy radical, i.e., -O-CO-alkyl.

The term "alkoxy" refers to the group R'-O-, wherein R' is an alkyl group as defined above.

The term "aralkyloxy" refers to the group Y-O-, wherein Y is aralkyl group as defined above.

The term "alkylthio" refers to the group R-S-, wherein R is an alkyl group as defined above.

The term "halogen" refers to fluorine, bromine, iodine and chlorine.

In the present invention, the expression "optionally substituted with" means that substitution can occur at one or more positions, preferably at one to three positions, and,

unless otherwise indicated, that the substituents are independently selected from the specified options.

"Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts which retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from potassium, sodium, ammonium, and quarternary ammonium hydroxide, such as for example tetramethylammonium hydroxide.

"Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, prodrug, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

"Pharmaceutically active metabolite" means a metabolic product of a compound of formula I which is pharmaceutically acceptable and effective.

An embodiment also relates to prodrugs of the compounds described above. The term "prodrug" refers to a compound that may be converted under physiological conditions or by solvolysis to any of the compounds of formula I or to a pharmaceutically acceptable salt of a compound of formula I. A prodrug may be inactive when administered to a subject but is converted *in vivo* to an active compound of formula I.

Preferably, the present invention relates to compounds of the above formula (I), wherein R^4 is hydrogen; alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, amino, mono- or di-alkylamino, carbamoyl, carbamoyloxy, acetoxy or carboxy; alkenyl; alkinyl; (C_3-C_7)-cycloalkyl; aryl optionally substituted with one to three substituents selected from the group consisting of alkyl,

alkoxy, hydroxy, halogen, amino, mono- or di-alkylamino, alkylthio or alkylcarbonylamino; aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, amino, mono- or di-alkylamino, or alkylthio; or heterocyclylalkyl.

More preferably, the present invention relates to compounds of the above formula (I), wherein R^4 is phenyl, methyl, t-butyl, 4-tButylphenyl, 4-methoxyphenyl, 2-aminoethyl, 2-dimethylaminoethyl, $ZHNCH_2CH_2$- ("Z" is the group benzyloxycarbonyl), 4-methylthiophenyl, cyclohexyl, 2-, 3-, or 4-hydroxyphenyl, 4-acetoaminophenyl, 4-fluorophenyl, ethyl, i-propyl, benzyl, 2-acetoxyethyl, ethylcarbamoyloxyethyl, diethylcarbamoylmethyl, phenylethyl, allyl, n-pentyl, 2-naphtyl, 4-fluorobenzyl, 2-furylmethyl or 2-hydroxyethyl.

Most preferably, the present invention relates to compounds of the above formula (I), wherein R^4 is phenyl, 4-hydroxyphenyl (R), 4-acetoaminophenyl, tertia-butyl, (R), ethyl, isopropyl, t-butyl, benzyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 2-acetoxyethyl, allyl, n-pentyl, 2-hydroxyethyl or methyl.

Preferably, the present invention relates to compounds of the above formula (I), wherein R^5 is $(C_1$-$C_6)$-alkylamino; hydroxy; $(C_3$-$C_7)$-cycloalkylamino optionally substituted by phenyl or benzyl; arylamino; aralkylamino having $(C_1$-$C_4)$-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of H_2NSO_2-, hydroxy, alkyl, benzyl, alkoxy carbamoyloxy or heterocyclyl; $(C_1$-$C_4)$-alkoxy; benzhydrazino; heterocyclyl optionally substituted by benzyl or benzhydryl; heterocyclylamino; heterocycloalkyamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonyl-amino or halogen; or aralkyloxy and aralkyl both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl.

More preferably, the present invention relates to compounds of the above formula (I), wherein R^5 is phenylethylamino; phenylethoxy; benzyloxy; 2-naphtylmethylamino; benzylpiperazino; 1,2,3,4-tetrahydroisoquinolino; t-butoxy; hydroxy; 4-$H_2NSO_2PhCH_2CH_2$; 2-, 3- or 4-hydroxyphenylethylamino; 2-, 3- or 4-hydroxyphenylethyl-N-methylamino; N-benzylphenethylamino; 4-t-butylbenzylamino; benzylamino; N-methylphenethylamino; 4-benzhydrylpiperazino; 2-phenylcyclopropyl-amino; thienylethylamino; 2-pyridylethylamino; 5-ethylpyrazol; 4,3-dimethoxyphenyl-ethylamino; benzylhydrazino; benzothiazol-2-ylmethyl-amino; 2-pyridin-4-yl-amino; 3,4-dimethoxy-phenyl-ethyl-methyl-amino; , bezothiazol-2-ylmethyl-amino; 2-pyridin-3-yl-ethylamino; pyridin-4-ylmethyl-amino; thiazol-2-ylamino; naphtalen-2-ylamino;4-chloro-phenyl-ethylamino; 4-methoxy-phenyl-ethylamino; 4-(1,2,3)thiadiazol-4-yl-benzylamino; 2-cyclohexylamino or1-benzyl-piperidin-4-ylamino.

Most preferably, the present invention relates to compounds of the above formula (I) wherein R^5 is phenylethylamino, 4, 3- dimethoxyphenylethylamino, thienylethylamino, 2-pyridylethylamino, 4-hydroxyphenylethylamino, N-methylphenethylamino, 2-hydroxyphenylethylamino, 3-hydroxyphenylethylamino 2-hydroxyphenylethyl-N-methylamino, 3-hydroxyphenylethyl-N-methylamino, 4-hydroxyphenylethyl-N-methylamino or benzylhydrazino.

Compounds of interest include compounds of formula (I) wherein R^1 and R^2 are methyl and R^3 is hydrogen and n is an integer of 0.

Examples of such compounds are;

a) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

b) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-(*S*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

d) N-{1-[(1-sec-Butyl-4-{2-[1-(4-tert-butyl-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

e) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(4-methoxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

f) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid phenethyl ester,

g) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid benzyl ester,

h) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[(naphthalen-2-ylmethyl)-carbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

i) N-{1-[(4-{2-[1-(2-Amino-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

j) N-{1-[(4-{2-[3-(4-Benzyl-piperazin-1-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

k) N-{1-[(1-sec-Butyl-4-{2-[3-(3,4-dihydro-1H-isoquinolin-2-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

l) N-{1-[(1-sec-Butyl-4-{2-[1-(2-dimethylamino-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

m) (2-{1-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl)-carbamic acid benzyl ester,

n) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(4-methylsulfanyl-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

o) N-[1-({1-sec-Butyl-4-[2-(1-cyclohexylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

p) N-{1-[(1-sec-Butyl-4-{2-[1-(*S*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

q) N-{1-[(1-sec-Butyl-4-{2-[1-(*R*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

r) N-{1-[(4-{2-[1-(4-Acetylamino-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

s) N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

t) N-[1-({1-sec-Butyl-4-[2-(1-(*R*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

u) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

v) N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

w) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

x) N-[1-({4-[2-(1-Benzylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

y) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

z) N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

aa) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

bb) Acetic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester,

cc) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid tert-butyl ester,

dd) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid,

ee) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ff) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

gg) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[2-(methyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

hh) N-{1-[(4-{2-[3-(4-Benzhydryl-piperazin-1-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ii) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

jj) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

kk) N-{1-[(4-{2-[2-(Benzyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ll) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-phenyl-cyclopropylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

mm) N-{1-[(1-sec-Butyl-4-{2-[2-(4-tert-butyl-benzylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

nn) N-[1-({4-[2-(2-Benzylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

oo) N-{1-[(4-{2-[2-(N'-Benzyl-hydrazinocarbonyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

pp) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenethylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

qq) N-[1-({4-[2-(1-Allylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

rr) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-4-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ss) N-(1-{[4-(2-{2-[(Benzothiazol-2-ylmethyl)-carbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-1-sec-butyl-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

tt) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-thiophen-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

uu) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-3-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

vv) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ww) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[(pyridin-4-ylmethyl)-carbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

xx) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3H-imidazol-4-yl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

yy) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(thiazol-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

zz) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(naphthalen-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

aaa) N-[1-({1-sec-Butyl-4-[2-(2-cyclohexylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

bbb) N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

ccc) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ddd) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-chloro-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

eee) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(1-pentylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

fff) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(naphthalen-2-ylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ggg) N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-benzylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

hhh) N-{1-[(1-sec-Butyl-4-{2-[1-(furan-2-ylmethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

iii) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{2-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

jjj) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(4-[1,2,3]thiadiazol-4-yl-benzylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

kkk) N-{1-[(4-{2-[2-(1-Benzyl-piperidin-4-ylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

lll) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

mmm) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

nnn)N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ooo)N-(1-{[1-sec-Butyl-4-(2-{1-dimethylcarbamoylmethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ppp)N-[1-({1-sec-Butyl-4-[2-(1-dimethylcarbamoylmethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

qqq) Ethyl-carbamic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester.

When R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 0, preferred compounds of formula (I) are those for which R^4 is phenyl, 4-hydroxyphenyl (R), 4-AcNHPh- (i.e., 4-acetoaminophenyl), t-butyl (R), ethyl, i-propyl, , t-butyl, benzyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 2-hydroxyethyl, 2-acetoxyethyl, allyl or n-pentyl and R^5 is phenylethylamino.

In particular, the following compounds of formula (I) are preferred in the present invention;

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-4-{2-[1-(*R*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-{1-[(4-{2-[1-(4-Acetylamino-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-(*R*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({4-[2-(1-Benzylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

Acetic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester,

N-[1-({4-[2-(1-Allylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(1-pentylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide.

When R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 0, other preferred compounds of formula (I) are those for which R^4 is methyl and R^5 is 4-hydroxy-phenylethylamino; N-methylphenethylamino; 2-hydroxyphenylethylamino; 3-hydroxy-phenylethylamino, benzylhydrazino; 4, 3-dimethoxyphenylethylamino, thienylethylamino, 2-pyridylethylamino. In particular, the following compounds of formula (I) are preferred in the present invention;

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[2-(methyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

N-{1-[(4-{2-[2-(N'-Benzyl-hydrazinocarbonyl)-1-methylsulfanyl-ethyl]- pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-thiophen-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-3-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide.

Other compounds of interest include compounds of formula (I) wherein R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 1. It may be the compound of formula N-[1-({1-sec-Butyl-4-[2-(1-methanesulfinyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide, for example.

Other compounds of interest include compounds of formula (I) wherein R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 2. For example, the present invention concerns the compound of formula N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide.

Another preferred embodiment of the present invention is the compounds of formula (I) wherein R^1 is methyl, R^2 and R^3 are hydrogen and n is an integer of 0.

Examples of such compounds are selected from the group consisting of,

a) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

b) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

d) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

e) N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

f) N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(2-methyl-propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide,

g) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-3-methyl-2-methylamino-butyramide,

h) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-3-methyl-2-methylamino-butyramide.

When R^1 is methyl, R^2 and R^3 are hydrogen and n is an integer of 0, preferred compounds of formula (I) are those for which R^4 is ethyl, phenyl, t-butyl, methyl, i-propyl and R^5 is phenylethylamino, 3-hydroxyphenylethylamino. In particular, the following compounds of formula (I) are preferred in the present invention;

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-3-methyl-2-methylamino-butyramide.

Another preferred embodiment of the present invention concerns compound of formula (I) wherein R^1 is methyl, R^2 and R^3 are hydrogen and n is an integer of 2. Examples of such compounds are selected from the group consisting of,

a) N-[1-({1-sec-Butyl-4-[2-(1-ethanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

b) N-[1-({4-[2-(1-Benzenesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

d) N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide.

When R^1 is methyl and R^2 and R^3 are hydrogen and n is an integer of 2, the preferred compound of formula (I) in this case is this for which R^4 is methyl and R^5 is phenylethylamino and having the following formula;

N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

Another preferred embodiment of the present invention concerns compounds of formula (I) wherein R^1 and R^3 are methyl, R^2 is hydrogen and n is an integer of 0. Examples of such compounds are selected from the group consisting of,

a) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide,

b) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide,

Another preferred embodiment of the present invention concerns compound of formula (I) wherein R^1, R^2 and R^3 are methyl and n is an integer of 0. Examples of such compounds are selected from the group consisting of,

a) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

b) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

c) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

d) N-{1-[(1-sec-Butyl-4-{2-[1-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

e) N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

f) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

g) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

h) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

i) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

j) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

k) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

l) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide.

m) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-pentylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

n) N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

o) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

p) N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

q) Ethyl-carbamic acid 3-(2-{3-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-methyl-3-methylsulfanyl-propionylamino}-ethyl)-phenyl ester.

When R^1, R^2 and R^3 are methyl and n is an integer of 0, the preferred compound of formula (I) is in this case this for which R^4 is methyl or ethyl and R^5 is phenylethylamino, 3-hydroxyphenylethylamino or 3-hydroxyphenylethyl-N-methyamino and having the following formula;

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

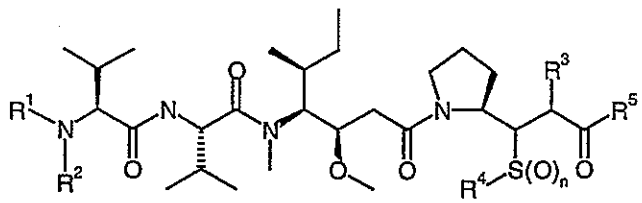
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide.

All of the stereoisomers in the formula (I) are included in the scope of the invention. But compounds having the stereostructural formula (I-1),



(I-I)

wherein R^1, R^2, R^3, R^4 , R^5 and n are as defined above,

as well as pharmaceutically acceptable salts thereof, prodrugs of the compound of formula (I-I) or those salts.

Specifically the present invention concerns *R*-configuration regarding $R^4S(O)n$ group and S-configuration regarding R^3 group which are preferable in terms of antitumor activity.

These compounds are effective at inhibiting or preventing the growth of tumors in premalignant and malignant cells and are useful for the treatment of carcinomas forming solid tumors, especially of colorectal cancer, lung cancer, breast cancer, stomach cancer, cervical cancer and bladder cancer. The compounds of this invention can be used to treat such tumors, to retard the development of such tumors, and to prevent the increase in number of tumors.

The anticancer therapeutic activity of compounds of this invention may be demonstrated by various standard *in vitro* assays. Such assays described below and in the examples are known to indicate anticancer activity and are assays for cancer therapeutics.

Compounds of this invention have the structure depicted in formula I, and anticancer activity as determined by any standard assay, especially assays for apoptosis. The compounds are particularly effective to induce apoptosis in carcinoma cells, causing the death of the cell. Thus a compound has the desired activity if the compound causes carcinoma cells to die when the cells are exposed to the compounds. Carcinoma cells for assays (for example breast, lung, colorectal, etc.) are readily obtained from cell depositories such as the American Type Culture Collection (ATCC) or may be isolated by skilled persons from cancer patients. The type of cancer against which the compound is most active is determined by the type of cell used in the assays.

Carcinoma cells, grown in culture, may be incubated with a specific compound and changes in cell viability may be determined for example, by dyes which selectively stain dead cells or by optical density (O.D.) measurement. If more than 10% of cells have died, the compound is active in inducing apoptosis. The compounds may not directly kill the cells (cellular toxicity) but may modulate certain intra- or extracellular events which result in apoptosis. The anticancer activity of the compounds of this invention may also be determined by assays that access the effects of compounds on cell growth and differentiation. Cell growth inhibition may be determined by adding the compound in question to carcinoma cells in culture with dyes or radioactive precursors, and determining by microscopic cell counting, scintillation counting , or O.D. measurement whether the number of cells has increased over the incubation period. If the number of cells has not increased, growth has been inhibited and the compound is regarded as having therapeutic activity. Similarly, the proportion of cells which have become differentiated after addition of a test compound may be determined by known methods (ie. measuring oxidative burst in HL-60 cells, an indicator of differentiation, by NBT). If 10% or more cells have differentiated, then the compound is regarded as having therapeutic activity.

In vivo assays are also useful to demonstrate anticancer activity. Compounds of this invention may act to reduce the size and/or the number of tumors in laboratory animals such as mice in which tumor growth has been induced. The type of tumor indicates the type of cancer against which primary activity is expected. Specific tumors may be induced by perturbing specific tissues with carcinogens, or by injecting specific types of carcinoma cells. Such an assay is provided in Example IIB. The compounds of the present invention show significant prophylactic and therapeutic activity when evaluated against NMU-induced mammary (breast) tumors in rats. Surprisingly the doses and regimens which are effective are free of significant toxicity. The compounds also show efficacy in reducing number of tumors during the course of the experiment (i.e. chemoprevention) at doses and regimens not associated with toxicity. Furthermore, the compounds are therapeutically active, i.e. are able to effect regression of established first primary tumors. The

compounds are also preventitive, i.e. able to significantly prevent formation of new tumors.

Antiproliferative activity assay was carried out as follows. A single suspension of tumor cells was inoculated to the serially diluted 96-well microtestplate. Then the testplate was incubated in the 5% CO_2 ambience at 37°C for 4 days (2 - 3x 10^3 cells/well). The degree of cell growth in a monolayer was measured by using WST-8 (Dojindo, Japan). IC_{50} values of drugs against tumor cells were calculated as the concentration of drug yielding 50% OD of the control growth. The results are shown in the following table I.

Table I: *In vitro* antitumor activity of selected compounds

Compound	HCT 116 IC_{50} (nM)
N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.33
N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.44
N-{1-[(1-sec-Butyl-4-{2-[1-(*R*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.6
N-{1-[(4-{2-[1-(4-Acetylamino-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.98
N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	0.5
N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	0.87
N-[1-({1-sec-Butyl-4-[2-(1-(*R*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.04
N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.78
N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.17

N-[1-({4-[2-(1-Benzylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.52
N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.3
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	0.12
N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	0.77
N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	0.65
N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.39
Acetic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester	0.19
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	0.6
N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[2-(methyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.87
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	0.64
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-	0.26

carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.04
N-[1-({4-[2-(1-Allylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.55
N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-thiophen-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.5
N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-3-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.91
N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide	0.9
N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(1-pentylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.75
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	0.91
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide	1.0
N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	0.19
N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.66

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide	0.11
N-(1-{[1-sec-Butyl-4-(2-{1-dimethylcarbamoylmethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	1.8
N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide	0.84
Ethyl-carbamic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester	0.97
Ethyl-carbamic acid 3-(2-{3-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-methyl-3-methylsulfanyl-propionylamino}-ethyl)-phenyl ester	0.57

The maximum tolerated doses (MTD) of the representative compounds;

- N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

- N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide, and

- N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

- N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

- N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

- N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

- N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide.

. of the present invention were examined by i.v. administration in mice. The respective MTD values of the compounds were 14, 18 and 10, 8, 8, 2 and 2 mg/kg.

Thus, in one embodiment, the compounds of the invention are therapeutically active, producing regression or remission of solid tumors.

Embodiments concern the use of a compound of formula (I) for the preparation of medicaments for the preparation of medicaments for the treatment of cell proliferative disorders, more preferably for the preparation of medicaments for the treatment of cancer, and most preferably for the treatment of colorectal cancer, lung cancer, breast cancer, stomach cancer, cervical cancer and bladder cancer.

A second aspect of the present invention provides a pharmaceutical composition comprising compound as defined above and a pharmaceutically acceptable carrier.

A third aspect of the present invention provides a use of a compound as defined above for the preparation of medicaments.

A fourth aspect of the present invention provides a use of compound as defined above for the preparation of medicaments for the treatment of cell proliferative disorders.

A fifth aspect of the present invention provides a use of compound as defined above for the preparation of medicaments for the treatment of cancer.

An embodiment may provide a method for treating a cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I).

Treatment of cancers may be accomplished by administering a compound of the invention systemically to a patient in an amount effective to treat the cancer. By inhibiting growth of cancer (carcinoma) cells is meant stopping growth, causing apoptosis, or causing differentiation, or otherwise changing the nature of the cell to render it innocuous. The compound may also be administered prophylactically, for example to a person at risk for cancer, or a person who has already undergone effective treatment generally in a lower dosage than for treatment. The amount of compound used is dependent on the type of cancer, the amount and size of the tumors and on the requirements of the patient. In general a daily dosage of about 0.1 mg/kg to about 100 mg/kg of body weight, preferably about 20 mg/kg to about 80 mg/kg is a helpful basic range, which may be varied by the skilled practitioner depending on the characteristics and requirements of the patient and his condition. The treatment is typically carried out for a

period of about three months, but this depends on the patient's condition and the practitioner's judgement. In prophylactic administration, the duration of administration again depends on the patients condition and the practitioner's plan, but will generally continue for a longer period of time than three months. For the treatments given above, the compound of the invention is administered systemically as a composition containing the compound of the invention, and a pharmaceutically acceptable carrier compatible with said compounds. In preparing such composition, any conventional pharmaceutically acceptable carrier can be used. Generally the preferred unit dosage form is tablets or capsules, which can be administered once or twice daily depending upon the weight and size of the patient. The compounds of this invention may be administered as the sole treatment, or may be used in conjunction with other chemical or biochemical treatments or with radiation or surgery.

The pharmaceutical compositions of this invention can be made up in any conventional form including: (a) a solid form for oral or suppository administration such as tablets, capsules, pills, powders, granules, and the like; (b) sterile, typically aqueous solution or suspension form for intravenous or parenteral administration and (c) preparations for topical administration such as solutions, suspensions, ointments, creams, gels, micronized powders, aerosols and the like. The pharmaceutical compositions may be sterilized and/or may contain adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, salts for varying the osmotic pressure, and/or buffers.

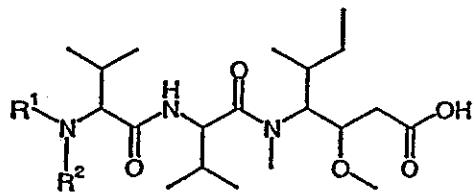
The compounds of the invention are especially useful in pharmaceutically acceptable oral modes. These pharmaceutical compositions contain one or more compounds of the invention or its pharmaceutically acceptable salts and its pharmaceutically acceptable hydrolyzable esters in association with a compatible pharmaceutically acceptable carrier material. Any conventional carrier material can be used. The carrier material can be an organic or inorganic inert carrier material suitable for oral administration. Suitable carriers include water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, petroleum jelly and the like. Furthermore, the pharmaceutical preparations may contain other pharmaceutically active agents. Additional additives such as flavoring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding.

The pharmaceutical preparations can be made up in any conventional oral dosage form including a solid form for oral administration such as tablets, capsules, pills, powders, granules, and the like. A preferred oral dosage form comprises tablets, capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. The oral dosages contemplated in accordance with the present invention will vary in

accordance with the needs of the individual patient as determined by the prescribing physician.

A sixth aspect of the present invention provides a process for the preparation of compounds as defined above comprising

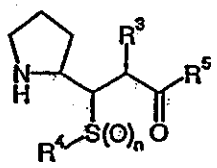
condensing an acid of the formula (II),



(II)

wherein R^1 and R^2 are as defined above.

with a compound of the formula (III),



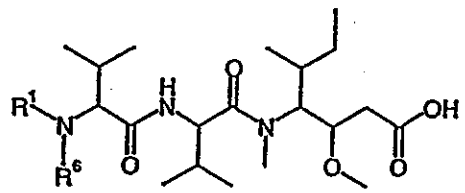
(III)

wherein R^3, R^4, R^5 and n are as defined above.

Preferably R^1 and R^2 are each independently alkyl, more preferably (C_1-C_6)-alkyl, and most preferably (C_1-C_4)-alkyl.

Compounds (I) may be prepared by condensing an acid of the formula (II) with a compound of formula (III) in the presence of a condensing agent, followed, if necessary, by removal of protecting group(s) and/or a salt formation, if necessary.

A seventh aspect of the present invention provides a process for the preparation of compounds as defined above comprising condensing an acid of the formula (IV),



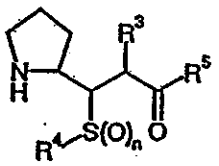
(IV)

wherein

R^1 is hydrogen or (C_1-C_4)-alkyl; and

R^6 is a protecting,

with a compound of the formula (III),



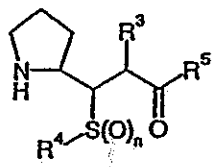
(III)

wherein R^3, R^4, R^5 and n are as defined above

The condensing agent may be e.g. dicyclohexylcarbodiimide (DCC), diphenyl phosphorylazide (DPPA), diethyl phosphorocyanide (DEPC), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), or the like in an inert solvent such as, for example, halogenated aliphatic hydrocarbon such as chloroform and dichloromethane, ethylacetate, tetrahydrofuran (THF), dimethylformamide (DMF) or acetonitrile, if necessary in the presence of an organic base such as, for example, triethylamine or diisopropylethylamine (DIPEA).

An eighth aspect of the present invention provides

compounds of the formula (III),

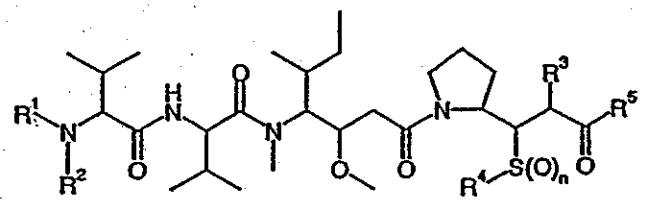


(III)

wherein R^3, R^4, R^5 and n are as defined above.

A ninth aspect of the present invention provides

a compound of the formula (I),



(I)

wherein

R^1, R^2 and R^3 are each independently hydrogen or (C_1-C_4)-alkyl;

R^4 is hydrogen;

alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbonyloxy or halogen;

alkenyl;

alkinyl;

(C_3-C_7)-cycloalkyl;

aryl optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl; or

heterocyclylalkyl;

R^5 is (C_1-C_6)-alkylamino;

hydroxy;

(C_3-C_7)-cycloalkylamino optionally substituted by phenyl or benzyl;

arylamino;

aralkylamino having (C_1-C_4)-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonyl-amino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

(C_1-C_4)-alkoxy;

benzhydrazino;

heterocyclyl optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, mono- or di-alkylamino, acylamino, alkoxycarbonylamino, phenyl or halogen;

heterocyclylamino;

heterocycloalkylamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen;

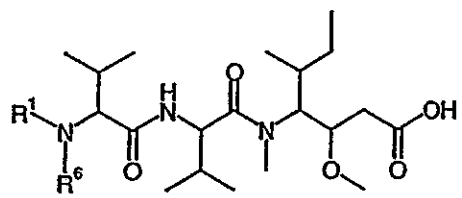
aralkyloxy and aralkyl both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluo$romethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl;

and

n is an integer of 0, 1 or 2;

and pharmaceutical acceptable salts thereof.

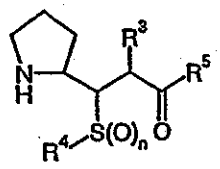
The compound of the present invention represented by the formula (I) wherein either R^1 or R^2 is a hydrogen atom can be prepared by condensing a tripeptide fragment of the following formula (IV)



(IV)

wherein R^1 is hydrogen or alkyl, preferably (C_1-C_6)-alkyl, and most preferably (C_1-C_4)-alkyl; R^6 is a protecting group, e.g. selected from t-butoxycarbonyl (Boc), carbobenzyloxy (Z) or 9-fluorenylmethoxycarbonyl (Fmoc) group;

with a fragment of the following formula (III)



(III)

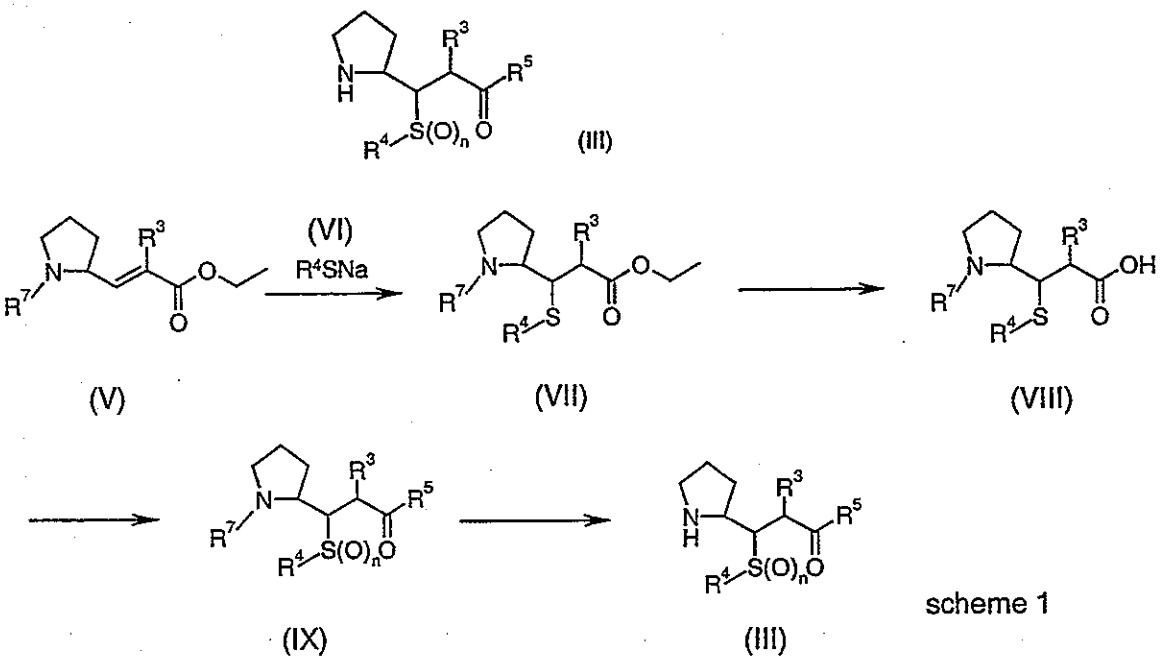
wherein R^3, R^4, R^5 and n are as defined above by using a condensing agent.

The condensing agent may be, e.g. dicyclohexylcarbodiimide (DCC), diphenyl phosphorylazide (DPPA), diethyl phosphorocyanide (DEPC), BOP reagent, or the like in an inert solvent such as, for example, halogenated aliphatic hydrocarbon such as chloroform and dichloromethane, ethylacetate, tetrahydrofuran (THF), dimethyl-

formamide (DMF) or acetonitrile, if necessary in the presence of an organic base such as, for example, triethylamine or diisopropylethylamine (DIPEA) at a temperature between –10°to 50°C, preferably 0°C to room temperature, and then the coupling product is deprotected by the procedures known to those in the art, e.g. by basic or acidic hydrolysis, hydrogenolysis or treatment with fluoride anion.

Another embodiment of the present invention concerns the preparation of compounds of formula (III).

Compounds of formula (III)



scheme 1

wherein R^3, R^4, R^5 and n are as defined above, can be prepared according to the following synthetic scheme 1.

According to scheme 1, compounds of formula (III) is prepared from compound of formula (V), wherein R^3 is hydrogen or alkyl, preferably (C_1-C_6)-alkyl, and most preferably (C_1-C_4)-alkyl; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group, prepared from N-Boc-prolinal by known methods (Heterocycles, 36 (9) 2073-2080, 1993), by reacting with a compound of formula (VI), a commercially available compound as the salt or prepared from the corresponding mercaptane with a base such as sodium hydroxide, sodium hydride, sodium carbonate or sodium hydrogen carbonate, potassium hydroxide, potassium hydride or potassium t-butoxide, lithium hydroxide, lithium hydride, methyl lithium or n-butyl lithium by conventional methods, conveniently in an inert organic solvent, such as tetrahydrofuran, acetonitrile, methanol, ethanol or DMF, at a temperature from about –40°C to the reflux temperature of the solvent to form a corresponding intermediate of formula (VII) wherein R^3 and R^4 are as defined in the

present invention; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group. Potassium thiomethoxide, in particular, can be alternatively prepared conveniently from the reaction of methyl thioacetate with potassium ethoxide in situ instead of using methylmercaptane gas.

The addition of potassium thioalkoxide in the presence of a proton source such as an alcohol or phenol, preferably phenol, proceeds smoothly at room temperature, giving the desired stereoisomers regarding sulfur group and R^3 in good yield and stereoselectivity. For example, the reaction of the compound formula (V), where R^3 is methyl, R7 is t-butoxycarbonyl group and the configuration of the proline 2-position is *S*, with potassium thiomethoxide or thioethoxide in the presence of phenol gives predominantly (2*S*)-2-[(1*R*,2*S*)-2-ethoxycarbonyl-1-methyl or ethyl-sulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

The intermediate of formula (VII), wherein R^3, R^4 and R^7 are as defined above, is hydrolyzed, if necessary, by conventional methods and then reacted with an alcohol or an amine, conveniently using an aforementioned condensing agent in an inert organic solvent, such as a halogenated aliphatic hydrocarbon, tetrahydrofuran, acetonitrile, or DMF, at a temperature of from about –20°C to the reflux temperature of the solvent, preferably from 0°C to room temperature, to form a corresponding compound of formula (IX) wherein R^3, R^4 and R^5 are as defined in the present invention; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group and n is an integer of 0.

The compound of formula (IX), wherein R^3, R^4 and R^5 are as defined above with n is an integer of 0; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group, can be optionally oxidized with m-chloroperbenzoic acid (mCPBA) by conventional methods, conveniently in an inert organic solvent, such as a halogenated aliphatic hydrocarbon, at a temperature of from about –40°C to the reflux temperature of the solvent to form a corresponding sulfoxide or sulfone derivative of formula (IX), wherein R^3, R^4 and R^5 are as defined in the present invention and n is an integer of 1 or 2; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group.

The compound of formula (I), wherein R^1, R^2, R^3, R^4 and R^5 are as defined in above with n is an integer of 0, can be also optionally oxidized with mCPBA by conventional methods, conveniently in an inert organic solvent, such as a halogenated aliphatic hydrocarbon, at a temperature of from about –40°C to the reflux temperature of the solvent to form a corresponding sulfoxide or sulfone derivative of formula (I), wherein R^1, R^2, R^3, R^4 and R^5 are as defined above ad n is an integer of 1 or 2.

Alternatively, the compound of formula (I), wherein R^1, R^2, R^3, R^4 and R^5 are as defined above with n is an integer of 1 or 2 but either R^1 or R^2 is a hydrogen atom, can be also prepared by oxidation of the coupling product obtained from (IV), wherein R^1 is alkyl group; R^6 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group, and (III), wherein R^3, R^4 and R^5 are as defined above with an integer of 0, with mCPBA followed by deprotection known to those in the art, e.g. by basic or acidic hydrolysis, hydrogenolysis or treatment with fluoride.

The compound of formula (IX), wherein R^3, R^4, R^5 and n are as defined above; R^7 is a protecting group selected from t-butoxycarbonyl, carbobenzyloxy or Fmoc group, is deprotected with trifluoroacetic acid (TFA) in an inert solvent such as a halogenated aliphatic hydrocarbon or without solvent at a temperature of from about –20°C to the reflux temperature of the solvent, preferably from 0°C to room temperature, to form a corresponding compound of formula (III) as the TFA salt.

EXAMPLES

The following Examples are provided to illustrate the invention and are not intended to limit it in any way. The compounds data were recorded as a TFA salt of a mixture of diastereomers regarding the chiral center of the carbon atom having the sulfur atom (*R*:*S*= 4:1 to 10:1) unless otherwise noted. The stereochemistry of the product was determined by NMR analysis of the bicyclic lactam formed after removing Boc group.

The retention time of each compound in HPLC was recorded using the following method unless otherwise noted.

column: Inertsil ODS-3/ 4.0x33 mm(GL Science Inc.)

mobile phase: 0.05% TFA-water : 0.05% TFA-acetonitrile,

flow rate: 1.0 ml/min

gradient: 10% MeCN at 0 min→95% MeCN at 4 min→95% MeCN at 5.5 min→10% MeCN at 6.0 min

Reference Example 1

Preparation of 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanylpropanoic acid

To a stirred solution of (*S*)-2-(2-ethoxycarbonyl-vinyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1 g, 3.71 mmol), prepared by a reported method (Heterocycles, 36 (9) 2073-2080, 1993), in THF (10 ml) was added NaSMe (95%: 781 mg, 11.1 mmol) at 0° C. The mixture was allowed to warm to room temperature and stirred for 16 hr. The mixture was quenched with 1N HCl, extracted with AcOEt, dried ($MgSO_4$) and concentrated *in vacuo* to give crude 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanylpropanoic acid (1.13 g), which was used without further purification in the next step.

Reference Example 2

Preparation of 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanyl-N-phenylethylpropanamide

To a stirred solution of the crude 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanylpropanoic acid (1.13 g) obtained above and phenylethylamine (0.61 ml, 4.83 mmol) in CH_2Cl_2 (10 ml) were added WSCI monohydrochloride (682 mg, 4.46 mmol), HOBt monohydrate (682 mg, 4.46 mmol) and diisopropylethylamine (1.94 ml, 11.1 mmol) at room temperature. After being stirred at room temperature for 14 hr, the mixture was evaporated *in vacuo*, extracted with AcOEt, washed with 1N HCl and H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (ca. 2.0 g) was purified by flash column chromatography (hexane : AcOEt=2 : 1) to give 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanyl-N-phenylethylpropanamide as an oil (1.15 g, 79%) which was the 5 : 1 (R : S) mixture of the two diastereomers at the newly formed chiral center determined by ^{1}H-NMR.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.45 (9H, s), 1.58-2.02(4H, m), 2.07(3H, s), 2.23-2.56(2H, m), 2.84(2H, t, J=6.9Hz), 3.19-3.30(1H, m), 3.30-3.69(4H, m), 3.82-4.00(4/5H, m), 4.03-4.14(1/4H, m), 6.32(1H, brs), 7.08-7.38(5H, m). LC-MS: 393 (MH^+), HPLC-RT: 3.90 min.

Reference Example 3

Preparation of 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-ethylsulfanyl-N-phenylethylpropanamide

To a stirred solution of (*S*)-2-(2-ethoxycarbonyl-vinyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (103 mg, 0.382 mmol) in THF (2 ml) was added EtSH (85 µl, 1.15 mmol) and NaH (60% in paraffin liquid: 46 mg, 1.15 mmol) at 0° C. The mixture was allowed to warm to room temperature and stirred for 7 hr. The mixture was quenched with 1N HCl, extracted with AcOEt, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give 2-(2-ethoxycarbonyl-vinyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (136 mg) as a crude oil, which was used without further purification in the next step.

To a stirred suspension of the crude 2-(2-ethoxycarbonyl-vinyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (136 mg) in THF (1 ml) and H_2O (1 ml) was added $LiOH.H_2O$ (48 mg, 1.14 mmol) at room temperature. The mixture was stirred at room temperature for 17 hr. The mixture was extracted with 1N NaOH and AcOEt. The aqueous

layer was acidified with 1N HCl, extracted with AcOEt, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give 2-(2-carboxy-vinyl)-pyrrolidine-1-carboxylic acid tert-butyl ester as a crude oil (109 mg). To a stirred solution of the crude oil (105 mg) in CH_3CN (2 ml) were added BOP reagent (306 mg, 0.692 mmol), phenethylamine (87 µl, 0.693 mmol), and diisopropylethylamine (121 µl, 0.695 mmol) at 0° C. The mixture was allowed to warm to room temperature and stirred for 12 hr. After being evaporated *in vacuo*, the mixture was dissolved in CH_2Cl_2. The solution was washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The residual oil was purified by preparative TLC (hexane : AcOEt = 1 : 1) to give 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-ethylsulfanyl-N-phenylethylpropanamide (104 mg, 67%) as an oil which was the 5 : 1 (R : S) mixture of the two diastereomers at the newly formed chiral center determined by ^{1}H-NMR.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 (3H, t, J=7.6Hz), 1.45 (9H, s), 1.61-2.04 (4H, m), 2.07-2.43 (2H, m), 2.53 (2H, q, J=7.6 Hz), 2.84 (2H, t, J=6.9 Hz), 3.20-3.35 (1H, m), 3.36-3.79 (4H, m), 3.80-3.98 (5/6H, m), 3.98-4.10 (1/6H, m), 6.46 (1H, brs), 7.15-7.38 (5H, m). LC-MS: 407 (MH^+), HPLC-RT: 3.90 min.

Example 1

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

To a stirred solution of 3-(N-tert-butoxycarbonyl-2'-pyrrolidinyl)-3-methylsulfanyl-N-phenylethylpropanamide (30.3 mg, 0.0772 mmol) in CH_2Cl_2 (0.5 ml) was added TFA (0.5 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 hr. The mixture was evaporated *in vacuo* to give 3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide TFA salt as a crude oil.

After the crude 3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide TFA salt obtained above was dissolved in DMF(2ml), the solution was added at 0° C to (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid which was prepared from (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid t-Bu ester (34 mg, 0.0700 mmol) by treating with TFA in CH_2Cl_2 according to the literature method (Chem. Pharm. Bull., 43(10), 1706-1718, 1995). To the solution were added diethyl phosphorocyanidate (95%: 12 µl, 0.0751 mmol) and triethylamine (49 µl, 0.352 mmol) at 0°C. After being

stirred at 0° C for 1 hr, the mixture was allowed to warm to room temperature and stirred for 20 hr. The mixture was quenched with saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude oil (90 mg), which was purified by preparative HPLC (column: ODS-80Ts, eluent: 39/31 H_2O : CH_3CN / 0.05% TFA). The appropriate fractions were lyophilized to obtain the title compound as a white amorphous powder (30 mg, 47%).

^1H NMR (270 MHz, $CDCl_3$): δ 0.65-1.09 (15H, m), 1.12 (3H, d, J=6.3 Hz), 1.30-2.65 (15H, m), 2.06 (3H, s), 2.83 (2H, t, J=7.6 Hz), 2.95 (6H, s), 3.00 (3H, s,), 3.30 (3H, s), 3.35-3.90 (4H, m), 3.95-4.12 (1H, m), 4.14-4.40 (1H, m), 4.60-4.85 (2H, m), 7.05-7.38 (5H, m). LC-MS: 704 (MH^+), HPLC-RT: 2.88 min.

The following compounds (Example 2-45) were obtained in a manner analogous to that of Example 1.

Example 2

N-[1-({1-sec-Butyl-4-[2-(1-(*S*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-tert-butylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^1H NMR (270 MHz, $CDCl_3$): δ 0.68-1.00 (15H, m), 1.07 (3H, d, J=6.6 Hz), 1.27 (9H, s), 1.45-2.45 (15H, m), 2.75 (2H, t, J=6.9 Hz), 2.88 (6H, s), 2.94 (3H, s,), 3.29 (3H, s), 3.32-3.90 (4H, m), 3.92-4.08 (1H, m), 4.22-4.32 (1H, m), 4.50-4.79 (2H, m), 7.05-7.32 (5H, m). LC-MS: 746 (MH^+), HPLC-RT: 3.20 min. (*S*-isomer).

Example 3

N-{1-[(1-sec-Butyl-4-{2-[1-(4-tert-butyl-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-tert-butyl-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.08 (15H, m), 1.13 (3H, d, J=6.6Hz), 1.28 (9H, s), 1.20-2.55 (15H, m), 2.79 (2H, t, J=7.3Hz), 2.95 (6H, s), 2.99 (3H, s), 3.26 (3H, s), 3.30-3.82 (4H, m), 3.92-4.10 (1H, m), 4.25-4.38 (1H, m), 4.61-4.82 (2H, m), 7.08-7.33 (5H, m). LC-MS: 822 (MH^+), HPLC-RT: 3.64 min. (*R*-isomer)

Example 4

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(4-methoxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-methoxy-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.08 (15H, m), 1.13 (3H, d, J=6.6Hz), 1.20-2.55 (15H, m), 2.79 (2H, t, J=7.3Hz), 2.95 (6H, s), 2.99 (3H, s), 3.27 (3H, s), 3.30-3.90 (4H, m), 3.77 (3H, s), 3.90-4.18 (1H, m), 4.20-4.35 (1H, m), 4.60-4.85 (2H, m), 6.79 (2H, d, J=8.9Hz), 7.32 (2H, d, J=8.5Hz), 7.10-7.40 (5H, m). LC-MS: 796 (MH^+), HPLC-RT: 3.14 min. (*R*-isomer)

Example 5

N-{1-[(1-sec-Butyl-4-{2-[1-(*S*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-hydroxy-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.18 (18H, m), 1.20-1.40 (2H, m), 1.50-2.90 (15H, m), 2.95 (6H, s), 3.01 (3H, s), 3.25(1H, s), 3.32 (2H, s), 3.35-4.10 (5H, m), 4.12-4.30 (1H, m), 4.50-4.78 (2H, m), 6.75(2/3H, d, J=8.6Hz), 6.82 (4/3H, d, J=8.6Hz), 7.08-7.35 (7H, m). LC-MS: 782 (MH^+), HPLC-RT: 2.87 min. (*S*-isomer)

Example 6

N-{1-[(1-sec-Butyl-4-{2-[1-(*R*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-hydroxy-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.68-1.20 (18H, m), 1.21-1.40 (2H, m), 1.50-2.90 (15H, m), 2.96 (6H, s), 3.03 (3H, s), 3.26 (3H, s), 3.32-3.70 (4H, m), 3.72-4.00 (1H, m), 4.15-4.35 (1H, m), 4.68-4.78 (2H, m), 6.75 (2H, d, J=8.6Hz), 7.08-7.35 (7H, m). LC-MS: 782 (MH^+), HPLC-RT: 2.88 min. (*R*-isomer)

Example 7

N-{1-[(4-{2-[1-(4-Acetylamino-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-Acetylamino-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.20 (18H, m), 1.21-2.95 (15H, m), 2.16 (3H, s), 2.79 (2H, t, J=7.3Hz), 2.96 (6H, s), 3.00 (3H, s), 3.25 (3H, s), 3.30-4.08 (5H, m), 4.20-4.35 (1H, m), 4.50-4.80 (2H, m), 7.08-7.40 (7H, m), 7.43 (2H, d, J=8.2Hz). LC-MS: 823 (MH^+), HPLC-RT: 2.82 min. (*R*-isomer)

Example 8

N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-fluoro-phenylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.67-1.09 (15H, m), 1.13 (3H, d, J=6.6Hz), 1.20-1.40 (2H, m), 1.42-2.62 (13H, m), 2.80 (2H, t, J=6.9Hz), 2.96 (6H, s), 2.98 (3H, s), 3.26 (3H, s), 3.27-4.08 (5H, m), 4.20-4.35 (1H, m), 4.60-4.80 (2H, m), 6.95 (2H, t, J=8.6Hz), 7.08-7.30 (5H, m), 7.36 (2H, dd, J=5.3, 8.9Hz). LC-MS: 784 (MH^+), HPLC-RT: 3.17 min. (*R*-isomer)

Example 9

N-[1-({1-sec-Butyl-4-[2-(1-(*R*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-tert-butylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.00 (15H, m), 1.06 (3H, d, J=6.4 Hz), 1.17 (9H, s), 1.35-2.55 (15H, m), 2.79 (2H, t, J=6.9 Hz), 2.88 (6H, s), 2.94 (3H, s), 3.21 (3H, s), 3.22-3.82 (4H, m), 3.92-4.05 (2H, m), 4.55-4.80 (2H, m), 6.95-7.30 (5H, m). LC-MS: 746 (MH^+), HPLC-RT: 3.16 min. (*R*-isomer)

Example 10

N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(2-hydroxy-ethylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.57-1.21(18H, m), 1.20-1.55(2H, m), 1.55-2.30(10H, m), 2.30-2.77(5H, m), 2.73(2H, t, J=6.59 Hz), 2.96(6H, s), 3.05(3H, s), 3.35(3H, s), 3.40-3.92(6H, m), 3.95-4.46(2H, m), 4.56-4.90(2H, m), 6.55(1H, brs), 7.08-7.39(5H, m), 7.92(1H, brs). LC-MS: 734 (MH^+), HPLC-RT: 2.70 min.

Example 11

Acetic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and acetic acid 2-(2-phenethylcarbamoyl-1-pyrrolidin-2-yl-ethylsulfanyl)-ethyl ester.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.57-1.20(18H, m), 1.20-1.45 (2H, m), 1.55-2.31(10H, m), 2.02(3H, s), 2.30-2.67(3H, m), 2.73(2H, t, J=6.11 Hz), 2.83(2H, t, J=6.93 Hz), 2.96(6H, s), 3.03(3H, s), 3.31(3H, s), 3.40-3.95(4H, m), 3.95-4.40(4H, m), 4.52-4.88(2H, m), 6.45(1H, brs), 7.08-7.39(5H, m), 7.79(1H, brs). LC-MS: 776 (MH^+), HPLC-RT: 2.86 min.

Example 12

3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid tert-butyl ester

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-propionic acid tert-butyl ester.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.68-1.20(18H, m), 1.20-1.42 (2H, m), 1.45(9H, s), 1.55-2.29(10H, m), 2.10(3H, s), 2.30-2.58(3H, m), 2.96(6H, s), 3.01(3H, s), 3.33(3H, s), 3.40-3.90(2H, m), 4.01-4.39(2H, m), 4.59-4.89(2H, m), 7.50(1H, brs). LC-MS: 657 (MH^+), HPLC-RT: 3.10 min.

Example 13

3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-propionic acid.

^{1}H NMR (270 MHz, DMSO-d6): δ 0.76(3H, m), 0.81-1.07(15H, m), 1.12-1.40 (2H, m), 1.55-2.18(10H, m), 2.01(3H, s), 2.20-2.66(3H, m), 2.67-2.84(6H, m), 3.01(3H, s), 3.20(3H, s), 3.24-3.80(2H, m), 3.80-4.37(2H, m), 4.49-4.79(2H, m), 8.93(1H, d, J=7.92 Hz), 9.50(1H, brs). LC-MS: 601 (MH^+), HPLC-RT: 2.51 min.

Example 14

N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.59 Hz), 0.85-1.19(15H, m), 1.20-1.42 (2H, m), 1.62-2.30(10H, m), 2.04(3H, s), 2.30-2.63(3H, m), 2.78-2.99(2H, m), 2.99(6H, s), 3.06(3H, s), 3.12(3H, s), 3.23-3.79(4H, m), 3.80-4.25(4H, m), 4.53-4.81(2H, m), 7.12(1H, brs), 7.32(2H, d, J=7.92 Hz), 7.79(2H, d, J=7.92 Hz), 7.65-7.82(3H, m). LC-MS: 783 (MH^+), HPLC-RT: 2.42 min.

Example 15

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(4-hydroxy-phenyl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.92 Hz), 0.89-1.19(15H, m), 1.20-1.42 (2H, m), 1.59-2.33(10H, m), 2.03(3H, s), 2.30-2.60(3H, m), 2.60-2.82(2H, m), 2.98(6H, s), 3.07(3H, s), 3.23(3H, s), 3.30-3.70(4H, m), 3.70-4.32(4H, m), 4.57-4.81(2H, m), 6.75(2H, d, J=8.57 Hz), 7.00(1H, brs), 7.01(2H, d, J=8.57 Hz), 7.30-8.60(2H, m). LC-MS: 720 (MH^+), HPLC-RT: 2.50 min.

Example 16

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[2-(methyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-methyl-3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.51-1.19(18H, m), 1.20-1.40 (2H, m), 1.55-2.30(10H, m), 2.01(3H, s), 2.30-2.71(3H, m), 2.71-3.10(14H, m), 3.10-3.88(4H, m), 3.31(3H, s), 3.95-4.40(2H, m), 4.47-4.91(2H, m), 6.99-7.38(5H, m), 7.56(1H, brs). LC-MS: 718 (MH^+), HPLC-RT: 2.92 min.

Example 17

N-{1-[(4-{2-[3-(4-Benzhydryl-piperazin-1-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 1-(4-benzhydryl-piperazin-1-yl)-3-methylsulfanyl-3-pyrrolidin-2-yl-propan-1-one.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.51-1.19(18H, m), 1.20-1.41 (2H, m), 1.55-2.20(10H, m), 1.99(3H, s), 2.20-2.75(3H, m), 2.75-4.55 (12H, m), 3.02(6H, s), 3.16(3H, s), 3.34(3H, s), 4.55-5.02(2H, m), 5.09-5.26(1H, m), 7.30-7.48(6H, m), 7.50-7.77(4H, m). LC-MS: 835 (MH^+), HPLC-RT: 2.57 min.

Example 18

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(2-hydroxy-phenyl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82(3H, t, J=6.59 Hz), 0.87-1.20(15H, m), 1.20-1.42 (2H, m), 1.59-2.34(10H, m), 2.00(3H, s), 2.34-2.65(3H, m), 2.65(2H, t, J=6.60 Hz), 2.97(6H, s), 3.07(3H, s), 3.32(3H, s), 3.37-3.91(4H, m), 3.91-4.35(2H, m), 4.57-4.88(2H, m), 6.10-8.15(3H, m), 6.55-7.17(4H, m). LC-MS: 720 (MH^+), HPLC-RT: 2.67 min.

Example 19

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(3-hydroxy-phenyl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.59 Hz), 0.87-1.20(15H, m), 1.20-1.40 (2H, m), 1.65-2.31(10H, m), 2.04(3H, s), 2.31-2.68(3H, m), 2.78(2H, t, J=6.60 Hz), 2.96(6H, s), 3.09(3H, s), 3.33(3H, s), 3.41-3.79(4H, m), 3.79-4.28(2H, m), 4.35-4.88(2H, m), 6.50-7.21(4H, m), 7.78(1H, brs). LC-MS: 720 (MH^+), HPLC-RT: 2.58 min.

Example 20

N-{1-[(4-{2-[2-(Benzyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-benzyl-3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.93 Hz), 0.87-1.17(15H, m), 1.17-1.40 (2H, m), 150-2.31(10H, m), 2.08(3H, s), 2.31-2.76(3H, m), 2.75-2.89(2H, m), 2.98(6H, s), 3.06(3H, s), 3.32(3H, s), 3.38-4.09(5H, m), 4.13-4.56(3H, m), 4.56-4.82(2H, m), 6.85-7.41(4H, m), 7.81(1H, brs). LC-MS: 794 (MH^+), HPLC-RT: 3.43 min.

Example 21

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-phenyl-cyclopropylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-(2-phenyl-cyclopropyl)-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.50-1.18(18H, m), 1.18-1.45 (2H, m), 155-2.31(10H, m), 2.11(3H, s), 2.31-2.72(3H, m), 2.72-2.95(1H, m), 2.97(6H, s), 3.03(3H, s), 3.32(3H, s), 3.35-4.09(4H, m), 4.10-4.43(1H, m), 4.50-4.83(2H, m), 6.88-7.40(4H, m), 7.68(1H, brs). LC-MS: 716 (MH^+), HPLC-RT: 2.90 min.

Example 22

N-{1-[(1-sec-Butyl-4-{2-[2-(4-tert-butyl-benzylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-(4-tert-butyl-benzyl)-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.50-1.20(18H, m), 1.20-2.24 (12H, m), 1.30(9H, s), 2.09(3H, s), 2.25-2.71(3H, m), 2.95(6H, s), 3.01(3H, s), 3.31(3H, s), 3.33-4.18(3H, m), 4.19-4.60(3H, m), 4.64-4.83(2H, m), 6.63(1H, brs), 7.23(2H, d, J=8.25 Hz), 7.34(2H, d, J=8.25 Hz), 7.56(1H, brs). LC-MS: 746 (MH^+), HPLC-RT: 3.41 min.

Example 23

N-[1-({4-[2-(2-Benzylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-benzyl-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.50-1.20(18H, m), 1.20-1.39 (2H, m), 1.45-2.31(10H, m), 2.08(3H, s), 2.31-2.68(3H, m), 2.96(6H, s), 3.02(3H, s), 3.30(3H, s), 3.33-4.12(3H, m), 4.18-4.62(3H, m), 4.62-4.83(2H, m), 6.79(1H, brs), 7.02-7.39(5H, m), 7.52(1H, brs). LC-MS: 690 (MH^+), HPLC-RT: 2.76 min.

Example 24

N-{1-[(4-{2-[2-(N'-Benzyl-hydrazinocarbonyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-propionic acid N'-benzyl-hydrazide.

^{1}H NMR (270 MHz, CD_3OD): δ 0.76(3H, t, J=7.02 Hz), 0.82-1.10(15H, m), 1.15-1.42 (2H, m), 1.55-2.18(10H, m), 1.98(3H, s), 2.18-2.59(3H, m), 2.80(6H, s), 3.05(3H, s), 3.22(3H, s), 3.34-3.73(3H, m), 3.80-4.38(2H, m), 4.51-4.78(2H, m), 7.25-7.47(5H, m). LC-MS: 705 (MH^+), HPLC-RT: 2.52 min.

Example 25

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenethylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-phenethyl-3-phenethylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80 – 1.10 (18H, m), 1.19 – 1.35 (2H, m), 1.79 – 2.50 (14H, m), 2.72 – 2.82 (4H, m), 2.95 (6H, s), 3.01 (3H, s), 3.22 (3H, s), 3.26 – 3.63 (4H, m), 3.70 – 3.82 (1H, m), 4.03 (1H, brs), 4.20 (1H, brs), 4.73 (2H, brs), 6.41 (1H, brs), 7.14 – 7.30 (10H, m), 7.66 (1H, brs). LC-MS: 794 (MH^+), HPLC-RT: 3.25 min.

Example 26

N-[1-({4-[2-(1-Allylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-allylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.79 – 1.15 (18H, m), 1.22 – 1.34 (2H, m), 1.66 – 2.53 (14H, m), 2.83 (2H, t, J = 7.9 Hz), 2.95 (6H, s), 3.01 (3H, s), 3.30 (3H, s), 3.35 – 3.82 (5H, m), 4.06 – 4.20 (2H, m), 4.73 (2H, t, J = 7.4 Hz), 5.03 (1H, d, J = 9.6 Hz), 5.10 (1H, d, J = 16.8 Hz) 5.62 – 5.80 (1H, m), 6.58 (1H, br s), 7.19 – 7.31 (5H, m), 7.60 (1H, brs). LC-MS: 730 (MH^+), HPLC-RT: 2.96 min.

Example 27

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-4-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-(2-pyridin-4-yl-ethyl)-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82 – 1.10 (18H, m), 1.23 – 1.48 (2H, m), 1.86 – 2.25 (5H, m), 2.05 (3H, s), 2.91 – 3.0 (2H,m), 2.97 (6H, s), 3.06 (3H, s), 3.30 (3H, s), 3.10 – 4.07 (7H, m), 4.73 (2H, brs), 7.79 (2H, brs), 8.75 (2H, brs). LC-MS: 705 (MH^+), HPLC-RT: 2.01 min.

Example 28

N-(1-{[4-(2-{2-[(Benzothiazol-2-ylmethyl)-carbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-1-sec-butyl-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-benzothiazol-2-ylmethyl-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.74 – 1.14 (18H, m), 1.20 – 1.38 (2H, m), 1.80 – 2.20 (7H, m), 2.13 (3H, s), 2.32 – 2.75 (5H, m), 2.94 (6H, brs), 3.33 (3H, s), 3.22 – 3.58 (2H, m), 3.65 – 6.79 (1H, m), 3.90 – 4.11 (1H, m), 4.36 (1H, brs), 4.78 – 4.92 (4H, m), 7.34 – 7.51 (2H, m), 7.82 – 8.00 (2H, m). LC-MS: 747 (MH^+), HPLC-RT: 2.73 min.

Example 29

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-thiophen-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-N-(2-thiophen-2-yl-ethyl)-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.79 – 1.13 (18H, m), 1.20 – 1.33 (2H, m), 1.85 – 2.58 (14H, m), 2.07 (3H, s), 2.97 (6H, brs), 3.03 (3H, s), 3.31 (3H, s), 3.36 – 3.69 (4H, m), 4.18 – 4.32 (1H, m), 4.66 – 4.80 (2H, m), 6.68 (1H, brs), 6.83 – 6.88 (1H, m), 6.91 – 6.94 (1H, m), 7.13 – 7.15 (1H, m), 7.56 (1H, brs). LC-MS: 710 (MH^+), HPLC-RT: 2.74 min.

Example 30

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-3-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-(2-pyridin-3-yl-ethyl)-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82 – 1.11 (18H, m), 1.20 – 1.40 (2H, m), 1.85 – 2.56 (12H, m), 2.04 (3H, s), 2.98 (6H, s), 2.89 – 3.02 (2H, m), 3.08 (3H, s), 3.32 (3H, s), 3.40 – 3.55 (4H, m), 3.80 – 4.50 (3H, m), 4.66 – 4.80 (2H, m), 7.67 – 7.88 (2H, brs), 8.26 – 8.38 (1H, m), 8.67 (1H, brs). LC-MS: 705 (MH^+), HPLC-RT: 1.99 min.

Example 31

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-(2-pyridin-2-yl-ethyl)-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81 – 1.09 (18H, m), 1.20 – 1.50 (2H, m), 1.70 – 2.70 (12H, m), 1.97 (3H, s), 2.85 – 3.12 (2Hm), 3.00 (6H, s), 3.07 (3H, s), 3.29 (3H, s), 3.36 – 3.86 (6H, m), 4.21 (1H, brs), 4.71 (2H, brs), 7.76 (1H, brs), 7.89 (1H, brs), 8.03 (1H, brs), 8.34 (1H, brs), 8.68 (1H, brs). LC-MS: 705 (MH^+), HPLC-RT: 2.00 min.

Example 32

N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[(pyridin-4-ylmethyl)-carbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-pyridin-4-ylmethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82 – 1.40 (20H, m), 1.73 – 2.27 (7H, m), 2.12 (3H, s), 2.35 – 2.70 (5H, m), 2.96 (6H, brs), 3.08 (3H, s), 3.33 (3H, s), 3.42 – 4.06 (6H, m), 4.30 (1H, brs), 4.42 – 4.57 (1H, m), 4.62 – 4.88 (3H, m), 7.88 (2H, brs), 8.80 (2H, brs). LC-MS: 691 (MH^+), HPLC-RT: 2.00 min.

Example 33

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3H-imidazol-4-yl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(3H-imidazol-4-yl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, DMSO-d6): δ 0.74 – 1.01 (18H, m), 1.25 – 1.28 (2H, m), 1.63 – 1.88 (7H, m), 1.95 (3H, s), 1.95 – 2.33 (7H, m), 2.77 (6H, s), 3.01 (3H, s), 3.21 (3H, s), 3.23 – 4.12 (7H, m), 4.50 – 4.71 (2H, m), 7.42 (1H, brs)8.06 (1H, brs), 8.92 – 8.99 (1H, m), 9.70 (1H, brs), 14.36 (1H, br s). LC-MS: 694 (MH^+), HPLC-RT: 2.06min.

Example 34

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(thiazol-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-N-thiazol-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.79 – 1.12 (18H, m), 1.20 – 1.50 (2H, m), 1.60 – 2.50 (12H, m), 2.14 (3H, s), 2.97 (6H, brs), 3.11 (3H, s), 3.31 (3H, s), 3.40 – 3.80 (3H, m), 4.01 (1H, brs), 4.38 (1H, brs), 4.67 – 4.78 (2H, m), 7.07 (1H, brs), 7.48 (1H, brs), 7.65 (1H, brs), 8.62 (1H, brs). LC-MS: 683 (MH^+), HPLC-RT: 2.67 min.

Example 35

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(naphthalen-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-naphthalen-2-yl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.52 – 1.50 (20H, m), 1.95 – 2.43 (12H, m), 2.17 (3H, s), 2.78 (3H, s), 2.95 (3H, s), 3.27 (3H, s), 3.45 – 4.08 (4H, m), 4.42 (1H, br s), 4.72 (2H, brs), 7.41 – 7.75 (7H, m), 8.33 (1H, brs), 8.93 (1H, brs). LC-MS: 726 (MH^+), HPLC-RT: 3.13 min.

Example 36

N-[1-({1-sec-Butyl-4-[2-(2-cyclohexylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-cyclohexyl-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82 – 1.33 (20H, m), 1.60 – 2.00 (15H, m), 2.10 (3H, s), 2.40 – 2.60 (5H, m), 2.99 (6H, s), 3.07 (3H, s), 3.32 (3H, s), 3.50 – 3.98 (7H, m), 4.29 (1H, brs), 4.73 (2H, brs), 6.08 (1H, brs), 7.77 (1H, brs). LC-MS: 682 (MH^+), HPLC-RT: 2.85 min.

Example 37

N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(3,4-dimethoxy-phenyl)-ethyl]-N-methyl-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81 – 1.11 (18H, m), 1.20- 1.40 (2H, m), 1.65 – 1.94 (7H, m), 2.10 (3H, s), 2.02 – 2.51 (5H, m), 2.81 (2H, brs), 2.98 (9H, brs), 3.07 (3H, s), 3.31 (3H, s), 3.40 – 4.00 (6H, m), 3.87, 3.85 (6H, 2s), 4.31 (1H, m), 4.73 (2H, br s), 6.03 – 6.67 (3H, m,), 7.71 (1H, brs). LC-MS: 778 (MH^+), HPLC-RT: 2.80 min.

Example 38

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.78 – 1.15 (18H, m), 1.20 – 1.40 (2H, m), 1.62 – 2.48 (12H, m), 2.06 (3H, s), 2.78 (2H, t, J = 7.6 Hz), 2.96 (6H, s), 3.01 (3H, s,), 3.31 (3H, s), 3.35 – 3.76 (5H, m), 3.86 (6H, s), 3.92 – 4.10 (1H, m), 4.15 – 4.30 (1H, m), 4.68 – 4.80 (1H, m), 6.40 (1H, brs), 6.72 – 6.81 (3H, m), 7.42 (1H, brs). LC-MS: 764 (MH^+), HPLC-RT: 2.69 min.

Example 39

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(1-pentylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-pentylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81-1.62 (27H, m), 1.72-2.40 (12H, m), 2.44-2.59 (5H, m), 2.73-2.90 (2H, m), 2.95 (6H, s), 3.02 (3H, s), 3.30 (3H, s), 3.30-3.86 (4H, m), 4.01-4.20 (2H, m), 4.73 (2H, brs), 7.18-7.28 (5H, m). LC-MS: 760 (M^+), HPLC-RT: 3.71 min (Waters).

Example 40

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(naphthalen-2-ylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(naphthalen-2-ylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.20 (18H, m), 1.40-2.60 (15H, m), 2.77 (2H, t, J=5.0Hz), 2.94 (6H, s), 2.96 (3H, s), 3.35 (3H, s), 3.50-3.80 (4H, m), 4.30-4.40 (2H, m), 4.65-4.75 (2H, m), 7.05-7.80 (12H, m). LC-MS: 816 (M^+), 817 ($M+H^+$), HPLC-RT: 3.90 min (Waters).

Example 41

N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-benzylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(4-fluoro-benzylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80-1.20 (18H, m), 1.30-2.20 (12H, m), 2.30-2.70 (5H, m), 2.88 (2H, m), 2.96 (6H, s), 3.01 (3H, s), 3.27 (3H, s), 3.30-4.90 (4H, m), 4.00-4.25 (2H, m), 4.74 (2H, m), 6.92-7.32 (9H, m). LC-MS: 798 (M^+), 799 ($M+H^+$), HPLC-RT: 3.21 min.

Example 42

N-{1-[(1-sec-Butyl-4-{2-[1-(furan-2-ylmethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(furan-2-ylmethylsulfanyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.20 (18H, m), 1.20-1.90 (12H, m), 1.90-2.55 (5H, m), 2.82 (2H, t, 6.9Hz), 2.96 (6H, s), 3.08 (3H, s), 3.26 (3H, s), 3.31-3.84 (4H, m), 4.05-4.27 (2H, m), 4.62-4.74 (2H, m), 6.18-6.55 (3H, m), 7.19-7.31 (5H, m). LC-MS: 770 (M^+), 771 ($M+H^+$), HPLC-RT: 3.42 min (Waters).

Example 43

N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{2-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-[2-(4-methoxy-phenyl)-ethyl]-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.20 (18H, m), 1.20-1.90 (12H, m), 2.07 (3H, s), 2.30-2.70 (3H, t, J=7.3 Hz), 2.95 (6H, s), 3.01 (3H, s), 3.30 (3H, s), 3.40-3.70 (4H, m), 3.78 (3H, s), 4.00-4.30 (2H, m), 4.75 (2H, m), 6.82 (2H, d, J=8.6Hz), 7.11 (2H, d, J=8.6Hz). LC-MS: 734 (M^+), 735 ($M+H^+$), HPLC-RT: 2.88 min.

Example 44

N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(4-[1,2,3]thiadiazol-4-yl-benzylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-3-pyrrolidin-2-yl-N-(4-[1,2,3]thiadiazol-4-yl-benzyl)-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.10 (18H, m), 1.20-2.00 (12H, m), 2.10 (3H, s), 2.30-2.70 (3H, m), 2.95 (6H, s), 3.01 (3H, s), 3.31 (3H, s), 3.54 (2H, m), 3.70-4.20 (2H, m), 4.30-4.80 (4H, m), 7.43 (2H, d, J=7.9Hz), 7.98 (2H, d, J=7.9Hz), 8.69 (1H, d, J=5.3 Hz). LC-MS: 774 (M^+), 775 ($M+H^+$), HPLC-RT: 2.92 min.

Example 45

N-{1-[(4-{2-[2-(1-Benzyl-piperidin-4-ylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-(1-benzyl-piperidin-4-yl)-3-methylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.70-1.20 (22H, m), 1.70-2.80 (15H, m), 2.06 (3H, s), 2.96 (9H, s), 3.33 (3H, s), 3.40-4.05 (6H, m), 4.20-4.40 (5H, m), 4.70 (2H, brs), 7.44 (5H, m). LC-MS: 773 (M^+), HPLC-RT: 2.33 min.

Example 46

N-[1-({1-sec-Butyl-4-[2-(1-methanesulfinyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

Preparation of 2-(methanesulfinyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a stirred solution of 2-(methanesulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (62 mg, 0.158 mmol) in CH_2Cl_2 (2 ml) wad added mCPBA (30 mg, 0.174 mmol) at 0□. After being stirred at 0□ for 1hr, the mixture was quenched with 1N NaOHaq., extracted with AcOEt, washed with saturated NaClaq., dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (CH_2Cl_2:MeOH=95:5) to give 2-(methanesulfinyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (39 mg, 61%) as colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.46(9H, s), 1.20-1.39(2H, m), 1.62-2.40 (6H, m), 2.47(3H, s), 2.83(2H, t, J=6.9 Hz), 3.13-3.33(1H, m), 3.35-3.70(3H, m), 3.75-3.95(1H, m), 3.95-4.15(1H, m), 7.10-7.38(5H, m). LC-MS: 409 (MH^+), HPLC-RT: 2.99 min.

The title compound was obtained in a manner analogous to that of Example 1 through the condensation of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methanesulfinyl -N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.09 (15H, m), 1.12 (3H, d, J=6.0 Hz), 1.27-2.72 (15H, m), 2.53 (3H, s), 2.82 (2H, t, J=6.9 Hz), 2.94 (6H, s), 3.03 (3H, s,), 3.29 (3H, s), 3.25-3.65 (4H, m), 3.70-4.05 (1H, m), 4.30-4.50 (1H, m), 4.60-4.85 (2H, m), 6.95-7.37 (5H, m). LC-MS: 720 (MH^+), HPLC-RT: 2.50 min.

Example 47

N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

Preparation of 2-(methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a stirred solution of 2-(methanesulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (130 mg, 0.331 mmol) in CH_2Cl_2 (4 m) wad added mCPBA (286 mg, 1.66 mmol) 0° C. After being stirred at RT for 2hr, the mixture was quenched with 1N NaOHaq., extracted with AcOEt, washed with saturated NaClaq., dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified with preparative TLC (n-Hex:AcOEt=1:3) to give 2-(methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (140 mg, quant) as colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.44(9H, s), 1.65-2.80 (6H, m), 2.82(2H, t, J=6.9 Hz), 2.90(3H, s), 3.00-4.00 (5H, m), 4.20-4.40(1H, m), 5.40-5.74(1H, m), 7.05-7.40(5H, m). LC-MS: 425 (MH^+), HPLC-RT: 3.45 min.

The title compound was obtained in a manner analogous to that of Example 1 through the condensation of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methanesulfonyl -N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.09 (15H, m), 1.14 (3H, d, J=6.3 Hz), 1.25-2.85 (17H, m), 2.94 (6H, s), 2.96 (3H, s), 2.99 (3H, s,), 3.30 (3H, s), 3.25-3.92 (5H, m), 4.00-4.25 (1H, m), 4.50-4.80 (2H, m), 7.05-7.38 (5H, m). LC-MS: 736 (MH^+), HPLC-RT: 2.67 min.

Example 48

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoylethyl)pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

To a stirred solution of 2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.15 g, 2.93 mmol) in CH_2Cl_2 (3 ml) was added TFA at 0° C. After being stirred at 0° C for 30 min, the mixture was evaporated *in vacuo* to give 3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide TFA salt as a crude oil (1.87 g), which was used without further purification in the next step [The diastereomers were separable by preparative HPLC (column: ODS-80Ts, eluent: 79/21 H_2O : CH_3CN / 0.05% TFA)].

To a stirred solution of (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid (1.12g, 2.05 mmol) which was prepared according to the literature method (Chem.Pharm.Bull, 43(10), 1706-1718, 1995) and the crude 3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide TFA salt (1.31 g, 2.05 mmol) obtained above in CH_2Cl_2 (3 ml) were added diisopropylethylamine (3.58 mL, 20.5 mmol), WSCI monohydrochloric acid (511 mg, 2.67 mmol), HOBt monohydrate (408 mg, 2.67 mmol) at 0° C. After being stirred at room temperature for 16 hr, the mixture was evaporated *in vacuo* and dried under a vacuum to give {1-[1-({1-sec-butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester (2.19 g) as a crude oil, which was used without further purification in the next step.

To a stirred solution of {1-[1-({1-sec-butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester (1.1 g) obtained above in tBuOH (36 ml) and H_2O (4 ml) was added $Pd(OH)_2$ on carbon (ca. 20 wt%, 1 g) at room temperature and then the mixture was set under H_2 atmosphere. After being stirred at room temperature for 14 hr, the mixture was filtrated through a pad of celite and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo* to give the crude gum (1.01 g), which was purified by preparative HPLC (column: ODS-80Ts, eluent: 57 / 43 H_2O : CH_3CN / 0.05% TFA). The appropriate fractions were lyophilized to obtain the title compound as a white amorphous powder (388 mg, 47%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81 (3H, t, J=6.93 Hz), 0.85-1.13(15H, m), 1.22-1.42(2H, m), 1.51-2.18(10H, m), 2.02(3H, s), 2.2-2.49(3H, m), 2.71(3H, s), 2.81(2H, t, J=6.6 Hz), 2.92(3H, s), 3.29(3H, s), 3.33-3.95(4H, m), 4.02-4.16(1H, m), 4.16-4.32(1H,

m), 4.56-4.97(2H, m), 6.59(1H, brs), 7.07-7.38(5H, m), 7.60(1H, brs), LC-MS: 690 (MH^+), HPLC-RT: 2.76 min. (*R*-isomer)

The following compounds (Example 49-53) were obtained in a manner analogous to that of Example 48.

Example 49

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-ethylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.68-1.10 (18H, m), 1.16 (3H, t, J=7.3Hz), 1.20-1.42 (2H, m), 1.55-2.18 (10H, m), 2.18-2.60(3H, m), 2.49 (2H, t, J=7.2Hz), 2.71 (3H, s), 2.83 (2H, t, J=6.9Hz), 3.03 (3H, s), 3.29 (3H, s), 3.20-3.78(4H, m), 3.97-4.12 (1H, m), 4.12-4.28(1H, m), 4.65-4.90 (2H, m), 7.08-7.32 (5H, m). LC-MS: 704 (MH^+), HPLC-RT: 2.87 min. (*R*-isomer)

Example 50

N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and N-phenethyl-3-phenylsulfanyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.15 (18H, m), 1.18-2.58 (15H, m), 2.71 (3H, s), 2.60-2.85 (2H, m), 3.03 (3H, s), 3.21 (3H, s), 3.22-3.95 (4H, m), 3.98-4.42 (2H, m), 4.50-4.85 (2H, m), 7.05-7.42 (10H, m). LC-MS: 752 (MH^+), HPLC-RT: 3.08 min. (*R*-isomer)

Example 51

N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-tert-butylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.40 (18H, m), 1.25 (9H, s), 1.50-2.65 (15H, m), 2.72 (3H, s), 2.75-2.95 (2H, m), 3.04 (3H, s), 3.28 (3H, s), 3.29-3.80 (4H, m), 3.92-4.22 (2H, m), 4.60-4.95 (2H, m), 7.00-7.40 (5H, m). LC-MS: 732 (MH^+), HPLC-RT: 3.25 min. (*R*-isomer)

Example 52

N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-isopropylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, 6.92 Hz), 0.88-1.11(15H, m), 1.11-1.45(8H, m), 1.50-2.21(11H, m), 2.21-2.60(3H, m), 2.71(3H, s), 2.84(3H, t, J=6.93 Hz), 3.03(3H, s), 3.32(3H, s), 3.39-3.78(4H, m), 3.93-4.29(2H, m), 4.63-4.90(2H, m), 6.70(1H, brs), 7.07-7.36(5H, m), 7.64(1H, brs). LC-MS: 718 (MH^+), HPLC-RT: 2.97 min. (*R*-isomer)

Example 53

N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(2-methyl-propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-(2-methyl-propane-2-sulfonyl)-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.93 Hz), 0.85-1.17(15H, m), 1.17-1.52(2H, m), 1.18(9H, s), 1.52-2.59(13H, m), 2.71(3H, s), 2.79(2H, t, J=6.93Hz), 2.92(3H, s), 3.10-3.76(4H, m), 3.29(3H, s), 3.85-4.41(2H, m), 4.52-4.90(2H, m), 6.41(1H, brs), 7.00-7.36(5H, m), 7.51(1H, brs). LC-MS: 764 (MH^+), HPLC-RT: 2.81 min. (*R*-isomer)

Example 54

N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

To a stirred solution of {1-[1-({1-sec-butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester (0.35 g) in CH_2Cl_2 (3 ml) wad added mCPBA (80%: 356 mg, 1.65 mmol) at room temperature. After being stirred at room temperature for 4hr, the mixture was quenched with 5N NaOH (10 ml), extracted with AcOEt, washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give {1-[1-({1-sec-butyl-2-methoxy-4-[2-(1-methylsulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester (311 mg) as a crude oil, which was used without further purification in the next step.

To a stirred solution of the crude {1-[1-({1-sec-butyl-2-methoxy-4-[2-(1-methylsulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester (311 mg) obtained above in tBuOH (9 ml) and H_2O (1 ml) was added $Pd(OH)_2$ on carbon(ca. 20 wt%, 1 g) at room temperature and then the mixture was set under H_2 atmosphere. After being stirred at room temperature for 13.5 hr, the mixture was filtrated through a pad of celite and washed with MeOH. The filtrate and washings were combined

and concentrated *in vacuo* to give the crude gum (285 mg), which was purified by preparative HPLC (column: ODS-80Ts, eluent: 40/30 H_2O : CH_3CN / 0.05% TFA). The appropriate fractions were lyophilized to give the title compound as a white amorphous powder (160 mg, 58%).

^1H NMR (270 MHz, $CDCl_3$): δ 0.49-1.14(18H, m), 1.20-1.39(2H, m), 1.48-2.59(13H, m), 2.71(3H, s), 2.77(2H, d, J=6.6 Hz), 2.95(3H, s), 3.01(3H, s), 3.02-3.98(4H, m), 3.28(3H, s), 4.02-4.38(2H, m), 4.42-4.95(2H, m), 6.27(1H, brs), 7.02-7.40(5H, m), 7.81(1H, brs). LC-MS: 722 (MH^+), HPLC-RT: 2.61 min. (*R*-isomer)

The following compounds (Example 55-57) were obtained in a manner analogous to that of Example 54.

Example 55

N-[1-({1-sec-Butyl-4-[2-(1-ethanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 54, the title compound was obtained starting from the oxidation of {1-[1-({1-sec-butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester with mCPBA followed by hydrogenolysis.

^1H NMR (270 MHz, $CDCl_3$): δ 0.70-1.18 (18H, m), 1.38 (3H, t, J=7.3Hz), 1.20-1.43 (2H, m), 1.55-2.86 (13H, m), 2.71 (3H, s), 2.78 (2H, t, J=7.3Hz), 3.00 (3H, s), 3.29 (3H, s), 3.02-3.81(6H, m), 3.81-3.97 (1H, m), 4.10-4.22 (1H, m), 4.55-4.88 (2H, m), 7.08-7.39 (5H, m). LC-MS: 736 (MH^+), HPLC-RT: 2.68 min. (*R*-isomer)

Example 56

N-[1-({4-[2-(1-Benzenesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide

In a similar manner to Example 54, the title compound was obtained starting from the oxidation of {1-[1-({1-sec-butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester with mCPBA followed by hydrogenolysis.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.65-1.18 (18H, m), 1.30-2.60 (15H, m), 2.71 (3H, s), 2.60-2.80 (2H, m), 2.99 (3H, s), 3.29 (3H, s), 3.10-3.75 (4H, m), 3.88-4.17 (2H, m), 4.60-4.88 (2H, m), 7.00-7.32 (5H, m), 7.40-7.75 (3H, m), 7.89 (1H, d, J=7.3 Hz). LC-MS: 784 (MH^+), HPLC-RT: 2.92 min. (*R*-isomer)

Example 57

N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide

In a similar manner to Example 54, the title compound was obtained starting from the oxidation of {1-[1-({1-sec-butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propylcarbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester with mCPBA followed by hydrogenolysis.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.81(3H, t, J=6.93 Hz), 0.85-1.15(15H, m), 1.15-1.49(8H, m), 1.50-2.67(13H, m), 2.71(3H, s), 2.78(2H, t, J=6.92 Hz), 3.00(3H, s), 3.10-3.79(4H, m), 3.28(3H, s), 3.95-4.37(2H, m), 4.45-4.98(2H, m), 6.31(1H, brs), 7.02-7.38(5H, m), 7.54(1H, brs). LC-MS: 750 (MH^+), HPLC-RT: 2.72 min. (*R*-isomer)

Example 58

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

Preparation of 2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred solution of (*S*)-2-(2-methoxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (200mg, 0.71 mmol) in THF (3 ml) wad added NaSMe (95%, 156 mg, 2.12 mmol) at room temperature. After being stirred in sealed tube at 150°C for 14hr, the mixture was cooled to room temperature and quenched with 1N HCl (20 ml), extracted with AcOEt, dried ($MgSO_4$) and concentrated *in vacuo* to give 2-(2-carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (223 mg) as a crude oil, which was used without further purification in the next step.

To a stirred solution of the crude 2-(2-carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (223mg) obtained above in CH_2Cl_2 (3 ml) was added phenethylamine(0.18 ml, 1.41 mmol), WSCI monohydrochloride(203 mg, 1.06 mmol), HOBt monohydrate(162 mg, 1.06 mmol) and diisopropylethylamine(0.37 ml, 2.12 mmol) at room temperature. After being stirred at room temperature for 4.5 hr, the mixture was quenched with 1N HCl (20 ml), extracted with AcOEt, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which was purified by flash column chromatography(hexane:AcOEt=3:1) to give 2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester as an oil(123mg, 43%).

The title compound was obtained in a manner analogous to that of Example 1 through condensation of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 2-methyl-3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide prepared from its N-Boc derivative obtained above.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.27(6H, d, J=7.6Hz), 1.45(9H, s), 1.58-2.25(4H, m), 2.26-2.45(4H, m), 2.84(2H, t, J=6.93 Hz), 3.13-3.75(5H, m), 3.83-4.04(1H, m), 6.03(1H, brs), 7.08-7.40(5H, m). LC-MS: 407(MH^+), HPLC-RT: 4.06 min.

The following Examples illustrate pharmaceutical preparations containing a compound provided by the present invention.

Example 59

N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide

In a similar manner to Example 48, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N-benzyloxycarbonyl-N-methyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 3-methylsulfanyl-N-phenethyl-3-pyrrolidin-2-yl-propionamide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.60-1.16 (18H, m), 1.16-1.42 (5H, m), 1.50-2.10 (9H, m), 2.07 (3H, s), 2.15-2.52 (3H, m), 2.72 (3H, s), 2.69-2.88 (2H, m), 3.01 (3H, s), 3.31 (3H, s), 3.26-3.77 (4H, m), 3.99-4.18 (1H, m), 4.18-4.30 (1H, m), 4.59-5.89 (2H, m), 7.02-7.36 (4H, m). LC-MS: 704 (MH^+), HPLC-RT: 2.88 min.

Example 60

N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

Preparation of (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a stirred solution of AcSMe (24.4 g, 0.27 mol) in THF (580 ml) cooled in an ice-bath was added KOEt (22.8 g, 0.27 mol). After stirring for 3.5 h at room temperature, phenol (11.9 ml, 0.14 mol) and a solution of (2*S*)-2-(2-benzyloxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15.6 g, 0.045 mol) in THF (50 ml) were successively added to the mixture. After 45 min, the mixture was quenched with saturated NH_4Cl aqueous solution and concentrated *in vacuo*. The residue was diluted with EtOAc (600 ml), and washed with 1N NaOH aqueous solution (300 ml x 3) and saturated brine (200 ml). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 9/1) to give (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-methylsulfanyl-propyl]-pyrrolidine-1-

carboxylic acid *tert*-butyl ester which was contaminated with PhOH. The collected fraction which included (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester was washed with 5N NaOH aqueous solution (300 ml) and H_2O (300 ml) to remove phenol, and dried over anhydrous $MgSO_4$. The organic layer was concentrated *in vacuo* to obtain (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12.5 g, 70%).

^{1}H NMR (400MHz, CDCl3) δ 1.10-1.39 (m, 3H), 1.46 (s, 9H), 1.64-1.76 (m, 1H), 1.81-1.97 (m, 3H), 2.06 (s, 3H), 2.52-2.68 (m, 1H), 3.12-3.25 (m, 1H + 5/9H), 3.34-3.62 (m, 1H + 4/9H), 3.82-4.04 (m, 1H), 5.04-5.26 (m, 2H), 7.26-7.40 (m, 5H) *(two rotational isomeric mixture)*; MS (ES) *m/z* 416 (M^+ + Na); HPLC (rt) 3.08 min.

Preparation of (2*S*)-2-[(1*R*,2*S*)-2-Carboxy-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.4 g, 11.2mmol) and $Pd(OH)_2$ on carbon(ca.20 wt%, 2.0 g) in EtOH (50 mL) was stirred at room temperature under H_2 atmosphere. After being stirred at room temperature for 14hr, the mixture was filtrated through a pad of celite and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo* to give a crude gum, which was purified by flush column chromatography (hexane:AcOEt=1:1) to give (2*S*)-2-[(1*R*,2*S*)-2-carboxy-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid tert-butyl ester as a gum (3.39 g, 98%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.39 (3H, d, J=5.94Hz), 1.45 (9H, s), 1.58-2.01 (5H, m), 2.12 (3H, s), 2.47-2.69 (1H, m), 3.11-3.75 (2H, m), 3.92-4.16 (1H, m). LC-MS: 304 (MH^+), HPLC-RT: 3.45 min.

Preparation of (2*S*)-2-{(1*R*,2*S*)-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred solution of (2*S*)-2-[(1*R*,2*S*)-2-carboxy-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.7 g, 5.6mmol) in CH_2Cl_2 (20mL) were added 3-hydroxyphenethylamine hydrobromide (2.44 g, 11.2mmol), BOP(3.72g, 8.4 mmol), HOBT (1.29 g, 8.4 mmol), and diisopropylethylamine (4.88 mL, 28.0 mmol) at room temperature. After being stirred at room temperature for 2hr, the mixture was

quenched with 1N HCl (80 mL x 3), extracted with AcOEt, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil, which was purified by flash column chromatography (hexane:AcOEt=1:1) to give (2*S*)-2-{(1*R*,2*S*)-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester as a gum (2.07 g, 87%).

^{1}H NMR (270MHz, CDCl3) δ 1.26-1.35 (m, 3H), 1.49 (s, 9H), 1.70-1.97 (m, 1H), 2.12 (s, 3H), 2.24-2.41 (m, 1H), 2.67-2.83 (m, 2H), 3.08-3.36 (m, 2H), 3.45-3.66 (m, 2H), 3.77-3.91 (m, 1H), 3.98-4.10 (m, 1H), 5.80 (br, 1H), 6.65-6.80 (m, 2H), 6.92 (brs, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.86 (br, 1H); MS (ES) *m/z* 423 (M^+ + 1); HPLC-RT: 3.57 min.

Preparation of the title compound

In a similar manner to Example 1, the title compound was obtained as single stereoisomer from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and (2*S*)-2-{(1*R*,2*S*)-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester. The stereochemistry of the product was retained as indicated in each component.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82 (3H, d, J=6.92Hz), 0.81-1.17 (15H, m), 1.17-1.41 (8H, m), 1.50-2.10 (9H, m), 2.05 (3H, s), 2.10-2.65 (3H, m), 2.65-2.84 (2H, m), 2.99 (6H, s), 3.11 (3H, s), 3.32 (3H, s), 3.22-3.60 (4H, m), 3.62-3.92 (1H, m), 3.92-4.11 (1H, m), 4.55-4.81 (2H, m), 6.60-6.85 (3H, m), 7.14 (1H, t, J=7.59Hz). LC-MS: 734 (MH^+), HPLC-RT: 2.62 min.

Example 61

N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

Preparation of (2*S*)-2-((1*R*,2*S*)-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

To a stirred solution of (2*S*)-2-[(1*R*,2*S*)-2-carboxy-1-methylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.70 g, 5.6 mmol) in CH_2Cl_2 (20 mL) were

added N-methyl-3-hydroxyphenethylamine hydrobromide (2.44 g, 11.2 mmol), BOP (3.72 g, 8.4 mmol), HOBT (1.29 g, 8.4 mmol), and diisopropylethylamine (4.88mL, 28.0mmol) at room temperature. After being stirred at room temperature for 2 hr, the mixture was quenched with 1N HCl (80 mL x 3), extracted with AcOEt, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil (3.83 g), which was then purified by flash column chromatography (hexane:AcOEt=1:1) to give (2*S*)-2-((1*R*,2*S*)-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester as a gum (1.38 g, 56%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.27 (3H, d, J=7,26 Hz), 1.30-1.56 (9H, m), 1.5-2.1 (5H, m), 1.99-2.33 (3H, m), 2.49-2.80 (1H, m), 1.90-2.88 (2H, m), 2.88-3.56 (3H, m), 3.56-4.15 (1H, m), 6.52-6.89 (3H, m), 7.00-7.21 (1H, m). LC-MS: 437 (MH^+), HPLC-RT: 3.90 min.

Preparation of the title compound

In a similar manner to Example 1, the title compound was obtained as single stereoisomer from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and (2*S*)-2-((1*R*,2*S*)-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. The stereochemistry of the product was retained as indicated in each component.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.62-1.17 (18H, m), 1.17-1.42 (5H, m), 1.45-2.10 (9H, m), 1.91-2.11 (3H, m), 2.11-2.62 (3H, m), 2.70-2.84 (2H, m), 2.99 (6H, s), 3.06 (3H, s), 3.30 (3H, s), 3.38 (3H, s), 3.20-3.65 (4H, m), 3.77-4.25 (2H, m), 4.40-4.95 (2H, m), 6.7.83 (3H, m), 6.92-7.18 (1H, m). LC-MS: 748 (MH^+), HPLC-RT: 2.78 min.

Example 62

N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

Preparation of (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-ethylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a stirred suspension of *t*-BuOK (609 mg, 5.43 mmol) in THF (90 ml) was added EtSH (8.04 ml, 0.11 mol). After stirring for 30 min at room temperature, a solution of (2*S*)-2-(2-benzyloxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.75 g, 10.8 mmol) in THF (75 ml) was added to the mixture. After 2.5h, the mixture was quenched with saturated NH_4Cl aqueous solution, and then concentrated *in vacuo*. The residue was diluted with EtOAc (400 ml), and washed with saturated NH_4Cl aqueous solution (150 ml), saturated $NaHCO_3$ aqueous solution (150 ml) and H_2O (150 ml). The organic layer was dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 12/1 to 8/1) to give (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-ethylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.66 g, 83%).

^{1}H NMR (400MHz, CDCl3) δ 1.19 (t, J = 7.4 Hz, 3H), 1.28-1.40 (m, 3H), 1.50 (s, 9H), 1.60-1.72 (m, 1H), 1.78-2.00 (m, 3H), 2.41-2.64 (m, 3H), 3.16-3.28 (m, 1H), 3.32-3.65 (m, 2H), 3.76-4.00 (m, 1H), 5.04-5.23 (m, 2H), 7.26-7.41 (m, 5H) *(two rotational isomeric mixture)*; MS (ES) *m/z* 430 (M^+ + Na); HPLC-RT: 3.20 min.

Preparation of (2*S*)-2-((1*R*,2*S*)-1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

In a similar manner to Example 61, (2*S*)-2-((1*R*,2*S*)-1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester was prepared from (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-ethylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester through hydrogenolysis followed by amidation with N-methyl-3-hydroxyphenethylamine hydrobromide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.05-1.55 (15H, m), 1..55-2.35 (5H, m), 2.38-2.70 (2H, m), 2.70-3.00 (5H, m), 3.05-4.28 (6H, m), 6.50-6.90 (3H, m), 7.00- 7.23(1H, m); LC-MS: 451 (MH^+), HPLC-RT: 4.12 min.

Preparation of the title compound

In a similar manner to Example 1, the title compound was obtained as single stereoisomer from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and (2*S*)-2-((1*R*,2*S*)-1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. The stereochemistry of the product was retained as indicated in each component.

^{1}H NMR (270 MHz, CD3OD): δ 0.75-1.50 (26H, m), 1.55-2.85 (13H, m), 2.85-3.20 (12H, m), 3.25-4.25 (10H, m), 4.55-4.92 (2H, m), 6.48-6.78 (3H, m), 6.92-7.18 (1H, m); LC-MS: 762 (MH^+), HPLC-RT: 2.94 min.

Example 63

N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

Preparation of (2*S*)-2-{(1*R*,2*S*)-1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner to Example 62, (2*S*)-2-{(1*R*,2*S*)-1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester was prepared from (2*S*)-2-[(1*R*,2*S*)-2-benzyloxycarbonyl-1-ethylsulfanyl-propyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester through hydrogenolysis followed by amidation with 3-hydroxyphenethylamine hydrobromide.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.20 (3H, t, J=7.3 Hz), 1.31 (3H, d, 6.9 Hz), 1.48 (9H, s), 1.55-2.40 (5H, m), 2.42-2.65 (2H, m), 2.67-2.85 (2H, m), 3.18-3.40 (2H, m), 3.45-3.85 (3H, m), 3.90-4.05 (1H, m), 5.99 (1H, brs), 6.62-6.80 (2H, m), 6.90 (1H, brs), 7.17 (1H, t, J=7.6Hz); LC-MS: 437 (MH^+), HPLC-RT: 3.77 min.

Preparation of the title compound

In a similar manner to Example 1, the title compound was obtained as single stereoisomer from the condensation reaction of (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and (2*S*)-2-{(1*R*,2*S*)-1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidine-1-carboxylic acid tert-butyl ester. The stereochemistry of the product was retained as indicated in each component.

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.57-1.60 (26H, m), 1.60-2.30 (8H, m), 2.30-2.85 (7H, m), 2.95 (6H, s), 3.00-3.20 (3H, m), 3.27 (3H, s), 3.30-3.95 (5H, m), 3.95-4.30 (2H, m), 4.30-4.90 (2H, m), 6.40 (1H, brs), 6.58-6.78 (2H, m), 6.93 (1H, S), 7.12 (1H, t, J=7.6 Hz). 7.79(1H, brs); LC-MS: 748 (MH^+), HPLC-RT: 2.72 min.

Example 64

N-(1-{[1-sec-Butyl-4-(2-{1-dimethylcarbamoylmethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide

In a similar manner to Example 1, the title compound was obtained starting from (3*R**,4*S**,5*S**)-4-[N,N-dimethyl-L-valyl-(N-methyl-L-valinamido)]-3-methoxy-5-methylheptanoic acid and 2-{1-dimethylcarbamoylmethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidine-1-carboxylic acid tert-butyl ester.

^{1}H NMR (270 MHz, CD_3OD): δ 0.75-1.18 (18H, m), 1.18-2.20 (11H, m), 2.21-2.81 (5H, m), 2.90 (6H, s), 3.00-3.20 (6H, m), 3.30 (3H, s), 3.25-3.90 (7H, m), 4.00-4.30 (2H, m), 4.60-5.00 (2H, m), 6.50-6.75 (3H, m), 6.98-7.15 (1H, m); LC-MS: 748 (MH^+), HPLC-RT: 2.41 min.

Example 65

Ethyl-carbamic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester

To a stirred solution of N-{1-[(1-sec-butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide (50 mg, 0.067 mmol) in CH_2Cl_2 (1 ml) was added N, N'-carbonyl diimidazole (33 mg, 0.204 mmol) and pyridine (0.020 ml, 0.202 mmol) at 0°C. After being stirred at room temperature for 24hr, the mixture was concentrated *in vacuo*. The resultig crude oil was dissolved in CH_3CN (1ml), and ethylamine hydrochloride (55 mg, 0.674 mmol) and pyridine (0.067 ml, 0.676 mmol) was added to the solution at 0°C. After being stirred at room temperature for 15hr, the mixture was concentrated *in vacuo* to give a crude oil, which was purified by preparative HPLC (column: ODS-80TS, eluent: 38:32 H_2O:CH_3CN/0.05%TFA). The appropriate fractions were lyophilized to give the title compound as a white amorphos powder (46mg, 84%).

^{1}H NMR (270 MHz, CD_3OD): δ 0.57-1.18 (21H, m), 1.25-1.50 (2H, m), 1.60-2.21 (9H, m), 2.23-2.85 (9H, m), 2.86 (6H, s), 3.08 (2H, q), 3.14 (3H, s), 3.31(3H, s), 3.30-3.95 (5H, m), 3.95-4.25 (2H, m), 4.60-4.95 (2H, m), 7.10- 7.35(5H, m); LC-MS: 805 (MH^+), HPLC-RT: 2.73 min.

Example 66

Ethyl-carbamic acid 3-(2-{3-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-methyl-3-methylsulfanyl-propionylamino}-ethyl)-phenyl ester

To a stirred solution of N-(1-{[1-sec-butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide (30 mg, 0.035 mmol) in CH_2Cl_2 (0.5 mL) were added ethyl isocyanate (0.042 mL, 0.53 mmol) and diisopropylethylamine (0.062 mL, 0.35 mmol) at room temperature. After being stirred at room temperature for 13hr, the mixture was concentrated *in vacuo* to give a crude oil (58 mg), which was purified by preparative HPLC (column:ODS-80Ts, eluent: 35/35 H_2O:CH_3CN/0.05%TFA). The appropriate fractions were lyophilized to give the title compound as a white amorphous powder (13 mg, 39%).

^1H NMR (270 MHz, $CDCl_3$): δ 0.68-1.19 (18H, m), 1.15-1.46 (8H, m), 1.50-2.10 (9H, m), 2.07 (3H, s), 2.10-2.68 (3H, m), 2.75-2.90 (2H, m), 2.94 (6H, s), 3.03 (3H, s), 3.32 (3H, s), 3.30-3.78 (4H, m), 3.95 (2H, q, J=6.93 Hz), 3.80-4.08 (1H, m), 4.08-4.37 (1H, m), 4.59-5.86 (2H, m), 6.81-7.09 (3H, m), 7.12-7.29 (1H, m); LC-MS: 805(MH^+), HPLC-RT: 2.70 min.

The following Examples illustrate pharmaceutical preparations containing a compound provided by the present invention.

Example 67

Tablet formation

Ingredients	mg/tablet		
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	5	25	100
anhydrous lactose	103	83	35
croscarmellose sodium	6	6	8
povidone K30	5	5	6
magnesium stearate	1	1	1
Total weight	120	120	150

Interlocking gelatin capsules each containing the following ingredients were manufactured in a known mannar.

Example 68

Ingredients	mg/tablet		
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	5	25	100
hydrous lactose	159	123	148
corn starch	25	35	40
talc	10	15	10
magnesium stearate	1	2	2
Total weight	200	200	300

Example 69

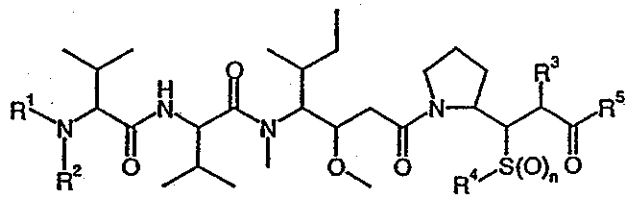
Injection solution/emulsion preparation

ingredients	mg/ml
N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide	1 mg
glycerol	10-50 mg
lecithin	20-50 mg
soy oil	1.5 mg
glycerol	8-12 mg
water	q.s. ml

5

Claims

1. A compound of the formula (I),



(I)

wherein

R^1, R^2 and R^3 are each independently hydrogen or $(C_1$-$C_4)$-alkyl;

R^4 is hydrogen;
alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, carboxy, alkoxycarbonyl, carbamoyloxy, alkylcarbonyloxy, carbamoyl or halogen;

alkenyl;

alkinyl;

$(C_3$-$C_7)$-cycloalkyl;

aryl optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, carbamoyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkyl-amino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoro-methoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl; or

heterocyclylalkyl;

R^5 is $(C_1$-$C_6)$-alkylamino;

hydroxy;

$(C_3$-$C_7)$-cycloalkylamino optionally substituted by phenyl or benzyl;

arylamino;

aralkylamino having $(C_1$-$C_4)$-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, carbamoyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

$(C_1$-$C_4)$-alkoxy;

benzhydrazino;

heterocyclyl optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, mono- or di-alkylamino, acylamino, alkoxycarbonylamino, phenyl or halogen;

heterocyclylamino;

heterocycloalkylamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen;

aralkyloxy and aralkyl both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl;

and

n is an integer of 0, 1 or 2;

and pharmaceutical acceptable salts thereof.

2. A compound of claim 1 wherein R^1 is (C_1-C_4)-alkyl.

3. A compound of claim 1 or 2 wherein R^1 is methyl.

4. A compound of claims 1 to 3 wherein R^2 is (C_1-C_4)-alkyl.

5. A compound of claims 1 to 4 wherein R^2 is methyl.

6. A compound of claims 1 to 5 wherein R^3 is hydrogen or methyl.

7. A compound of claims 1 to 6 wherein R^4 is hydrogen; alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, amino, mono- or di-alkylamino, carbamoyl, carbamoyloxy, acetoxy or carboxy;alkenyl; alkinyl; (C_3-C_7)-cycloalkyl; aryl optionally substituted with one to three substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, amino, mono- or di-alkylamino, alkylthio or alkylcarbonylamino; aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, amino, mono- or di-alkylamino, or alkylthio; or heterocyclylalkyl.

8. A compound of claims 1 to 7 wherein R^4 is phenyl, methyl, t-butyl, 4-tButylphenyl, 4-methoxyphenyl, 2-aminoethyl, 2-dimethylaminoethyl, $ZHNCH_2CH_2$-, 4-methylthiophenyl, cyclohexyl, 2-, 3-, or 4-hydroxyphenyl, 4-acetoaminophenyl, 4-fluorophenyl, ethyl, i-propyl, benzyl, 2-acetoxyethyl, 2-diethylcarbamoyloxyethyl, phenylethyl, allyl, n-pentyl, 2-naphtyl, 4-fluorobenzyl, 2-furylmethyl or 2-hydroxyethyl.

9. A compound of claims 1 to 8 wherein

R^5 is (C_1-C_6)-alkylamino;

hydroxy;

(C_3-C_7)-cycloalkylamino optionally substituted by phenyl or benzyl;

arylamino;

aralkylamino having (C_1-C_4)-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of H_2NSO_2-, hydroxy, alkyl, benzyl, alkoxy, carbamoyloxy or heterocyclyl;

(C_1-C_4)-alkoxy;

benzhydrazino;

heterocyclyl optionally substituted by benzyl or benzhydryl;

heterocyclylamino;

heterocycloalkyamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen; or

aralkyloxy and aralkyl both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl.

10. A compound of claims 1 to 9 wherein R^5 is phenylethylamino; phenylethoxy; benzyloxy; 2-naphtylmethylamino; benzylpiperazino; 1,2,3,4-tetrahydroisoquinolino; t-butoxy; hydroxy; 4-$H_2NSO_2PhCH_2CH_2$; 2-, 3- or 4-hydroxyphenylethylamino; N-benzylphenethylamino; 4-t-butylbenzylamino; benzylamino; N-methylphenethylamino; 2-, 3- or 4-hydroxyphenylethyl-N-methylamino; 4-benzhydrylpiperazino; 2-phenylcyclopropylamino; thienylethylamino; 2-pyridylethylamino; 5-ethylpyrazol; 4,3-dimethoxyphenylethylamino; benzylhydrazino; benzothiazol-2-ylmethyl-amino; 2-pyridin-4-yl-amino; 3,4-dimethoxy-phenyl-ethyl-methyl-amino; , bezothiazol-2-ylmethyl-amino; 2-pyridin-3-yl-ethylamino; pyridin-4-ylmethyl-amino; thiazol-2-ylamino; naphtalen-2-ylamino;4-chloro-phenyl-ethylamino; 4-methoxy-phenyl-ethylamino; 4-(1,2,3)thiadiazol-4-yl-benzylamino; 2-cyclohexylamino or1-benzyl-piperidin-4-ylamino.

11. A compound of claims 1 to 10 wherein n is an integer of 0.

12. A compound of claims 1 to 10 wherein R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 0.

13. A compound of claim 12 selected from the group consisisting of

a) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

b) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-(*S*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

d) N-{1-[(1-sec-Butyl-4-{2-[1-(4-tert-butyl-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

e) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(4-methoxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

f) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid phenethyl ester,

g) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid benzyl ester,

h) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[(naphthalen-2-ylmethyl)-carbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

i) N-{1-[(4-{2-[1-(2-Amino-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

j) N-{1-[(4-{2-[3-(4-Benzyl-piperazin-1-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

k) N-{1-[(1-sec-Butyl-4-{2-[3-(3,4-dihydro-1H-isoquinolin-2-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

l) N-{1-[(1-sec-Butyl-4-{2-[1-(2-dimethylamino-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

m) (2-{1-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl)-carbamic acid benzyl ester,

n) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(4-methylsulfanyl-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

o) N-[1-({1-sec-Butyl-4-[2-(1-cyclohexylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

p) N-{1-[(1-sec-Butyl-4-{2-[1-(*S*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

q) N-{1-[(1-sec-Butyl-4-{2-[1-(*R*)-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

r) N-{1-[(4-{2-[1-(4-Acetylamino-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

s) N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

t) N-[1-({1-sec-Butyl-4-[2-(1-(*R*)-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

u) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

v) N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

w) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

x) N-[1-({4-[2-(1-Benzylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

y) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

z) N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

aa) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

bb) Acetic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester,

cc) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid tert-butyl ester,

dd) 3-[1-(4-{[2-(2-Dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-3-methylsulfanyl-propionic acid,

ee) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ff) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

gg) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[2-(methyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

hh) N-{1-[(4-{2-[3-(4-Benzhydryl-piperazin-1-yl)-1-methylsulfanyl-3-oxo-propyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ii) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

jj) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

kk) N-{1-[(4-{2-[2-(Benzyl-phenethyl-carbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ll) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-phenyl-cyclopropylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

mm) N-{1-[(1-sec-Butyl-4-{2-[2-(4-tert-butyl-benzylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

nn) N-[1-({4-[2-(2-Benzylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

oo) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenethylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

pp) N-[1-({4-[2-(1-Allylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide

qq) N-{1-[(4-{2-[2-(N'-Benzyl-hydrazinocarbonyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

rr) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-4-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ss) N-(1-{[4-(2-{2-[(Benzothiazol-2-ylmethyl)-carbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-1-sec-butyl-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

tt) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-thiophen-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

uu) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-3-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

vv) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(2-pyridin-2-yl-ethylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ww) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{1-methylsulfanyl-2-[(pyridin-4-ylmethyl)-carbamoyl]-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

xx) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3H-imidazol-4-yl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

yy) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(thiazol-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

zz) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(naphthalen-2-ylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

aaa) N-[1-({1-sec-Butyl-4-[2-(2-cyclohexylcarbamoyl-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

bbb) N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

ccc) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ddd) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-chloro-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

eee) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(1-pentylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

fff) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-(naphthalen-2-ylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

ggg) N-{1-[(1-sec-Butyl-4-{2-[1-(4-fluoro-benzylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

hhh) N-{1-[(1-sec-Butyl-4-{2-[1-(furan-2-ylmethylsulfanyl)-2-phenethylcarbamoyl-ethyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

iii) N-(1-{[1-sec-Butyl-2-methoxy-4-(2-{2-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

jjj) N-{1-[(1-sec-Butyl-2-methoxy-4-{2-[1-methylsulfanyl-2-(4-[1,2,3]thiadiazol-4-yl-benzylcarbamoyl)-ethyl]-pyrrolidin-1-yl}-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide, and

kkk) N-{1-[(4-{2-[2-(1-Benzyl-piperidin-4-ylcarbamoyl)-1-methylsulfanyl-ethyl]-pyrrolidin-1-yl}-1-sec-butyl-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

lll) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

mmm) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

nnn) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ooo) N-(1-{[1-sec-Butyl-4-(2-{1-dimethylcarbamoylmethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

ppp) N-[1-({1-sec-Butyl-4-[2-(1-dimethylcarbamoylmethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

qqq) Ethyl-carbamic acid 2-{1-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-phenethylcarbamoyl-ethylsulfanyl}-ethyl ester.

14. A compound of claims 1 to 10 wherein R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 1.

15. A compound of claim 14 which is N-[1-({1-sec-Butyl-4-[2-(1-methanesulfinyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide.

16. A compound of claim 1, wherein R^1 and R^2 are methyl, R^3 is hydrogen and n is an integer of 2.

17. A compound of claim 16 which is N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide.

18. A compound of claim 1 wherein R^1 is methyl, R^2 and R^3 are hydrogen and n is an integer of 0.

19. A compound of claim 18, selected from the group consisting of,

a) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

b) N-[1-({1-sec-Butyl-2-methoxy-4-oxo-4-[2-(2-phenethylcarbamoyl-1-phenylsulfanyl-ethyl)-pyrrolidin-1-yl]-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

d) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

e) N-[1-({1-sec-Butyl-4-[2-(1-isopropylsulfanyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide, and

f) N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(2-methyl-propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide,

g) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-3-methyl-2-methylamino-butyramide,

h) N-(1-{[1-sec-Butyl-4-(2-{1-tert-butylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-ethyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-3-methyl-2-methylamino-butyramide.

20. A compound of claim 1 wherein R^1 is methyl, R^2 and R^3 are hydrogen and n is an integer of 2.

21. A compound of claim 20, selected from the group consisting of,

a) N-[1-({1-sec-Butyl-4-[2-(1-ethanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

b) N-[1-({4-[2-(1-Benzenesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-1-sec-butyl-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide,

c) N-[1-({1-sec-Butyl-4-[2-(1-methanesulfonyl-2-phenethylcarbamoyl-ethyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-3-methyl-2-methylamino-butyramide, and

d) N-{1-[(1-sec-Butyl-2-methoxy-4-oxo-4-{2-[2-phenethylcarbamoyl-1-(propane-2-sulfonyl)-ethyl]-pyrrolidin-1-yl}-butyl)-methyl-carbamoyl]-2-methyl-propyl}-3-methyl-2-methylamino-butyramide.

22. A compound of of claim 1 wherein R^1 and R^3 are methyl and R^2 is hydrogen and n is an integer of 0.

23. A compound of claim 22, selected from the group consisting of,

a) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide, and

b) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-methylamino-3-methyl-butyramide.

24. A compound of claim 1 wherein R^1, R^2 and R^3 are methyl and n is an integer of 0.

25. A compound of claim 24, selected from the group consisting of,

a) N-[1-({1-sec-Butyl-2-methoxy-4-[2-(1-methylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

b) N-[1-({1-sec-Butyl-4-[2-(1-tert-butylsulfanyl-2-phenethylcarbamoyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

c) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-ethylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

d) N-{1-[(1-sec-Butyl-4-{2-[1-(4-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

e) N-{1-[(1-sec-Butyl-4-{2-[1-(3-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

f) N-{1-[(1-sec-Butyl-4-{2-[1-(2-hydroxy-phenylsulfanyl)-2-phenethylcarbamoyl-propyl]-pyrrolidin-1-yl}-2-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2-methyl-propyl}-2-dimethylamino-3-methyl-butyramide,

g) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

h) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

i) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-t-butylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

j) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(4-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

k) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide, and

l) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(2-hydroxy-phenyl)-ethylcarbamoyl]-1-methylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

m) N-(1-{[1-sec-Butyl-4-(2-{2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-1-pentylsulfanyl-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

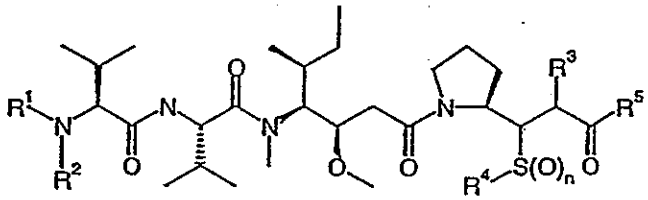
n) N-[1-({1-sec-Butyl-4-[2-(2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-1-methylsulfanyl-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

o) N-[1-({1-sec-Butyl-4-[2-(1-ethylsulfanyl-2-{[2-(3-hydroxy-phenyl)-ethyl]-methyl-carbamoyl}-propyl)-pyrrolidin-1-yl]-2-methoxy-4-oxo-butyl}-methyl-carbamoyl)-2-methyl-propyl]-2-dimethylamino-3-methyl-butyramide,

p) N-(1-{[1-sec-Butyl-4-(2-{1-ethylsulfanyl-2-[2-(3-hydroxy-phenyl)-ethylcarbamoyl]-propyl}-pyrrolidin-1-yl)-2-methoxy-4-oxo-butyl]-methyl-carbamoyl}-2-methyl-propyl)-2-dimethylamino-3-methyl-butyramide,

q) Ethyl-carbamic acid 3-(2-{3-[1-(4-{[2-(2-dimethylamino-3-methyl-butyrylamino)-3-methyl-butyryl]-methyl-amino}-3-methoxy-5-methyl-heptanoyl)-pyrrolidin-2-yl]-2-methyl-3-methylsulfanyl-propionylamino}-ethyl)-phenyl ester.

26. A compound of claim 1 having the formula (I-I),



(I-I)

wherein R^1, R^2, R^3, R^4, R^5 and n are defined according to claim 1 to 25,

and pharmaceutical acceptable salts thereof.

27. A pharmaceutical composition comprising compound of any one of claims 1 to 26 and a pharmaceutically acceptable carrier.

28. The pharmaceutical composition of claim 27 which is suitable for oral or parenteral administration.

29. The use of a compound as defined in any one of claims 1-26 for the preparation of medicaments.

30. The use of compound as defined in any one of claims 1-26 for the preparation of medicaments for the treatment of cell proliferative disorders.

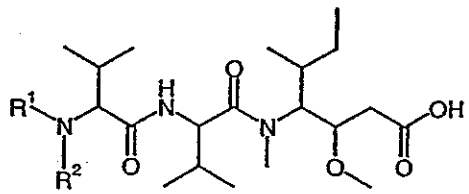
31. The use of compound as defined in any one of claims 1- 26 for the preparation of medicaments for the treatment of cancer.

32. A use of claim 31 wherein the cancer is a solid tumor.

33. A use of claim 31 wherein the cancer is colorectal cancer, lung cancer, breast cancer, stomach cancer, cervical cancer and bladder cancer.

34. A process for the preparation of compounds of any of claims 1 to 26 comprising

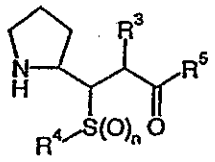
condensing an acid of the formula (II),



(II)

wherein R^1 and R^2 are as defined in claims 1 to 26

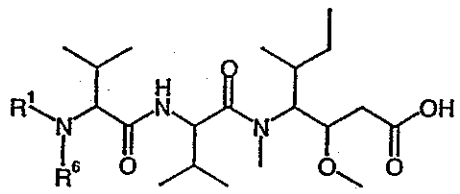
with a compound of the formula (III),



(III)

wherein R^3, R^4, R^5 and n are as defined in claims 1 to 26.

35. A process for the preparation of compounds of any of claims 1 to 26 comprising condensing an acid of the formula (IV),



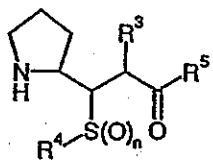
(IV)

wherein

R^1 is hydrogen or (C_1-C_4)-alkyl; and

R^6 is a protecting,

with a compound of the formula (III),

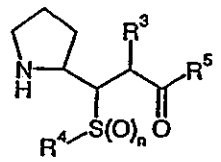


(III)

wherein R^3, R^4, R^5 and n are as defined in claim 34,

in the presence of a condensing agent, optionally followed by removal of protecting group(s) and/or formation of pharmaceutically acceptable salts.

36. Compounds of the formula (III),

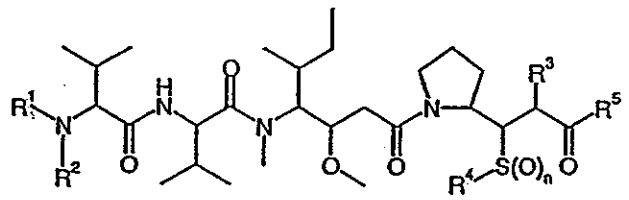


(III)

wherein R^3, R^4, R^5 and n are as defined in claim 34,

37. The compounds of any claims 1 to 26 to use in therapy.

38. A compound of the formula (I),



(I)

wherein

R^1, R^2 and R^3 are each independently hydrogen or (C_1-C_4)-alkyl;

R^4 is hydrogen;

alkyl optionally substituted with one to three substituents selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbonyloxy or halogen;

alkenyl;

alkinyl;

(C_3-C_7)-cycloalkyl;

aryl optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

aralkyl with the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl; or

heterocyclylalkyl;

R^5 is (C_1-C_6)-alkylamino;

hydroxy;

(C_3-C_7)-cycloalkylamino optionally substituted by phenyl or benzyl;

arylamino;

aralkylamino having (C_1-C_4)-alkylene and the aryl group optionally substituted with one to three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonyl-amino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino or benzyl;

(C_1-C_4)-alkoxy;

benzhydrazino;

heterocyclyl optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, mono- or di-alkylamino, acylamino, alkoxycarbonylamino, phenyl or halogen;

heterocyclylamino;

heterocycloalkylamino with the heterocyclyl group optionally substituted with one to three substituents selected from the group consisting of benzyl, benzhydryl, alkyl, hydroxy, alkoxy, alkylcarbamoyloxy, amino, dialkylamino, acylamino, alkoxycarbonylamino or halogen;

aralkyloxy and aralkyl both optionally substituted with one to three substituents from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluo$romethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, heterocyclyl, 1,3-dioxolyl, 1,4-dioxolyl, amino, aminosulfonyl or benzyl;

and

n is an integer of 0, 1 or 2;

and pharmaceutical acceptable salts thereof.

39. The novel compounds, novel pharmaceutical compositions, processes and methods as well as the use of such compounds substantially as described hereinbefore.