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(54) **Title**: ALPHA HELIX MIMETICS AND METHODS RELATING THERETO

(57) **Abstract**: Alpha-helix mimetic structures and compounds represented by the formula (I) wherein the general formula and the definition of each symbol are as defined in the specification, a compound relating thereto, and methods relating thereto, are disclosed. Applications of these compounds in the treatment of medical conditions, e.g., cancer diseases, fibrotic diseases, and pharmaceutical compositions comprising the mimetics are further disclosed.

# DESCRIPTION

# ALPHA HELIX MIMETICS AND METHODS RELATING THERETO

## Technical Field

The present invention relates generally to alpha-helix mimetic structures and to a compound relating thereto. The invention also relates to applications in the treatment of medical conditions, e.g., cancer diseases, fibrotic diseases, and pharmaceutical compositions comprising the mimetics.

## Background Art

Recently, non-peptide compounds have been developed which more closely mimic the secondary structure of reverse-turns found in biologically active proteins or peptides. For example, U.S. Pat. No. 5,440,013 to Kahn and published PCT applications nos. WO94/03494, WO01/00210A1, and WO01/16135A2 to Kahn each disclose conformationally constrained, non-peptidic compounds, which mimic the three-dimensional structure of reverse-turns. In addition, U.S. Pat. No. 5,929,237 and its continuation-in-part U.S. Pat. No. 6,013,458, both to Kahn, disclose conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins. In relation to reverse-turn mimetics, Kahn disclosed new conformationally constrained compounds which mimic the secondary structure of alpha-helix regions of biologically active peptide and proteins in WO2007/056513 and WO2007/056593. Moreover, Odagami et al. disclosed new conformationally constrained compounds which mimic the secondary structure of alpha-helix regions of biologically active peptide and proteins in WO2009/148192, WO2010/044485 and WO2010/128685.

Despite their pharmacological merits, the use of the alfa helix mimetics can sometimes be compromised due to inadequate oral bioavailability.

While significant advances have been made in the synthesis and identification of conformationally constrained, reverse-turn and alpha-helix mimetics, there remains a need in the art for small molecules which mimic the secondary structure of peptides. There is also a need in the art for libraries containing such members, as well as techniques for synthesizing and screening the library members against targets

of interest, particularly biological targets, to identify bioactive library members.

The present invention also fulfills these needs, and provides further related advantages by providing conformationally constrained compounds which mimic the secondary structure of alpha-helix regions of biologically active peptides and proteins.

Wnt signaling pathway regulates a variety of processes including cell growth, oncogenesis, and development (Moon et al., 1997, Trends Genet. 13, 157-162; Miller et al., 1999, Oncogene 18, 7860-7872; Nusse and Varmus, 1992, Cell 69, 1073-1087; Cadigan and Nusse, 1997, Genes Dev. 11, 3286- 3305; Peifer and Polakis, 2000 Science 287, 1606-1609; Polakis 2000, Genes Dev. 14, 1837-1851). Wnt signaling pathway has been intensely studied in a variety of organisms. The activation of TCF4/β-catenin mediated transcription by Wnt signal transduction has been found to play a key role in its biological functions (Molenaar et al., 1996, Cell 86:391-399; Gat et al., 1998 Cell 95:605- 614; Orford et al., 1999 J. Cell. Biol. 146:855-868; Bienz and Clevers, 2000, Cell 103:311-20).

In the absence of Wnt signals, tumor suppressor gene adenomatous polyposis coli (APC) simultaneously interacts with the serine kinase glycogen synthase kinase (GSK)-3β and β-catenin (Su et al., 1993, Science 262, 1734-1737: Yost et al., 1996 Genes Dev. 10, 1443-1454: Hayashi et al., 1997, Proc. Natl. Acad. Sci. USA, 94, 242-247: Sakanaka et al., 1998, Proc. Natl. Acad. Sci. USA, 95, 3020-3023: Sakanaka and William, 1999, J. Biol. Chem 274, 14090-14093). Phosphorylation of APC by GSK-3β regulates the interaction of APC with β-catenin, which in turn may regulate the signaling function of β-catenin (B. Rubinfeld et al., Science 272, 1023, 1996). Wnt signaling stabilizes β-catenin allowing its translocation to the nucleus where it interacts with members of the lymphoid enhancer factor (LEF1)/T-cell factor (TCF4) family of transcription factors (Behrens et al., 1996 Nature 382, 638-642: Hsu et al., 1998, Mol. Cell. Biol. 18, 4807-4818: Roose et al., 1999 Science 285, 1923-1926).

Recently c-myc, a known oncogene, was shown to be a target gene for β-catenin/TCF4-mediated transcription (He et

al., 1998 Science 281 1509-1512: Kolligs et al., 1999 Mol. Cell. Biol. 19, 5696-5706). Many other important genes, including cyclin D1, and metalloproteinase, which are also involved in oncogenesis, have been identified to be regulated by TCF4/β-catenin transcriptional pathway (Crawford et al., 1999, Oncogene 18, 2883-2891: Shtutman et al., 1999, Proc. Natl. Acad. Sci. USA., 11, 5522-5527: Tetsu and McCormick, 1999 Nature, 398, 422-426). Moreover, overexpression of several downstream mediators of Wnt signaling has been found to regulate apoptosis (Moris et al., 1996, Proc. Natl. Acad. Sci. USA, 93, 7950-7954: He et al., 1999, Cell 99, 335-345 : Orford et al, 1999 J. Cell. Biol., 146, 855-868: Strovel and Sussman, 1999, Exp. Cell. Res., 253, 637-648). Overexpression of APC in human colorectal cancer cells induced apoptosis (Moris et al., 1996, Proc. Natl. Acad. Sci. USA., 93, 7950-7954), ectopic expression of β-catenin inhibited apoptosis associated with loss of attachment to extracellular matrix (Orford et al, 1999, J. Cell Biol.146, 855-868). Inhibition of TCF4/β-catenin transcription by expression of dominant-negative mutant of TCF4 blocked Wnt-1-mediated cell survival and rendered cells sensitive to apoptotic stimuli such as anti-cancer agent (Shaoqiong Chen et al., 2001, J. Cell. Biol., 152, 1, 87-96) and APC mutation inhibits apoptosis by allowing constitutive survivin expression, a well-known anti-apoptotic protein (Tao Zhang et al., 2001, Cancer Research, 62, 8664-8667).

Although mutations in the Wnt gene have not been found in human cancer, a mutation in APC or β-catenin, as is the case in the majority of colorectal tumors, results in inappropriate activation of TCF4, overexpression of c-myc and production of neoplastic growth (Bubinfeld et al, 1997, Science, 275, 1790-1792: Morin et al, 1997, Science, 275, 1787-1790: Casa et al, 1999, Cell. Growth. Differ. 10, 369-376). The tumor suppressor gene (APC) is lost or inactivated in 85% of colorectal cancers and in a variety of other cancers as well (Kinzler and Vogelstein, 1996, Cell 87, 159-170). APCs principal role is that of a negative regulator of the Wnt signal transduction cascade. A center feature of this pathway involves the modulation of the stability and localization of a

cytosolic pool of β-catenin by interaction with a large Axin-based complex that includes APC. This interaction results in phosphorylation of β-catenin thereby targeting it for degradation.

CREB binding proteins (CBP)/p300 were identified initially in protein interaction assays, first through its association with the transcription factor CREB (Chrivia et al, 1993, Nature, 365, 855-859) and later through its interaction with the adenoviral-transforming protein E1A (Stein et al., 1990, J. Viol., 64, 4421-4427: Eckner et al., 1994, Genes. Dev., 8, 869-884). CBP had a potential to participate in variety of cellular functions including transcriptional coactivator function (Shikama et al., 1997, Trends. Cell. Biol., 7, 230-236: Janknecht and Hunter, 1996, Nature, 383, 22-23). CBP/p300 potentiates β-catenin-mediated activation of the siamois promoter, a known Wnt target (Hecht et al, 2000, EMBO J. 19, 8, 1839-1850). β-catenin interacts directly with the CREB-binding domain of CBP and β-catenin synergizes with CBP to stimulate the transcriptional activation of TCF4/β-catenin (Ken-Ichi Takemaru and Randall T. Moon, 2000 J. Cell. Biol., 149, 2, 249-254).

**Summary of the Invention**

The present invention relates generally to alpha-helix mimetic structures and to a compound relating thereto. The invention also relates to applications in the treatment of medical conditions, e.g., cancer diseases, fibrotic diseases, and pharmaceutical compositions comprising the mimetics.

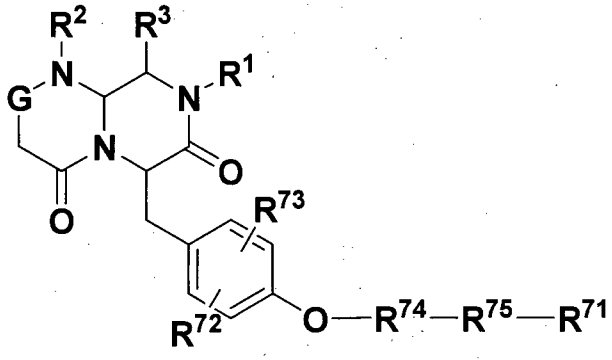
From the above background discussions, it is seen that TCF4/β-catenin and CBP complex of Wnt pathway can be taken as target molecules for the regulation of cell growth, oncogenesis and apoptosis of cells, etc. Accordingly, the present invention also addresses a need for compounds that block TCF4/β-catenin transcriptional pathway by inhibiting CBP, and therefore can be used for treatment of cancer, especially colorectal cancer, and fibrotic diseases. In aspects thereof, the present invention is directed to a new type of conformationally constrained compounds, which mimic the secondary structure of alpha-helix regions of biologically active peptides and proteins. This invention also discloses

libraries containing such compounds, as well as the synthesis and screening thereof.

Another embodiment of the present invention is to provide a prodrug of said alpha-helix mimetics in an attempt to improve oral bioavailability.

Accordingly, the present invention includes the following embodiments.

(1) A compound having the following general formula (I):



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are independently selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, $-NR^6-$, -O-, $-CH_2-$, $-CHR^6-$ or $-C(R^6)_2-$, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)- or $-(SO_2)-$; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl,

optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl; and
$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;
or a pharmaceutically acceptable salt thereof.

(2) The compound according to (1) mentioned above, wherein, in the formula (I),
$R^{74}$ is a bond; and
$R^{75}$ is -(CO)-.

(3) The compound according to (1) mentioned above, wherein, in the formula (I),
$R^{74}$ is a bond; and
$R^{75}$ is -(CO)-O-.

(4) The compound according to (1) mentioned above, wherein, in the formula (I),
$R^{74}$ is optionally substituted lower alkylene; and
$R^{75}$ is -O-.

(5) The compound according to (1) mentioned above, wherein, in the formula (I),
$R^{74}$ is optionally substituted lower alkylene; and
$R^{75}$ is -O-(CO)-O-.

(6) The compound according to any one of (1) to (5) mentioned above, wherein, in the formula (I),
wherein G is -NH-, $-NR^6-$, -O-, or $-CH_2-$; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl,
$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted aryl or optionally substituted heteroaryl.

(7) The compound according to (6) mentioned above, wherein, in the formula (I),
wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety.

(8) The compound according to (6) mentioned above, wherein, in the formula (I),
wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl, optionally substituted

heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl.

(9) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl, or optionally substituted heteroaryl.

(10) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^3$ is hydorogen or $C_{1-4}$ alkyl.

(11) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen.

(12) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen.

(13) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is $-NR^6-$ wherein $R^6$ is lower alkyl or lower alkenyl.

(14) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is $-CH_2-$.

(15) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl,optionally substituted

naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl.

(16) The compound according to any one of (7)-(14) mentioned above, wherein, in the formula (I),
wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted

benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl.

(17) The compound according to (15) mentioned above, wherein, in the formula (I),
wherein $R^3$ is hydrogen, or $C_{1-4}$ alkyl.

(18) The compound according to (15) mentioned above, wherein, in the formula (I),
wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(19) The compound according to (6) mentioned above, wherein, in the formula (I),
wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and
$R^{72}$ and $R^{73}$ are hydrogen;
$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl,

optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is hydrogen or $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(20) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted

benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(21) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted

benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(22) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl,

optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(23) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted

heteroaryl.

(24) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(25) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl,

optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(26) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally

substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(27) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted

pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(28) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl,

optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(29) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally

substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(30) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl,

optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(31) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl,

optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(32) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a

bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(33) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(34) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower

alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(35) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted

thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(36) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally

substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(37) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally

substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(38) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted

naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(39) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally

substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(40) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl,

optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(41) The compound according to (6) mentioned above, wherein, in the formula (I),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally

substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(42) The compound according to (13) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(43) The compound according to (14) mentioned above, wherein, in the formula (I),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

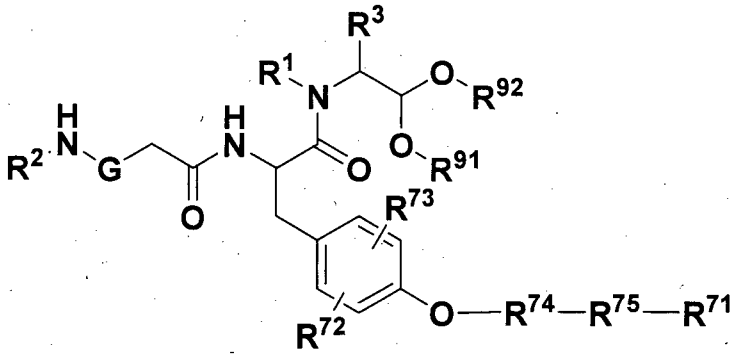
$R^{72}$ and $R^{73}$ are hydrogen;

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(44) A compound having the following general formula (II):



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are independently selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, $-NR^6-$, -O-, $-CH_2-$, $-CHR^6-$ or $-C(R^6)_2-$, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)- or $-(SO_2)-$; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl;

$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

$R^{91}$ is selected from optionally substituted alkyl, linker or solid support; and

$R^{92}$ is selected from optionally substituted alkyl, linker or solid support;

or a salt thereof.

(45) The compound according to (44) mentioned above, wherein, in the formula (II),

$R^{74}$ is a bond; and

$R^{75}$ is -(CO)-.

(46) The compound according to (44) mentioned above, wherein, in the formula (II),

$R^{74}$ is a bond; and

$R^{75}$ is -(CO)-O-.

(47) The compound according to (44) mentioned above, wherein, in the formula (II),

$R^{74}$ is optionally substituted lower alkylene; and

$R^{75}$ is -O-.

(48) The compound according to (44) mentioned above, wherein, in the formula (II),

$R^{74}$ is optionally substituted lower alkylene; and

$R^{75}$ is -O-(CO)-O-.

(49) The compound according to any one of (44) to (48) mentioned above, wherein, in the formula (II),

wherein G is -NH-, $-NR^6-$, -O-, or $-CH_2-$; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl,

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted aryl or optionally substituted heteroaryl.

(50) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl.

(51) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl.

(52) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-;

Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl, or optionally substituted heteroaryl.

(53) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein $R^3$ is hydorogen or $C_{1-4}$ alkyl.

(54) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;
$R^{72}$ and $R^{73}$ are hydrogen.

(55) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;
$R^{72}$ and $R^{73}$ are hydrogen.

(56) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein G is $-NR^6-$ wherein $R^6$ is lower alkyl or lower alkenyl.

(57) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein G is $-CH_2-$.

(58) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl,optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted

pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl.

(59) The compound according to any one of (50)-(57) mentioned above, wherein, in the formula (II),
wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted

thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl.

(60) The compound according to (59) mentioned above, wherein, in the formula (II),
wherein $R^3$ is hydrogen, or $C_{1-4}$ alkyl.

(61) The compound according to (59) mentioned above, wherein, in the formula (II),
wherein $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(62) The compound according to (49) mentioned above, wherein, in the formula (II),
wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and
$R^{72}$ and $R^{73}$ are hydrogen;
$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl,

optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is hydrogen or $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(63) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted

thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(64) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted

imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(65) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(66) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(67) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(68) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted

pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl; $R^3$ is $C_{1-4}$ alkyl; $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(69) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted

benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(70) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally

substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(71) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl,

optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(72) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted

benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(73) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl,

optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(74) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted

thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(75) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(76) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(77) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted

quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(78) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted

naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(79) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein G is $-NH-$, $-NR^6-$, or $-O-$; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted

pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(80) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is optionally substituted $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally

substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(81) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein G is -NH-, or -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted

cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(82) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally

substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(83) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted

pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(84) The compound according to (49) mentioned above, wherein, in the formula (II),

wherein G is -NH-, -O-; wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl,

optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(85) The compound according to (56) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is

optionally substituted aryl or optionally substituted heteroaryl.

(86) The compound according to (57) mentioned above, wherein, in the formula (II),

wherein $R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

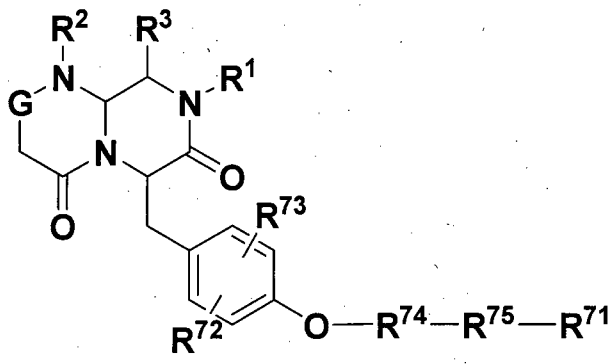
$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

(87) A process for preparing a compound having the following general formula (I):



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, $-NR^6-$, -O-, -CH2-, $-CHR^6-$ or $-C(R^6)_2-$,

wherein

$R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$,

wherein

$W^{21}$ is $-(CO)-$ or $-(SO_2)-$;

$W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene;

Rb is a bond or optionally substituted lower alkylene;

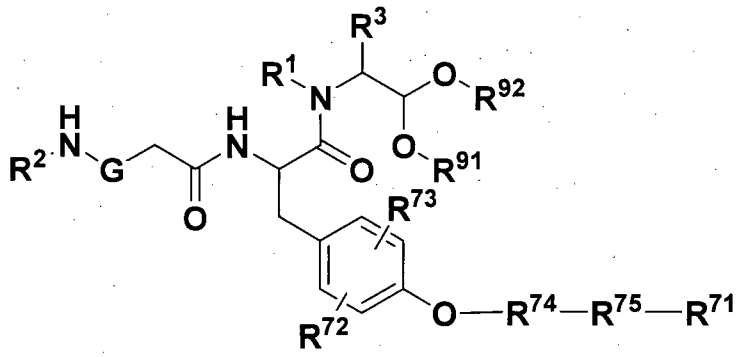
and

$R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or

optionally substituted heterocycloalkyl; and

$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

or a salt thereof, which comprises reacting a compound having the following general formula (II):



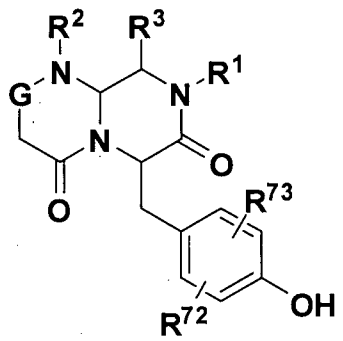
wherein

$R^{91}$ is selected from optionally substituted alkyl, linker or solid support;

$R^{92}$ is selected from optionally substituted alkyl, linker or solid support; and

the other symbols are as defined above, or a salt thereof, with an acid.

or reacting a compound having the following general formula (I'):



wherein

the symbols are defined above, or a salt thereof, with an acylating reagents or an alkylating reagent represented by the formula: $R^{71}$-$R^{75}$-$R^{74}$-X or $(R^{71}$-$R^{75}$-$R^{74})_2O$ wherein X is a leaving group or a hydroxy group and $R^{71}$, $R^{75}$ and $R^{74}$ are as defined above, or a carbamate forming reagent represented by the formula O=C=N-$R^{71'}$ wherein N-$R^{71'}$ corresponds to an amino acid moiety.

Examples of the leaving group include a halogen atom

such as chlorine atom, bromine atom, iodine atom and the like.

The present invention is also directed to libraries containing one or more compounds of formula (I) above, as well as methods for synthesizing such libraries and methods for screening the same to identify biologically active compounds.

In another embodiment, a pharmaceutical composition comprises the compound of formula (I) or pharmaceutically acceptable salt thereof, and, if necessary, together with a pharmaceutical acceptable carrier or diluent. Compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier or diluent are also disclosed.

In another embodiment, there is a method of treating a cancerous condition or fibrosis by administering the compound of formula (I). The present invention also provides methods for preventing or treating disorders associated with Wnt signaling pathway. Disorders that may be treated or prevented using a compound or composition of the present invention include tumor or cancer (e.g., KSHV-associated tumor), fibrotic diseases, restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, tuberous sclerosis complex, hair loss, and Alzheimer's disease. Such methods comprise administering to a subject in need thereof a compound or composition of the present invention in an amount effective to achieve the desired outcome.

These and other aspects of this invention will be apparent upon reference to the attached figure and following detailed description. To this end, various references are set forth herein, which describe in more detail certain procedures, compounds and/or compositions, and are incorporated by reference in their entirety.

**Brief Description of Drawings**

Figures 1, 2, 3 and 4 provide a general synthetic scheme for preparing alpha-helix mimetics of the present invention.

**Detailed Description of The Invention**

The present invention relates generally to alpha-helix mimetic structures and to a compound relating thereto. The present invention is also directed to conformationally

constrained compounds that mimic the secondary structure of alpha-helix regions of biological peptide and proteins (also referred to herein as "alpha-helix mimetics"), and is also directed to chemical libraries relating thereto. The compound of the present invention is useful as bioactive agents, including (but not limited to) use as diagnostic, prophylactic and/or therapeutic agents. The alpha-helix mimetic structure libraries of this invention are useful in the identification of bioactive agents having such uses. In the practice of the present invention, the libraries may contain from tens to hundreds to thousands (or greater) of individual alpha-helix structures (also referred to herein as "members").

**DEFINITIONS**

Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

"Lower", unless indicated otherwise, means that the number of the carbon atoms constituting the given radicals is between one and six.

"Optionally substituted", unless otherwise stated, means that a given radical may consist of only hydrogen substituents through available valencies or may further comprise one or more non-hydrogen substituents through available valencies. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given radical that is specified to be substituted. Examples of substituents include, but are not limited to, $-R^8$, -OH, $-OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, -COOH, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NH_2$, $-NHR^8$, $-NR^8R^4$, -SH, $-SR^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2NR^8R^4$ $-SO_3H$, $-SOR^8$, $-NHC(NH_2)(=NH)$, $-NHC(NHR^8)(=NR^4)$, $-OP(=O)(OH)_2$, $-OP(=O)(ONa)_2$, $-OP(=O)(OR^8)_2$, $-OP(=O)(OR^8)(OH)$, $-OP(=O)(OH)-O-P(=O)(OH)_2$, $-OP(=O)(ONa)-O-OP(=O)(ONa)_2$, -CN, $-NO_2$ and halogen, wherein $R^8$ and $R^4$ is independently selected from linear or branched chain, cyclic or noncyclic, substituted or unsubstituted, alkyl chain, aryl, arylalkyl, heterocycloalkyl moieties. In addition, the substituents may be protected by a protecting group, or may itself be a protecting group.

"Halogen" means fluorine, chlorine, bromine or iodine.

"Halo" means fluoro, chloro, bromo or iodo.

"Alkyl" means a linear or branched, saturated, aliphatic radical having a chain of carbon atoms. $C_{X-Y}$ alkyl is typically used where X and Y indicate the number of carbon atoms in the chain. The number of carbon atoms in the chain is preferably 1 to 20, more preferably 1 to 18, further preferably 1 to 12. Non-exclusive examples of alkyl include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, *sec*-pentyl, 2-methylbutyl, isopentyl, neopentyl, *tert*-pentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, nonanyl, isononanyl, decanyl, isodecanyl, undecanyl, isoundecanyl, dodecanyl, isododecanyl, tridecanyl, isotridecanyl, tetradecanyl, isotetradecanyl, pentadecanyl, isopentadecanyl, hexadecanyl, isohexadecanyl, heptadecanyl, isoheptadecanyl, octadecanoyl, isooctadecanoyl, nonadecanyl, isononadecanyl, eicosanyl, isoeicosanyl and the like.

"Alkenyl" means a linear or branched, carbon chain that contains at least one carbon-carbon double bond. $C_{X-Y}$ alkenyl is typically used where X and Y indicate the number of carbon atoms in the chain. The number of carbon atoms in the chain is preferably 2 to 10, more preferably 2 to 6. Non-exclusive examples of alkenyl include ethenyl (vinyl), allyl, isopropenyl, 2-methylallyl, 1-pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means a linear or branched, carbon chain that contains at least one carbon-carbon triple bond. $C_{X-Y}$ alkynyl is typically used where X and Y indicate the number of carbon atoms in the chain. The number of carbon atoms in the chain is preferably 2 to 10, more preferably 2 to 6. Non-exclusive examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Alkylene", unless indicated otherwise, means a linear or branched, saturated, aliphatic, polyvalent carbon chain. $C_{X-Y}$ alkylene is typically used where X and Y indicate the number of carbon atoms in the chain. The number of carbon atoms in the chain is preferably 1 to 10, more preferably 1 to 6. Non-exclusive examples of alkylene include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), methylmethylene ($-CH(CH_3)-$), 1,2-propylene ($-CH_2CH(CH_3)-$), 1,3-propylene ($-CH_2CH_2CH_2-$), 1,2-

butylene (-$CH_2CH(CH_2CH_3)$-), 1,3-butylene (-$CH_2CH_2CH(CH_3)$-), 1,4-butylene (-$CH_2CH_2CH_2CH_2$-), 2-methyltetramethylene (-$CH_2CH(CH_3)CH_2CH_2$-), pentamethylene (-$CH_2CH_2CH_2CH_2CH_2$-), 1,2,3-propanetriyl, 1,3,3-propanetriyl and the like.

"Oxy" means the radical -O-. It is noted that the oxy radical may be further substituted with a variety of substituents to form different oxy groups including hydroxy, alkoxy, aryloxy, heteroaryloxy and the like.

"Thio" means the radical -S-. It is noted that the thio radical may be further substituted with a variety of substituents to form different thio groups including mercapto, alkylthio, arylthio, heteroarylthio and the like.

"Sulfinyl" means the radical -SO-. It is noted that the sulfinyl radical may be further substituted with a variety of substituents to form different sulfinyl groups including alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl and the like.

"Sulfonyl" means the radical -$SO_2$-. It is noted that the sulfonyl radical may be further substituted with a variety of substituents to form different sulfonyl groups including alkylsulfonyl, arysulfonyl, heteroarylsulfonyl and the like.

"Alkoxy" means an oxygen moiety having a further alkyl substituent. $C_{X-Y}$ alkoxy is typically used where X and Y indicate the number of carbon atoms in the chain. The number of carbon atoms in the chain is preferably 1 to 10, more preferably 1 to 6. Non-exclusive examples of alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, pentoxy, isopentoxy, neopentoxy, *tert*-pentoxy, hexyloxy, isohexyloxy, and the like.

"Heteroatom" refers to an atom that is not a carbon atom and hydrogen atom. Particular examples of heteroatoms include, but are not limited to nitrogen, oxygen, and sulfur.

"Aryl" means a monocyclic or polycyclic radical wherein each ring is aromatic or when fused with one or more rings forms an aromatic ring. $C_{X-Y}$ aryl is typically used where X and Y indicate the number of carbon atoms in the ring assembly. The number of carbon atoms in the ring is preferably 6 to 14, more preferably 6 to 10. Non-exclusive examples of aryl include phenyl, naphthyl, indenyl, azulenyl, biphenyl, fluorenyl, anthracenyl, phenalenyl and the like.

"Heteroaryl" means a monocyclic or polycyclic aromatic radical wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. "X-Y menbered heteroaryl" is typically used where X and Y indicate the number of carbon atoms and heteroatoms in the ring assembly. The number of carbon atoms and heteroatoms in the ring is preferably 5 to 14, more preferably 5 to 10. Monocyclic heteroaryl groups include, but are not limited to, cyclic aromatic groups having five or six ring atoms, wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. The nitrogen atoms can be optionally quaternerized and the sulfur atoms can be optionally oxidized. Non-exclusive examples of monocyclic heteroaryl group of this invention include, but are not limited to, those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, 1,3,4-thiadiazole, triazole and tetrazole. "Heteroaryl" also includes, but is not limited to, bicyclic or tricyclic rings, wherein the heteroaryl ring is fused to one or two rings independently selected from the group consisting of an aryl ring, a cycloalkyl ring, and another monocyclic heteroaryl or heterocycloalkyl ring. Non-exclusive examples of bicyclic or tricyclic heteroaryl include, but are not limited to, those derived from benzofuran (ex. benzo[b]furan), benzothiophene (ex. benzo[b]thiophene), benzimidazole, benzotriazine (ex. benzo[e][1,2,4]triazine, benzo[d][1,2,3]triazine), pyridopyrimidine (ex. pyrido[4,3-d]pyrimidine, pyrido[3,4-d]pyrimidine, pyrido[3,2-d]pyrimidine, pyrido[2,3-d]pyrimidine), pyridopyrazine (ex. pyrido[3,4-b]pyrazine, pyrido[2,3-b]pyrazine), pyridopyridazine (ex. pyrido[2,3-c]pyridazine, pyrido[3,4-c]pyridazine, pyrido[4,3-c]pyridazine, pyrido[3,2-c]pyridazine), pyridotriazine (ex. pyrido[2,3-d][1,2,3]triazine, pyrido[3,4-d][1,2,3]triazine, pyrido[4,3-d][1,2,3]triazine, pyrido[3,2-d][1,2,3]triazine, pyrido[3,4-e][1,2,4]triazine, pyrido[3,2-e][1,2,4]triazine), benzothiadiazole (ex. benzo[c][1,2,5]thiadiazole), furopyridine (ex. furo[3,2-b]pyridine, furo[3,2-c]pyridine, furo[2,3-c]pyridine, furo[2,3-b]pyridine), oxazolopyridine (ex. oxazolo[4,5-b]pyridine, oxazolo[4,5-c]pyridine, oxazolo[5,4-

c]pyridine, oxazolo[5,4-b]pyridine), thiazolopyridine (ex. thiazolo[4,5-b]pyridine, thiazolo[4,5-c]pyridine, thiazolo[5,4-c]pyridine, thiazolo[5,4-b]pyridine), imidazopyridine (ex. imidazo[1,2-a]pyridine, imidazo[4,5-c]pyridine, imidazo[1,5-a]pyridine), quinazoline, thienopyridine (ex. thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, thieno[2,3-b]pyridine), indolizine, quinoline, isoquinoline, phthalazine, quinoxaline, cinnoline, naphthyridine, quinolizine, indole, isoindole, indazole, indoline, benzoxazole, benzopyrazole, benzothiazole, pyrazolopyridine (ex. pyrazolo[1,5-a]pyridine), imidazopyrimidine (ex. imidazo[1,2-a]pyrimidine, imidazo[1,2-c]pyrimidine, imidazo[1,5-a]pyrimidine, imidazo[1,5-c]pyrimidine), pyrrolopyridine (ex. pyrrolo[2,3-b]pyridine, pyrrolo[2,3-c]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-b]pyridine), pyrrolopyrimidine (ex. pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-d]pyrimidine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine), pyrrolopyrazine (ex. pyrrolo[2,3-b]pyrazine, pyrrolo[1,2-a]pyrazine), pyrrolopyridazine (ex. pyrrolo[1,2-b]pyridazine), triazopyridine (ex. triazo[1,5-a]pyridine), pteridine, purine, carbazole, acridine, permidine, 1,10-phenanthroline, phenoxathiin, phenoxazine, phenothiazine, phenazine and the like. The bicyclic or tricyclic heteroaryl rings can be attached to the parent molecule through either the heteroaryl group itself or the aryl, cycloalkyl, or heterocycloalkyl group to which it is fused.

"Cycloalkyl" means a non-aromatic, saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring radical. $C_{X-Y}$ cycloalkyl is typically used where X and Y indicate the number of carbon atoms in the ring assembly. The number of carbon atoms in the ring is preferably 3 to 10, more preferably 3 to 8. Non-exclusive examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, bicyclo[2.2.1]hept-1-yl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or

S. $C_{X-Y}$ heterocycloalkyl is typically used where X and Y indicate the number of carbon atoms and heteroatoms in the ring assembly. The number of carbon atoms and heteroatoms in the ring is preferably 3 to 10, more preferably 3 to 8. Non-exclusive examples of heterocycloalkyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolidinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl, and the like.

Moreover, the above-mentioned definitions can apply to groups wherein the above-mentioned substituents are connected. For example, "arylalkyl" means linear or branched alkyl group which is substituted by aryl groups, such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl and the like.

"Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure when the ring atoms that are common to both rings are directly bound to each other. Non-exclusive examples of common fused rings include decalin, naphthalene, anthracene, phenanthrene, indole, furan, benzofuran, quinoline, and the like. Compounds having fused ring systems may be saturated, partially saturated or aromatic.

"Bridging ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where two ring atoms that are common to both rings are not directly bound to each other. Non-exclusive examples of common compounds having a bridging ring include adamantine, borneol, norbornane, 7-oxabicyclo[2.2.1]heptane, and the like.

"Amino acid moiety", but not limited to, means natural and unnatural amino acid.

Examples of amino acid moiety include glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), methionine (Met), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), histidine (His), lysine (Lys), arginine (Arg), serine (Ser), threonine (Thr), aspartic acid (Asp), glutamic acid (Glu), asparagine (Asn), glutamine (Gln), cysteine (Cys), praline (Pro), ornithine (Orn), sarcosine (Sar), β-alanine (β-Ala), γ-aminobutyric acid (GABA) and the like.

When the amino acid moiety has a functional group in the side chain, the functional group of the amino acid can be protected with a protecting group. Examples of the amino acid moiety with protected side chain include γ-Bzl-Glu or β-Bzl-Asp, wherein a carboxyl group at the γ-position of Glu or β-position of Asp is protected with a benzyl group; γ-tBu-Glu or β-tBu-Asp, wherein a carboxyl group at the γ-position of Glu or β-position of Asp is protected with a tert-butyl group; ε-Z-Lys, ε-Boc-Lys, ε-iPr-ε-Boc-Lys, wherein a ε-amino group of Lys is protected; S-phenylcarbamoyl-Cys wherein a SH group of Cys is protected with a phenylcarbamoyl group; S-Trt-Cys wherein an SH group of Cys is protected with a trityl group; a derivative wherein oxygen of a hydroxyl group of Tyr and Ser is protected with Bzl and the like.

"Protected derivatives" means derivatives of compound in which a reactive site or sites are blocked with protecting groups. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Isomers" mean any compound having an identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality. A mixture of the two enantiomeric forms is termed a "racemic mixture". A compound that has more than one chiral center has $2^{n-1}$ enantiomeric pairs, where *n* is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents

attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (*e.g.*, see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

"Animal" includes humans, non-human mammals (*e.g.*, mice, rats, dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (*e.g.*, birds, and the like).

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, *i.e.*, the "side effects" of such therapy.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salt" or "salt" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-

carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Amount effective to treat" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Amount effective to prevent" means that amount which, when administered to an animal for preventing a disease, is sufficient to effect such prophylaxis for the disease.

"Treatment" or "treat" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., arresting further development of the pathology and/or symptomatology), or

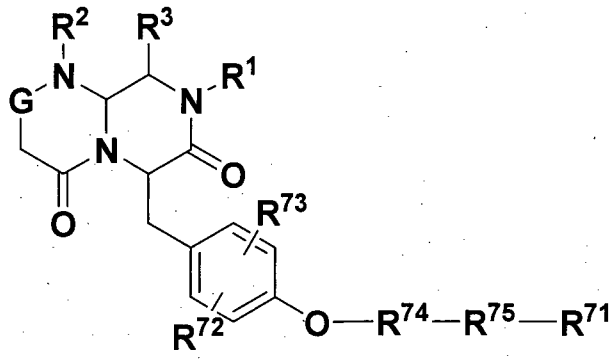
(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., reversing the pathology and/or symptomatology).

It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included.

**ALPHA-HELIX MIMETIC**

In one aspect of the present invention, a compound

having an alpha-helix mimetic structure is disclosed having the following formula (I):



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, $-NR^6-$, -O-, $-CH_2-$, $-CHR^6-$ or $-C(R^6)_2-$,

wherein

$R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$,

wherein

$W^{21}$ is -(CO)- or $-(SO_2)-$;

$W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene;

Rb is a bond or optionally substituted lower alkylene;

and

$R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,

optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl; and

$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

or a pharmaceutically acceptable salt thereof.

In one embodiment, $R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted amino acid moiety.

Examples of optionally substituted alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, *tert*-pentyl, *sec*-pentyl, 2-methylbutyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, nonanyl, isononanyl, decanyl, isodecanyl, undecanyl, isoundecanyl, dodecanyl, isododecanyl, tridecanyl, isotridecanyl, tetradecanyl, isotetradecanyl, pentadecanyl, isopentadecanyl, hexadecanyl, isohexadecanyl, heptadecanyl, isoheptadecanyl, octadecanyl, isooctadecanyl, nonadecanyl, isononadecanyl, eicosanyl, isoeicosanyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, carboxymethyl, carboxyethyl (e.g., 2-carboxyethyl), carboxypropyl, carboxybutyl, carbamoylmethyl, carbamoylethyl, carbamoylpropyl, carbamoylbutyl, methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, methylthiomethyl, methylthioethyl, methylthiopropyl, methylthiobutyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and the like.

Examples of optionally substituted alkenyl group including ethenyl, 2-carboxyethenyl, allyl, 1-propenyl, 2-methylallyl and the like.

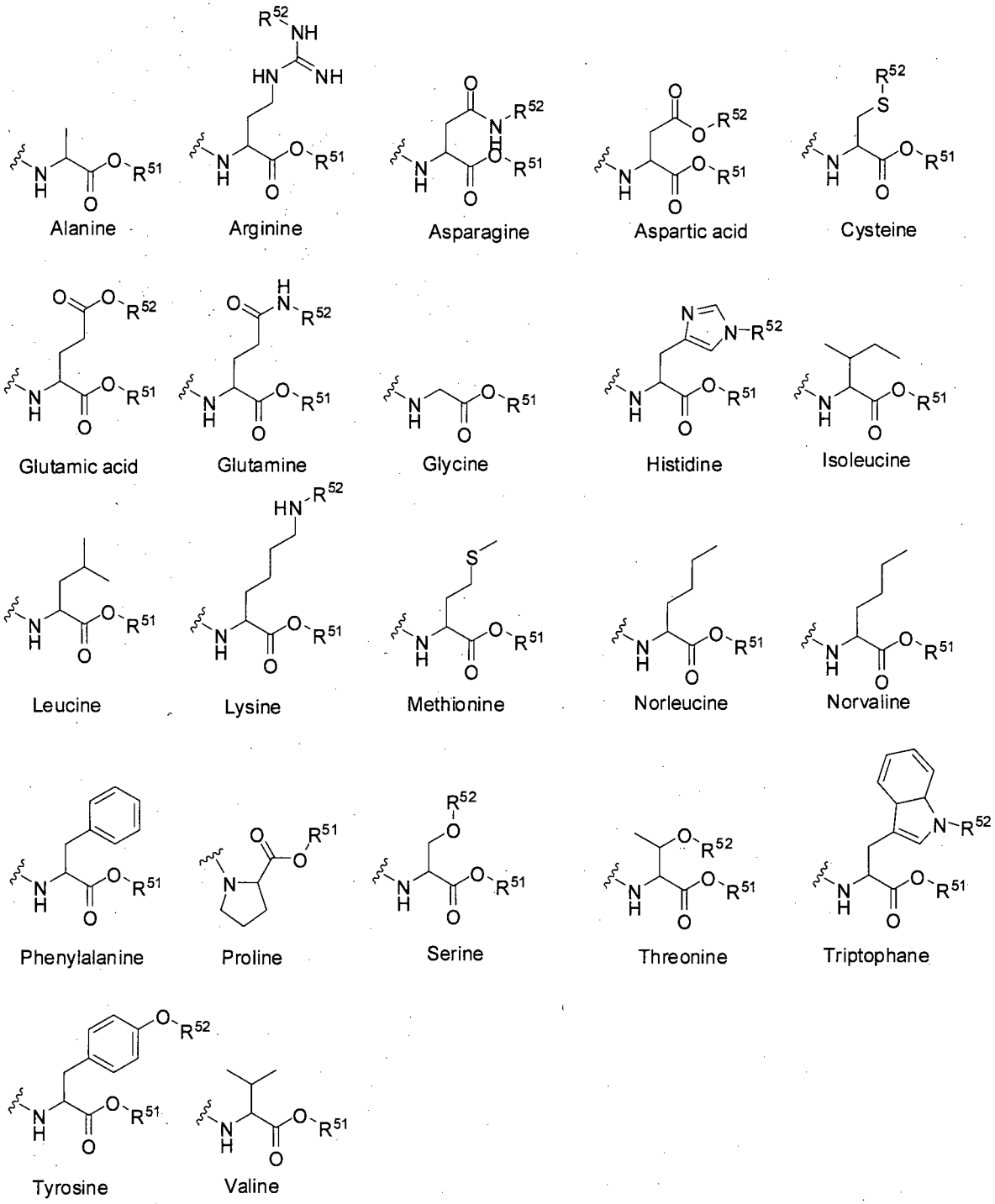
Examples of alkynyl group include 1-propynyl, ethynyl and the like.

Examples of optionally substituted aryl and optionally substituted heteroaryl include biphenyl, phenyl, 2-carboxyphenyl, 2-hydroxyphenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, imidazolyl, tetrahydronaphthyl, naphthyl,

quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl and the like.

Examples of optionally substituted cycloalkyl and optionally substituted heterocycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolidinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl, 4-(1-piperidino)-1-piperidyl, and the like.

Examples of optionally substituted amino acid moiety is, but not limited to, selected from one of following moiety:




wherein $R^{51}$ and $R^{52}$ are independently selected from hydrogen, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl and the like.

Examples of optionally substituted alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, *tert*-pentyl, *sec*-pentyl, 2-methylbutyl, hexyl, isohexyl, heptyl, isoheptyl,

octyl, isooctyl, nonanyl, isononanyl, decanyl, isodecanyl, undecanyl, isoundecanyl, dodecanyl, isododecanyl, tridecanyl, isotridecanyl, tetradecanyl, isotetradecanyl, pentadecanyl, isopentadecanyl, hexadecanyl, isohexadecanyl, heptadecanyl, isoheptadecanyl, octadecanyl, isooctadecanyl, nonadecanyl, isononadecanyl, eicosanyl, isoeicosanyl, 2-carboxyethyl and the like.

Prefered examples of optionally substituted alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decanyl, undecanyl, dodecanyl, tridecanyl, tetradecanyl, pentadecanyl, hexadecanyl, heptadecanyl, octadecanyl, nonadecanyl, eicosanyl, 2-carboxyethyl and the like.

Most preferred examples of optionally substituted alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decanyl, undecanyl, dodecanyl, tridecanyl, tetradecanyl, pentadecanyl, hexadecanyl, heptadecanyl, octadecanyl, 2-carboxyethyl and the like.

Examples of substituents for $R^{71}$ include $-R^8$, -OH, $-OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, -COOH, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NH_2$, $-NHR^8$, $-NR^8R^4$, -SH, $-SR^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2NR^8R^4$ $-SO_3H$, $-SOR^8$, $-NHC(NH_2)(=NH)$, $-NHC(NHR^8)(=NR^4)$, -CN, $-NO_2$ and halogen, wherein $R^8$ and $R^4$ is independently selected from linear or branched chain, cyclic or noncyclic, substituted or unsubstituted, alkyl chain, aryl, arylalkyl and cycloheteroalkyl moieties.

Prefered examples of the substituents include -OH, -COOH, $-OC(O)R^8$, $-OC(O)OR^8$, $-NH_2$, -SH, $-SO_3H$, $-SOR^8$, halogen, and cycloheteroalkyl (e.g., 1-piperidino).

In another embodiment, $R^{72}$ and $R^{73}$ are independently hydorogen or halogen.

Examples of halogen include fluorine, chlorine, bromine or iodine.

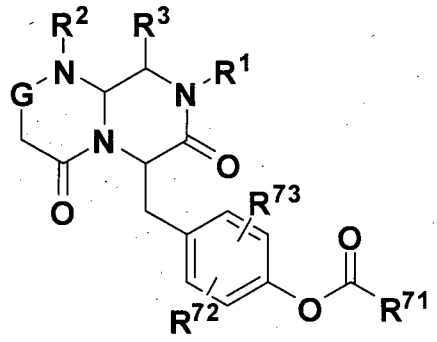
$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-; and

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-.

Preferred combinations of $R^{74}$ and $R^{75}$ are as follows.

(i) A compound having the formula (Ia) wherein $R^{74}$ is a bond and $R^{75}$ is -(CO)-:



wherein each symbol is as defined above.

In the combination, $R^{71}$ is preferably optionally substituted alkyl or optionally substituted amino acid moiety.

(ii) A compound having the formula (I) wherein $R^{74}$ is a bond and $R^{75}$ is -(CO)-O-. In the combination, $R^{71}$ is preferably optionally substituted alkyl.

(iii) A compound having the formula (I) wherein $R^{74}$ is optionally substituted lower alkylene and $R^{75}$ is -O-. In the combination, $R^{71}$ is preferably optionally substituted alkyl.

(iv) A compound having the formula (I) wherein $R^{74}$ is optionally substituted lower alkylene and $R^{75}$ is -O-. In the combination, $R^{71}$ is preferably optionally substituted alkyl.

In one embodiment, G is -NH-, $-NR^6-$, -O-, —CH2-, $-CHR^6-$ or $-C(R^6)_2-$, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl.

G is preferably -NH-, $-NR^6-$, $-CH_2-$, or -O-, more preferably $-NR^6-$ or $-CH_2-$.

Examples of alkyl group include $C_{1-4}$ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and the like.

Examples of alkenyl group include ethenyl, allyl, 1-propenyl, 2-methylallyl and the like.

Examples of alkynyl group include 1-propynyl, ethynyl and the like.

$R^6$ is preferably optionally substituted alkyl or optionally substituted alkenyl, more preferably lower alkyl (ex. methyl) or lower alkenyl (ex. allyl).

In one embodiment, $R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl, each of which is represented by the formula -Ra-$R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl.

In another embodiment, $R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl, each of which is represented by the formula -Ra-$R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted bicyclic fused aryl or optinally substituted bicyclic fused heteroaryl.

Examples of lower alkylene group include methylene, ethylene, methylmethylene, 1,2-propylene, 1,3-propylene, 1,2-butylene, 1,3-butylene, 1,4-butylene, 1,2,3-propanetriyl, 1,3,3-propanetriyl and the like.

Examples of aryl group and heteroaryl group include biphenyl, phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, imidazolyl, tetrahydronaphthyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl.

Examples of cycloalkyl group and heterocycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and the like.

In a particular embodiment of formula (I), in the above-mentioned embodiments Ra is optionally substituted lower

alkylene and $R^{10}$ is optionally substituted aryl or optionally substituted heteroaryl.

Examples of lower alkylene group include methylene, ethylene, methylmethylene, 1,2-propylene, 1,3-propylene, 1,2-butylene, 1,3-butylene, 1,4-butylene, 1,2,3-propanetriyl, 1,3,3-propanetriyl and the like.

Examples of aryl group and heteroaryl group include biphenyl, phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, imidazolyl, tetrahydronaphthyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl and the like.

Prefered examples of lower alkylene group include methylene or ethylene and the like.

Prefered examples of aryl group and heteroaryl group include bicyclic fused aryl group and bicyclic fused heteroaryl group such as naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl and the like.

Examples of substituents for $R^1$ include $-R^8$, $-OH$, $-OR^8$, $-COOH$, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NH_2$, $-NHR^8$, $-NR^8R^4$, $-SH$, $-SR^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2NR^8R^4$ $-SO_3H$, $-SOR^8$, $-NHC(NH_2)(=NH)$, $-NHC(NHR^8)NR^4$, $-OP(=O)(OH)_2$, $-OP(=O)(ONa)_2$, $-CN$, $-NO_2$ and halogen, wherein $R^8$ and $R^4$ is independently selected from linear or branched chain, cyclic or noncyclic, substituted or unsubstituted, alkyl chain, aryl and arylalkyl moieties.

Prefered examples of the substituents include $-NH_2$, $-OH$,

$-OR^8$, -COOH, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NHR^8$, $-NR^8R^4$, or halogen. More prefered examples of the substituents include $-NH_2$, -OH, -COOH, $-CONH_2$, or halogen.

In one embodiment, $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)- or $-(SO_2)-$; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl and the like.

Examples of lower alkylene group for $W^{22}$ include methylene, ethylene, propylene, butylene and the like.

Examples of lower alkylene group for Rb include methylene, ethylene, methylmethylene, 1,2-propylene, 1,3-propylene, 1,2-butylene, 1,3-butylene, 1,4-butylene, 1,2,3-propanetriyl, 1,3,3-propanetriyl and the like.

Examples of optionally substituted alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, carbamoylmethyl, carbamoylethyl, carbamoylpropyl, carbamoylbutyl, methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, methylthiomethyl, methylthioethyl, methylthiopropyl, methylthiobutyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and the like.

Examples of alkenyl group include ethenyl, allyl, 1-propenyl, 2-methylallyl and the like.

Examples of alkynyl group include 1-propynyl, ethynyl and the like.

Examples of aryl group and heteroaryl group include biphenyl, phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thinyl, furyl, thiazolyl, oxazolyl, imidazolyl, tetrahydronaphthyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl,

benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl and the like.

Examples of cycloalkyl group and heterocycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and the like.

In a particular embodiment of formula (I), in the above-mentioned embodiments $R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

Examples of lower alkylene group for Rb include methylene, ethylene, methylmethylene, 1,2-propylene, 1,3-propylene, 1,2-butylene, 1,3-butylene, 1,4-butylene, 1,2,3-propanetriyl, 1,3,3-propanetriyl and the like.

Examples of aryl group and heteroaryl group include biphenyl, phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, imidazolyl, tetrahydronaphthyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, benzotriazinyl, indenyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridotriazinyl, benzofuryl, benzothienyl, indolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, furopyridinyl, thienopyridinyl, pyrropyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl and the like.

Prefered example of aryl group and heteroaryl group include monocyclic aryl group or monocyclic heteroaryl group such as phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thienyl, furyl, thiazolyl, oxazolyl, imidazolyl and the like.

Examples of substituents for $R^{20}$ include $-R^8$, $-OH$, $-OR^8$, $-COOH$, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NH_2$, $-NHR^8$, $-NR^8R^4$, $-SH$, $-SR^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2NR^8R^4$ $-SO_3H$, $-SOR^8$, $-NHC(NH_2)(=NH)$, $-NHC(NHR^8)NR^4$, $-OP(=O)(OH)_2$, $-OP(=O)(ONa)_2$, $-CN$, $-NO_2$ and halogen, wherein $R^8$ and $R^4$ is independently selected from linear or branched chain, cyclic or noncyclic,

substituted or unsubstituted, alkyl chain, aryl and arylalkyl moieties.

Prefered examples of the substituents include $-NH_2$, $-OH$, $-OR^8$, $-COOH$, $-CONH_2$, $-CONHR^8$, $-CONR^8R^4$, $-NHR^8$, $-NR^8R^4$, or halogen.

In one embodiment, $R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl.

Examples of alkyl group include $C_{1-4}$ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and the like.

Prefered examples of alkyl group include methyl, ethyl and the like.

Examples of alkenyl group include ethenyl, allyl, 1-propenyl, 2-methylallyl and the like.

Examples of alkynyl group include 1-propynyl, ethynyl and the like.

$R^3$ is preferably hydrogen or $C_{1-4}$ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, more preferably methyl or ethyl.

The general synthesis of the compounds in this invention may be synthesized by the technique illustrated in Figures 1, 2,3 and 4.

Referring to Figures 1, 2, 3 and 4, for example, a Compound IX may have the indicated structure wherein $R^1$ and $R^3$ are as defined above, and $R^{91}$ and $R^{92}$ are a protective group suitable for use in synthesis, where this protection group may be joined to a polymeric solid support or linker to enable solid-phase synthesis. Suitable $R^{91}$ and $R^{92}$ groups include optionally substituted alkyl groups and, in a preferred embodiment, both of $R^{91}$ and $R^{92}$ are a methyl or ethyl group. Such Compound IX may be readily synthesized by reductive amination of $H_2N-R^1$ with $CH(OR^{91})(OR^{92})-C(=O)R^3$, by reductive amination of $R^{1a}$-CHO (wherein $R^1$ equals to $CH_2-R^{1a}$) with $CH(OR^{91})(OR^{92})-CHR^3NH_2$, by a displacement reaction between $H_2N-R^1$ and $CH(OR^{91})(OR^{92})-CHR^3$-LG (wherein LG refers to a leaving group, e.g., a halogen (Hal) group) or by a displacement reaction between LG-$R^1$ and $CH(OR^{91})(OR^{92})-CHR^3-NH_2$ (wherein LG refers to a

leaving group, e.g., a halogen (Hal) group).

A Compound III may have the indicated structure wherein PG is an amino protection group suitable for use in peptide synthesis, and A is defined as $CH\text{-}CH_2(C_6H_3R^{72}R^{73})\text{-}O\text{-}R^{74}\text{-}R^{75}\text{-}R^{71}$ or $CH\text{-}CH_2(C_6H_3R^{72}R^{73})\text{-}O\text{-}PG'$. PG' is a phenol protection group suitable for use in peptide synthesis. Preferred amino protection groups include 9H-fluorenylmethyloxycarbonyl (Fmoc), t-butyl dimethylsilyl (TBDMS), t-butyloxycarbonyl (BOC), methyloxycarbonyl (MOC), and allyloxycarbonyl (Alloc). Prefered phenol protection groups include methyl, ethyl, benzyl (Bzl), dichlorobenzyl ($Cl_2$-Bzl), t-butyl, chloro-trityl(Cl-Trt), bromo-benzyloxycarbonyl (Br-Z). N-Protected amino acids are commercially available; for example, Fmoc amino acids are available from a variety of sources. In the case of the azido derivative of an amino acid serving as the Compound III, such compounds may be prepared from the corresponding amino acid by the reaction disclosed by Zaloom et al. (J. Org. Chem. 46:5173-76, 1981).

A Compound VI of this invention may have the indicated structure wherein G and $R^2$ are as defined above. Other suitable Compounds VI are commercially available from a variety of sources or can be prepared by methods well known in organic chemistry.

Compound X, XI, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX and XXI are commercially available from a variety of sources or can be prepared by methods well known in organic chemistry.

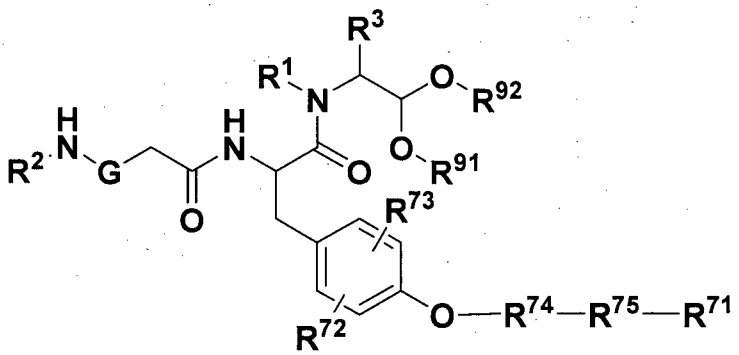
As illustrated in Figures 1, 2, 3, and 4 the alpha-helix mimetic compounds of formula (I) may be synthesized by reacting a Compound IX with a Compound X to yield a combined Compound III, followed by treating the combined Compound III with piperidine to provide Compound IV. The Compound IV reacting with Compound VI sequentially to provide a combined Compound II, and then cyclizing this intermediate to yield an alpha-helix mimetic structure of formula (I). Or, as illustrated in Figures 1, 2, 3 and 4, the alpha-helix mimetic compounds of formula (I) may be synthesized by reacting a Compound VI with a Compound XV to yield a combined Compound VII, followed by treating the Compound VII with lithiun hydroxide, sodium hydroxide or potassium hydroxide to provide

Compound VIII. The Compound VIII reacting with Compound IX sequentially to provide a combined Compound II, and then cyclizing this intermediate to yield an alpha-helix mimetic structure of formula (I). Or as illustrated in Figures 1, 2, 3 and 4, Compund I' was synthesized by mentioned same above, and then Compound I' was acylated or alkylated to yield an alpha-helix mimetic structure of formula (I). .

The preparation method of Compond (I) is not limited in the methods described herein. For example, the compounds of the present invension can be produced by modifying or converting a substituent of a compound serving as a precursor of the compounds according to method or combination of methods described in ordinary publications in the field of chemistry.

The syntheses of representative Compounds of this invention are described in working Examples.

A compound having the following general formula (II) is a novel intermediate compound for preparing the compound of the formula (I).



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid;

$R^{72}$ and $R^{73}$ are independently selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, -$NR^6$-, -O-, —$CH_2$-, -$CHR^6$- or -$C(R^6)_2$-, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is -$W^{21}$-$W^{22}$-Rb-$R^{20}$, wherein $W^{21}$ is -(CO)- or -($SO_2$)-; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl;

$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

$R^{91}$ is selected from optionally substituted alkyl, linker or solid support; and

$R^{92}$ is selected from optionally substituted alkyl, linker or solid support.

Examples and preferable embodiments of G, $R^1$, $R^2$, $R^3$, $R^{71}$, $R^{72}$, $R^{73}$, $R^{74}$, and $R^{75}$ in the formula (II) are the same as those for the formula (I).

Examples of optionally substituted alkyl for $R^{91}$ and $R^{92}$ include those as defined for $R^{71}$ and the like.

Examples of linker and solid support for $R^{91}$ and $R^{92}$ include those for preparing the libraries as explained below.

The cyclization reaction of Compound (II) for preparing Compound (I) is explained in detail in the following.

This cyclization reaction can be carried out by reacting the Compound (II) with an acid.

The order of addition of the reagents is not particularly limited, and, for example, an acid may be added to Compound (II) or vice versa.

The acid to be used in the cyclization reaction is not particularly limited, and examples thereof include inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid and the like; organic acids such as formic

acid, acetic acid, trifluoroacetic acid, propionic acid, methanesulfonic acid, *p*-toluenesulfonic acid, trifluoromethanesulfonic acid; hydrogen chloride solution; hydrogen bromide solution; hydrogen fluoride and the like.

In addition, water, anisole, m-cresol, ethanedithiol, thioanisole or triisopropylsilane can be used with along the acid.

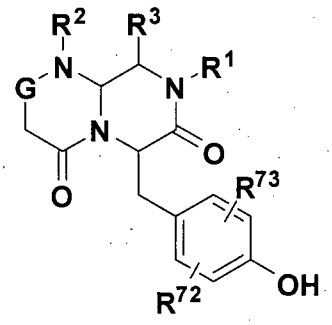
The amount of the acid to be used in the cyclization reaction is generally 0.001 mol to 1000 mol, preferably 1 mol to 100 mol, more preferably 5 mol to 50 mol, relative to 1 mol of Compound (II).

The cyclization reaction may be performed with or without solvent. The solvent to be used in the cyclization reaction may be any as long as it does not inhibit the reaction. Examples thereof include ethers such as tetrahydrofuran (THF), methyl tert-butyl ether, 1,4-dioxane, diethylene glycol dimethyl ether (diglyme), ethylene glycol dimethyl ether, 1,3-dioxolane, 2-methyltetrahydrofuran and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), sulfolane, N-methyl-2-pyrrolidinone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI), hexamethyl phosphoramide (HMPA), acetonitrile, propionitrile and the like; halogenated solvents such as methylene chloride, 1,2-dichloroethane, carbon tetrachloride, monochlorobenzene and the like; aromatic hydrocarbon such as benzene, toluene, xylene and the like; water and the like, and a mixed solvent thereof. When a mixed solvent is used, the solvents may be mixed at optional ratios.

While the reaction temperature in the cyclization reaction depends on the reagent to be used and the like, it is generally from -40°C to 120°C, preferably from -20°C to 60°C, more preferably from -10°C to 40°C. The reaction time is generally 0.5 hr to 96 hr, preferably 1 hr to 48 hr.

The compound (I) to be obtained in the cyclization reaction can be isolated and purified by a conventional method such as extraction, water-washing, acid washing, alkali washing, crystallization, recrystallization, silica gel column chromatography.

A compound having the following general formula (I') is a intermediate compound for preparing the compound of the formula (I).



wherein
$R^{72}$ and $R^{73}$ are independently selected from hydrogen or halogen;
G is -NH-, $-NR^6-$, -O-, —CH2-, $-CHR^6-$ or $-C(R^6)_2-$, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;
$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;
$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$ or $-(SO_2)-$; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl;
$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;
or a salt thereof.

Examples and preferable embodiments of $R^{72}$, $R^{73}$, G, $R^1$, $R^2$, and $R^3$ in the formula (I') are the same as those for the formula (I).

The acylating reaction, alkylating reaction or carbamate forming reaction of Compound (I') for preparing Compound (I) is explained in detail in the following.

This acylating, alkylating or carbamate forming reaction can be carried out by reacting the Compound (I') with an

acylating, alkylating or carbamate forming reagent.

The order of addition of the reagents is not particularly limited, and, for example, an acid may be added to Compound (I') or vice versa.

The acylating or alkylating reagent to be used in the acylating or alkylating reaction is not particularly limited, and examples thereof include acyl halide such as acetyl chloride, propionyl chloride, butyryl chloride, isobutyryl chloride, pentanoyl chloride, 2-methylbutyryl chloride, 3-methylbutyryl chloride, pivaloyl chrolide, hexanoyl chloride, 2-methylpentanoyl chloride, 3-methylpentanoyl chloride, 4-methylpentanoyl chloride, 2,3-dimethylbutanoyl chloride, 3,3-dimethylbutanoyl chrolide, 2,2-dimethylbutanoyl chrolide, heptanoyl chloride, isoheptanoyl chloride, octanoyl chloride, isooctanoyl chloride, nonanoyl chloride, isononanoyl chloride, decanoyl chloride, isodecanoyl chloride, undecanoyl chloride, isoundecanoyl chloride, dodecanoyl chloride, isododecanoyl chloride, tridecanoyl chloride, isotridecanoyl chloride, tetradecanoyl chloride, isotetradecanoyl chloride, pentadecanoyl chloride, isopentadecanoyl chloride, palmitoyl chloride, isopalmitoyl chloride, heptadecanoyl chloride, isoheptadecanoyl chloride, stearoyl chloride, isostearoyl chloride, nonadecanoyl chloride, isononadecanoyl chloride, icosanoyl chloride, isoicosanoyl chloride, henicosanoyl chloride, isohenicosanoyl chloride and the like; acid anhydride such as acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, pentanoic anhydride, 2-methylbutyric anhydride, 3-methylbutyric anhydride, pivalic anhydride, hexanoic anhydride, 2-methylpentanoic anhydride, 3-methylpentanoic anhydride, 4-methylpentanoic anhydride, 2,3-dimethylbutanoic anhydride, 3,3-dimethylbutanoic anhydride, 2,2-dimethylbutanoic anhydride, heptanoic anhydride, isoheptanoic anhydride, octanoic anhydride, isooctanoic anhydride, nonanoic anhydride, isononanoic anhydride, decanoic anhydride, isodecanoic anhydride, undecanoic anhydride, isoundecanoic anhydride, dodecanoic anhydride, isododecanoic anhydride, tridecanoic anhydride, isotridecanoic anhydride, tetradecanoic anhydride, isotetradecanoic anhydride, pentadecanoic anhydride, isopentadecanoic anhydride, palmitoic

anhydride, isopalmitoic anhydride, heptadecanoic anhydride, isoheptadecanoic anhydride, stearoic anhydride, isostearoic anhydride, nonadecanoic anhydride, isononadecanoic anhydride, icosanoic anhydride, isoicosanoic anhydride, henicosanoic anhydride, isohenicosanoic anhydride, succinic anhydride, phthalic anhydride, maleic anhydride and the like.

The carbamate forming reagent to be used in the carbamate forming reaction is not particularly limited, and examples thereof include 2-isocyanatopropanoic acid, 4-guanidino-2-isocyanatobutanoic acid, 4-amino-2-isocyanato-4-oxobutanoic acid, 2-isocyanatosuccinic acid, 2-isocyanato-3-mercaptopropanoic acid, 2-isocyanatopentanedioic acid, 5-amino-2-isocyanato-5-oxopentanoic acid, 2-isocyanatoacetic acid, 3-(1H-imidazol-4-yl)-2-isocyanatopropanoic acid, 2-isocyanato-3-methylpentanoic acid, 2-isocyanato-4-methylpentanoic acid, 6-amino-2-isocyanatohexanoic acid, 2-isocyanato-4-(methylthio)butanoic acid, 2-isocyanatohexanoic acid, 2-isocyanatohexanoic acid, 2-isocyanato-3-phenylpropanoic acid, 3-hydroxy-2-isocyanatopropanoic acid, 3-hydroxy-2-isocyanatobutanoic acid, 3-(3a,7a-dihydro-1H-indol-3-yl)-2-isocyanatopropanoic acid, 3-(4-hydroxyphenyl)-2-isocyanatopropanoic acid, 2-isocyanato-3-methylbutanoic acid, tert-butyl 2-isocyanatopropanoate, tert-butyl 4-guanidino-2-isocyanatobutanoate, tert-butyl 4-amino-2-isocyanato-4-oxobutanoate, 4-tert-butoxy-3-isocyanato-4-oxobutanoic acid, tert-butyl 2-isocyanato-3-mercaptopropanoate, 5-tert-butoxy-4-isocyanato-5-oxopentanoic acid, tert-butyl 5-amino-2-isocyanato-5-oxopentanoate, tert-butyl 2-isocyanatoacetate, tert-butyl 3-(1H-imidazol-4-yl)-2-isocyanatopropanoate, tert-butyl 2-isocyanato-3-methylpentanoate, tert-butyl 2-isocyanato-4-methylpentanoate, tert-butyl 6-amino-2-isocyanatohexanoate, tert-butyl 2-isocyanato-4-(methylthio)butanoate, tert-butyl 2-isocyanatohexanoate, tert-butyl 2-isocyanatohexanoate, tert-butyl 2-isocyanato-3-phenylpropanoate, tert-butyl 3-hydroxy-2-isocyanatopropanoate, tert-butyl 3-hydroxy-2-isocyanatobutanoate, tert-butyl 3-(3a,7a-dihydro-1H-indol-3-yl)-2-isocyanatopropanoate, tert-butyl 3-(4-hydroxyphenyl)-2-isocyanatopropanoate, tert-butyl 2-isocyanato-3-methylbutanoate, benzyl 2-isocyanatopropanoate,

benzyl 4-guanidino-2-isocyanatobutanoate, benzyl 4-amino-2-isocyanato-4-oxobutanoate, 4-ethoxy-3-isocyanato-4-oxobutanoic acid, ethyl 2-isocyanato-3-mercaptopropanoate, 5-(benzyloxy)-4-isocyanato-5-oxopentanoic acid, benzyl 5-amino-2-isocyanato-5-oxopentanoate, benzyl 2-isocyanatoacetate, benzyl 3-(1H-imidazol-4-yl)-2-isocyanatopropanoate, benzyl 2-isocyanato-3-methylpentanoate, benzyl 2-isocyanato-4-methylpentanoate, benzyl 6-amino-2-isocyanatohexanoate, benzyl 2-isocyanato-4-(methylthio)butanoate, benzyl 2-isocyanatohexanoate, benzyl 2-isocyanatohexanoate, benzyl 2-isocyanato-3-phenylpropanoate, benzyl 3-hydroxy-2-isocyanatopropanoate, benzyl 3-hydroxy-2-isocyanatobutanoate, benzyl 3-(3a,7a-dihydro-1H-indol-3-yl)-2-isocyanatopropanoate, benzyl 3-(4-hydroxyphenyl)-2-isocyanatopropanoate, benzyl 2-isocyanato-3-methylbutanoate and the like.

The alkylating reagent to be used in the alkylating reaction is not particularly limited, and examples thereof include 1-chlorodiethyl carbonate, 3-methoxy-1-propanol, 3-methoxy-1-propanyl chloride, 3-methoxy-1-propanyl chloride, 2-methyl-1-propionyloxxypropyl chloride, pivaloyloxymethyl chloride, acetyloxymethyl chloride and the like.

In addition, inorganic base such as sodium carbonate, sodium bicarbonate, potassium carbonate, cecium carbonate and the like; organic base such as triethylamine, pyridine, diisopropylamine and the like; can be used with along the acylating reagent.

The amount of the acylating, alkylating or carbamate forming reagent to be used in the reaction is generally 1 equivalent to 100 equivalent, preferably 1 equivalent to 10 equivalent, more preferably 1 equivalent to 5 equivalent, relative to 1 mol of Compound (I').

The acylating, alkylating or carbamate forming reaction may be performed with or without solvent. The solvent to be used in the acylating reaction may be any as long as it does not inhibit the reaction. Examples thereof include ethers such as tetrahydrofuran (THF), methyl tert-butyl ether, 1,4-dioxane, diethylene glycol dimethyl ether (diglyme), ethylene glycol dimethyl ether, 1,3-dioxolane, 2-methyltetrahydrofuran and the like; aprotic polar solvents such as N,N-dimethylformamide

(DMF), N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), sulfolane, N-methyl-2-pyrrolidinone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI), hexamethyl phosphoramide (HMPA), acetonitrile, propionitrile and the like; halogenated solvents such as methylene chloride, 1,2-dichloroethane, carbon tetrachloride, monochlorobenzene and the like; aromatic hydrocarbon such as benzene, toluene, xylene and the like; water and the like, and a mixed solvent thereof. When a mixed solvent is used, the solvents may be mixed at optional ratios.

While the reaction temperature in the acylation, alkylating or carbamate forming reaction depends on the reagent to be used and the like, it is generally from -40°C to 120°C, preferably from -20°C to 60°C, more preferably from -10°C to 40°C. The reaction time is generally 0.5 hr to 96 hr, preferably 1 hr to 48 hr.

The compound (I) to be obtained in the acylation, alkylating or carbamate formation reaction can be isolated and purified by a conventional method such as extraction, water-washing, acid washing, alkali washing, crystallization, recrystallization, silica gel column chromatography.

The alkylating reaction can also be carried out according to Mitsunobu reaction (e.g., Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. C. Organic Letters 2002, 4, 3839-3841) using $R^{71}$-$R^{75}$-$R^{74}$-OH as an alkylating reagent.

In the Mitsunobu reaction, compound (I') and 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of $R^{71}$-$R^{75}$-$R^{74}$-OH are reacted in inert solvent with the coexistence of 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of azodicarboxylates such as ethyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine and 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of phosphines such as triphenylphosphine, tributylphosphine.

Examples of the inert solvent include ethers such as tetrahydrofuran (THF), methyl tert-butyl ether, 1,4-dioxane, diethylene glycol dimethyl ether (diglyme), ethylene glycol dimethyl ether, 1,3-dioxolane, 2-methyltetrahydrofuran and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO),

sulfolane, N-methyl-2-pyrrolidinone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI), hexamethyl phosphoramide (HMPA), acetonitrile, propionitrile and the like; halogenated solvents such as methylene chloride, 1,2-dichloroethane, carbon tetrachloride, monochlorobenzene and the like; aromatic hydrocarbon such as benzene, toluene, xylene and the like. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, tetrahydrofuran, etc. are preferable.

Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

Furthermore continuing the explanation, the compounds of the present invention, salts thereof and derivatives thereof useful as prodrugs are excellent in pharmacological action selectivity, safety (various toxicities and safety pharmacology), pharmacokinetic performance, physicochemical property and the like, and therefore the usefulness as active ingredients of medicaments can be confirmed.

Examples of tests concerning pharmacological action selectivity include, but not be limited to, the following list including inhibition or activation assays on various pharmacological target receptors, inhibition assays on various pharmacological target enzymes, ion channels or transporters, cell tests to be used for the evaluation for various pharmacological action, and the like.

Examples of tests concerning safety include, but not be limited to, the following list including cytotoxic tests (e.g., tests using HL60 cells, hepatocytes, etc., and the like), genotoxicity tests (e.g., Ames test, mouse lymphoma TK test, chromosomal aberration test, micronucleus test and the like), skin sensitization tests (e.g., Buehler method, GPMT method, APT method, LLNA test and the like), skin photosensitization tests (e.g., Adjuvant and Strip method and the like), eye irritation tests (e.g., single instillation, short-term continuation instillation, repetitive instillation and the like), safety pharmacology tests for the cardiovascular system (e.g., telemetry method, APD method, hERG inhibition assay and the like), safety pharmacology tests for the central nervous

system (e.g., FOB method, modified version of Irwin method and the like), safety pharmacology tests for the respiratory system (e.g., measurement method using a respiratory function measuring apparatus, measurement method using a blood gas analyzer and the like), general toxicity tests, and the like.

Examples of tests concerning pharmacokinetic performance include, but not be limited to, the following list including cytochrome P450 enzyme substrate, inhibition or induction tests, cell permeability tests (e.g., tests using CaCO-2 cells, MDCK cells etc., and the like), drug transporter ATPase assay, oral absorption tests, blood concentration transition measurement tests, metabolism tests (e.g., stability test, metabolite molecular species test, reactivity test and the like), solubility tests (e.g., solubility test based on turbidity method and the like), and the like.

Examples of tests concerning physicochemical property include, but not be limited to, the following list including chemical stability test (e.g., stability test using HPLC etc., and the like), partition coefficient (e.g., partition test using octanol phase/water phase and the like), ionization constant test, crystallization test, and the like.

The compound of the present invention is useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents. For example, the compound of the present invention may be used for modulating a cell signaling transcription factor related peptides in a warm-blooded animal, by a method comprising administering to the animal an effective amount of the compound of formula (I).

In another embodiment, there is a method of treating a cancerous condition or fibrosis by administering the compound of formula (I). The compounds of the formula (I) can be used for inhibiting or treating disorders modulated by Wnt-signaling pathway, such as cancer, such as colorectal cancer, and so forth.

In another embodiment, a pharmaceutical composition comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof, and, if desired or necessary,

together with a pharmaceutical acceptable carrier. In another aspect, it is an object of the present invention to provide a pharmaceutical composition comprising an effective amount of the compound having general formula (I) and pharmaceutically acceptable carrier, which can be used for treatment of disorders modulated by Wnt signaling pathway, especially by TCF4-β-catenin-CBP complex.

Further, the present invention is to provide a method for inhibiting the growth of tumor cells by using the above-described composition of the present invention; a method for inducing apoptosis of tumor cells by using the above-described composition of the present invention; a method for treating a disorder modulated by TCF4-β-catenin-CBP complex by using the above-described composition of the present invention; and a method of treating cancer such as colorectal cancer by administering the composition of the present invention together with other anti-cancer agent such as 5-fluorouracil (5-FU), taxol, cisplatin, mitomycin C, tegafur, raltitrexed, capecitabine, and irinotecan, etc.

In another aspect of this invention, libraries containing alpha-helix mimetic structures of the present invention are disclosed. Once assembled, the libraries of the present invention may be screened to identify individual members having bioactivity. Such screening of the libraries for bioactive members may involve; for example, evaluating the binding activity of the members of the library or evaluating the effect the library members have on a functional assay. Screening is normally accomplished by contacting the library members (or a subset of library members) with a target of interest, such as, for example, an antibody, enzyme, receptor or cell line. Library members which are capable of interacting with the target of interest, are referred to herein as "bioactive library members" or "bioactive mimetics". For example, a bioactive mimetic may be a library member which is capable of binding to an antibody or receptor, or which is capable of inhibiting an enzyme, or which is capable of eliciting or antagonizing a functional response associated, for example, with a cell line. In other words, the screening of the libraries of the present invention determines which

library members are capable of interacting with one or more biological targets of interest. Furthermore, when interaction does occur, the bioactive mimetic (or mimetics) may then be identified from the library members. The identification of a single (or limited number) of bioactive mimetic(s) from the library yields alpha-helix mimetic structures which are themselves biologically active, and thus are useful as diagnostic, prophylactic or therapeutic agents, and may further be used to significantly advance identification of lead compounds in these fields.

Synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, in combination with the first, second and third component pieces of this invention. More specifically, any amino acid sequence may be added to the N-terminal and/or C-terminal of the conformationally constrained alpha-helix mimetic. To this end, the mimetics may be synthesized on a solid support (such as PAM resin) by known techniques (see, e.g., John M. Stewart and Janis D. Young, Solid Phase Peptide Synthesis, 1984, Pierce Chemical Comp., Rockford, III.) or on a silyl-linked resin by alcohol attachment (see Randolph et al., J. Am Chem. Soc. 117:5712-14, 1995).

In addition, a combination of both solution and solid phase synthesis techniques may be utilized to synthesize the peptide mimetics of this invention. For example, a solid support may be utilized to synthesize the linear peptide sequence up to the point that the conformationally constrained alpha-helix is added to the sequence. A suitable conformationally constrained alpha-helix mimetic structure which has been previously synthesized by solution synthesis techniques may then be added as the next "amino acid" to the solid phase synthesis (i.e., the conformationally constrained alpha-helix mimetic, which has both an N-terminus and a C-terminus, may be utilized as the next amino acid to be added to the linear peptide). Upon incorporation of the conformationally constrained alpha-helix mimetic structures into the sequence, additional amino acids may then be added to complete the peptide bound to the solid support. Alternatively,

the linear N-terminus and C-terminus protected peptide sequences may be synthesized on a solid support, removed from the support, and then coupled to the conformationally constrained alpha-helix mimetic structures in solution using known solution coupling techniques.

As to methods for constructing the libraries, traditional combinatorial chemistry techniques (see, e.g., Gallop et al., J. Med. Chem. 37:1233-1251, 1994) permit a vast number of compounds to be rapidly prepared by the sequential combination of reagents to a basic molecular scaffold. Combinatorial techniques can be used to construct peptide libraries derived from the naturally occurring amino acids. For example, by taking 20 mixtures of 20 suitably protected and different amino acids and coupling each with one of the 20 amino acids, a library of 400 (i.e., $20^2$) dipeptides is created. Repeating the procedure seven times results in the preparation of a peptide library comprised of about 26 billion (i.e., $20^8$) octapeptides.

Specifically, synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, such as those disclosed, for example, in WO 2005/116032, which is incorporated herein by reference.

In a further aspect of this invention, the present invention provides methods for screening the libraries for bioactivity and isolating bioactive library members.

In one embodiment, data of biological activity is determined in the following manner. All of compounds are assayed by using a method of the following reporter gene assay, and at least exemplified compounds showed inhibitory activity more than 49% at the concentration of 10 microM (μM).

**Reporter Gene Assay**

Screening for inhibitoty action of the Wnt signaling pathway can be carried out according to the following procedure using the stably transfected cell line Hek-293,STF1.1.

Growth Medium: DMEM, 10%FBS, Pen-Strep, supplemented with 400 μg/mL G418 to maintain selection of SuperTOPFLASH driven Luciferase gene

1. On the day prior to assay, split cells into a white opaque 96-well plate at 20,000 cells per well in 200 microliters of complete growth medium
2. Incubate the plate overnight at 37°C, 5% $CO_2$ and allow the cells to attach
3. Next day, prepare the inhibitors to be tested in complete growth medium, without G418, at 2X the desired final concentration (all conditions are done in duplicates)
4. Carefully remove the old medium from each well using a multiple pipettor
5. Add 50 microliters of fresh growth medium (without G148) containing the inhibitor to each well
6. Be sure to include 2 wells containing medium only, 2 wells for stimulation control, 2 wells for DMSO control, and wells for the positive control ICG-001 (2, 5, and 10 micromolar)
7. Once all inhibitors and controls are added, incubate the plate for 1 hour at 37°C, 5%$CO_2$
8. While plate is incubating, prepare fresh 20 mM LiCl in complete growth medium (without G418)
9. After 1 hour, remove plate from incubator and add 50 microliters of the medium containing 20 mM LiCl to each well, except for the two wells of the unstimulated control (add 50 microliters of just complete medium)
10. Incubate the plate for 24 hours at 37°C, 5%$CO_2$
11. After 24 hours, add 100 microliters of BrightGlo (Promega, Cat. #: G7573) to each well
12. Shake plate for 5 minutes to ensure complete lysis
13. Read plate on the Packard TopCount

The libraries of the present invention also can be screened for bioactivity by other various techniques and methods. For example, the screening assay may be performed by (1) contacting the mimetics of a library with a biological

target of interest, such as a receptor, to allow binding between the mimetics of the library and the target to occur, and (2) detecting the binding event by an appropriate assay, such as the calorimetric assay disclosed by Lam et al. (Nature 354:82- 84, 1991) or Griminski et al. (Biotechnology 12:1008-1011, 1994) (both of which are incorporated herein by reference). In a preferred embodiment, the library members are in solution and the target is immobilized on a solid phase. Alternatively, the library may be immobilized on a solid phase and may be probed by contacting it with the target in solution.

A method for carrying out a binding assay also can be applied as follows. The method can include providing a composition that includes a first co-activator, an interacting protein, and a test compound. The amino acid structure of the first co-activator includes a binding motif of LXXLL, LXXLI or FxxFF wherein X is any amino acid. The method further includes detecting an alteration in binding between the first co-activator and the interacting protein due to the presence of the compound, and then characterizing the test compound in terms of its effect on the binding. The assay may be carried out by any means that can measure the effect of a test compound on the binding between two proteins. Many such assays are known in the art and can be utilized in the method of the present invention, including the so-called Two-Hybrid and Split-Hybrid systems. The Two-Hybrid system, and various means to carry out an assay using this system, are described in, e.g., U.S. Patent 6,410,245. The Split-Hybrid system has been described by, e.g., Hsiu-Ming Shiu et al. Proc. Natl. Acad. Sci. USA, 93:13896-13901, November 1996; and John D. Crispino, et al. Molecular Cell, 3:1-20, February 1999. In the Split-Hybrid system, a fusion protein is utilized where protein X is fused to the lexA DNA binding domains (pLexA) and protein Y is fused to the transcription activator VP16 (pSHM.1- LacZ ). Interaction between lexA-X and VP16-Y leads to the expression of the Tetracycline repressor protein (TetR). TetR prevents transcription of the HIS3 reporter gene, making the cells unable to grow on media lacking histidine. Disruption of protein-protein interaction will restore the ability of the cells to grow on such media by shutting down expression of the

tetracycline repressor. Accordingly, compounds of the present invention may be added to the growing cells, and if the addition of the compound restores the ability of the cells to grow on the media, the compound may be seen as an effective disruptor of the protein-protein interaction. The yeast strains required to make the Split-Hybrid system work can be employed with two hybrid LexA/VP16 constructs such as those described by Stanley M. Hollenberg, et al. Molecular and Cellular Biology 15(7):3813-3822, July 1995. A useful modification of the Split-Hybrid system was utilized by Takemaru, K. I. and Moon, R. T. J. of Cell Biol. 149:249-254, 2000.

Other assay formats can also be suitable. For example, reporter gene assays for AP-1, ELISA, for example, blocking the production of IL-2 by a T-cell line after stimulation with CD3 and CD28 to look for inhibitors of IL-2 transcription. Direct binding assays (between coactivators and their partners) can be performed by surface plasmon resonance spectroscopy (Biacore, Sweden, manufactures suitable instruments) or ELISA.

Exemplary transcriptional regulators include, without limitation, VP16, VP64, p300, CBP, PCAF.SRC1 PvALF, AtHD2A and ERF-2. See, for example, Robyr et al. (2000) Mol. Endocrinol. 14:329-347; Collingwood et al. (1999) J. Mol. Endocrinol. 23:255-275; Leo et al. (2000) Gene 245:1-11; Manteuffel-Cymborowska (1999) Acta Biochim. Pol. 46:77-89; McKenna et al. (1999) J. Steroid Biochem. Mol. Biol. 69:3-12; Malik et al. (2000) Trends Biochem. Sci. 25:277-283; and Lemon et al. (1999) Curr. Opin. Genet. Dev. 9:499-504. Other exemplary transcription factors include, without limitation, OsGAI, HALF-1, C1, AP1, ARF-5, -6, -7, and -8, CPRF1, CPRF4, MYC-RP/GP, and TRAB1. See, for example, Ogawa et al. (2000) Gene 245:21 -29; 5 Okanami et al. (1996) Genes Cells 1 :87-99; Goff et al. (1991 ) Genes Dev. 5:298 -309; Cho et al. (1999) Plant Mol. Biol. 40:419-429; Ulmason et al. (1999) Proc. Natl. Acad. Sci. USA 96:5844-5849; Sprenger-Haussels et al. (2000) Plant J. 22:1-8; Gong et al. (1999) Plant Mol. Biol. 41 :33-44; and Hobo et al. (1999) Proc. Natl. Acad. Sci. USA 96:15,348-15,353.

The transcriptional coactivator can be a human

transcriptional coactivator. In another embodiment, the transcriptional coactivator is a member of the p300/CBP family of co-activators which have histone acetyltransferase activity. p300 is described for example by Eckner et al, 1994 and CBP by Bannister and Kouzarides, 1996. For the 5 purposes of the present invention, reference to p300/CBP refers to human allelic and synthetic variants of p300, and to other mammalian variants and allelic and synthetic variants thereof, as well as fragments of said human and mammalian forms of p300. In one aspect of the assay, the interacting protein is a transcription factor or a second co-activator. In one aspect of the assay, the interacting protein is any one of RIP140; SRC-1 (NCoA-1); TIF2 (GRIP-1; SRC-2); p (CIP; RAC3; ACTR; AIB-1; TRAM-1; SRC-3); CBP (p300); TRAPs (DRIPs); PGC-1; CARM-1; PRIP (ASC- 2; AIB3; RAP250; NRC); GT-198; and SHARP (CoAA; p68; p72). In another aspect of the assay, the interacting protein is any one of TAL 1; p73; MDm2; TBP; HIF-1; Ets-1; RXR; p65; AP-1; Pit-1; HNF-4; Stat2; HPV E2; BRCA1; p45 (NF-E2); c-Jun; c-myb; Tax; Sap 1; YY1; SREBP; ATF-1; ATF-4; Cubitus; Interruptus; Gli3; MRF; AFT-2; JMY; dMad; PyLT: HPV E6; CITTA; Tat; SF-1; E2F; junB; RNA helicase A; C/EBP β; GATA-1; Neuro D; Microphthalimia; E1A; TFIIB; p53; P/CAF; Twist; Myo D; pp9O RSK; c-Fos; and SV40 Large T. In another aspect of the assay, the interacting protein is any one of ERAP140; RIP140; RIP160; Trip1; SWI1 (SNF); ARA70; RAP46; TIF1; TIF2; GRIP1; and TRAP. In another aspect of the invention, the interacting protein is any one of VP16; VP64; p300; CBP; PCAF; SRC1 PvALF; AtHD2A; ERF-2; OsGAI; HALF- 1; C1; AP-1; ARF-5; ARF-6; ARF-7; ARF-8; CPRF1; CPRF4; MYC-RP/GP; and TRAB1. In another aspect of the invention, the first co-activator is CBP or p300.

The test compound is selected from compounds as described herein. For example, compounds having the formula (I). Typically, a test compound can be evaluated at several different concentrations, where these concentrations will be selected, in part, based on the conditions of the assay, e.g., the concentrations of the first co-activator and the interacting protein. Concentrations in the range of about 0.1 to 10 μM may be used. In one aspect, the assay evaluates the

relative efficacy of two compounds to affect the binding interaction between two proteins, where at least one of those two compounds is a compound of the present invention. The more effective compound can than serve as a reference compound in a study of the relationship between compound structure and compound activity.

Compounds of general formula (I) may inhibit CBP-mediated transcriptional activation in cancer cells due to their specific binding to CBP. The compounds of the present invention may also inhibit the survivin expression in SW480 cells, and therefore, inhibit the oncogenic activity in cancer cells.

The compounds of the present invention can be used for inhibiting cancer cells, and thus, would be useful for the regulation of cell growth. The compounds of the present invention can be also advantageously used for inducing apoptosis in cells.

The present invention is also related to prodrugs using the libraries containing one or more compounds of formula (I). A prodrug is typically designed to release the active drug in the body during or after absorption by enzymatic and/or chemical hydrolysis. The prodrug approach is an effective means of improving the oral bioavailability or i.v. administration of poorly water-soluble drugs by chemical derivatization to more water-soluble compounds. The most commonly used prodrug approach for increasing aqueous solubility of drugs containing a hydroxyl group is to produce esters containing an ionizable group; e.g., phosphate group, carboxylate group, alkylamino group (Fleisher et al., Advanced Drug Delivery Reviews, 115-130, 1996; Davis et al., Cancer Res., 7247-7253).

Prodrugs can result in sustained plasma drug levels due to continuous generation of the active form from plasma reservoir of prodrug that may require formulations that provide a sustained release of the active form.

In other aspects, the present invention provides pharmaceutical compositions containing a compound having the general formula (I). These compositions may be used in various methods (e.g., treating cancer, fibrosis or Alzheimer's

disease) of the present invention as described in detail below.

The pharmaceutical composition of the present invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions (e.g., injection) used for parenteral (particularly, intravenous), intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. In addition, pH may be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of

dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound, e.g., a compound having general formula (I) in the required amount, in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, syrup, granule or capsules.

Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, syrup, granule and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an

excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent I such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

For transdermal administration, the active compounds are formulated into ointments, salves, gels, creams or transdermal patches according to conventional method as generally known in the art.

For transdermal administration, suitable carriers include an oily base, an emulsifier, an emulsion stabilizer, solubilizing agent, powder component, polymer component, adhesion improver, film former, pH adjuster, antioxidant, antiseptic, preservative and the like.

Examples of the oily base include higher alcohols such as oleyl alcohol, stearyl alcohol, cetostearyl alcohol, cetanol, benzyl alcohol and the like, fatty acid esters such as ethyl acetate, isopropyl acetate, butyl acetate, diisopropyl adipate, diethyl sebacate, isopropyl myristate, octyldodecyl oleate, octyldodecyl myristate, isostearyl myristate, lanolin and the like, medium-chain triglycerides such as beef fat, olive oil and the like, fatty acid such as squalene, squalane and the like, jojoba oil, cetaceum, white petrolatum, liquid paraffin, microcrystalline wax, terpenes such as l-menthol, d-camphor, cineol, geraniol, limonene, pulegone, thymol, aphidicolin, forskolin, phytanic acid,

phytol and the like, carboxylates of terpenoids such as menthyl lactate and the like, crotamiton, esters such as diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, 2-methoxyethanol, 1,2-dimethoxyethane, etc. and the like.

Examples of the emulsifier include polyoxyethylene hydrogenated castor oil, sorbitan monostearate, sorbitan monopalmitate, glyceryl monostearate, sorbitan monolaurate, polyoxyethylene polyoxypropylene block copolymer, polysorbates (for example, polysorbate 60), sodium lauryl sulfate, sucrose fatty acid ester, lecithin and the like.

Examples of the emulsion stabilizer include higher alcohols such as cetostearyl alcohol and the like, acrylic acid polymer, carboxyvinyl polymer, polysaccharides such as xanthan gum, etc. and the like.

Examples of the solubilizing agent include water-soluble components capable of dissolving poorly water-soluble components. Examples of the component include polyvalent alcohols such as propylene glycol, 1,3-butylene glycol, glycerol and the like, low-molecular ketones such as methyl ethyl ketone, cyclohexanone and the like, macrogols and the like.

Examples of the organic and inorganic powder components include zinc oxide, titanium oxide, magnesium stearate, talc, magnesium carbonate, magnesium oxide, silicic anhydride, silicic hydride, magnesium silicate, kaolin, AEROSIL, acid clay, mica, cornstarch, aluminum metasilicate and the like.

Examples of the polymer component include acrylic acid polymer, carboxyvinyl polymer, polysaccharides such as xanthan gum and the like, polypeptides and the like.

Examples of the adhesion improver include higher alcohols such as cetostearyl alcohol and the like, acrylic acid polymer, carboxyvinyl polymer, polysaccharides such as xanthan gum and the like, polypeptides and the like.

Examples of the film forming agent include higher alcohols such as cetostearyl alcohol and the like, acrylic acid polymer, carboxyvinyl polymer, polysaccharides such as xanthan gum and the like, polypeptides, collodion, polyvinylpyrrolidone, polyvinyl alcohol, celluloses such as nitrocellulose, etc. and the like.

Examples of the pH adjuster include organic acids such as citric acid, lactic acid, tartaric acid, stearic acid, palmitic acid, oleic acid and the like, organic acid salts such as sodium pyrophosphate and the like, inorganic bases such as sodium hydroxide and the like, organic amines such as diisopropanolamine, triethanolamine, etc. and the like.

Examples of the antioxidant include dibutylhydroxytoluene (BHT), butylhydroxyanisole (BHA), α-tocopherol, erythorbic acid, sodium pyrosulfite, sodium ascorbate and the like. Examples of the stabilizer include EDTA-2Na and the like.

Examples of the antiseptic or preservative include parabens such as methylparaben and the like, benzyl alcohol, sodium dehydroacetate, sorbic acid and the like.

The transdermal patch is a laminate of an adhesive base on a backing layer. As the backing layer, a flexible material capable of freely following the stretch and shrinkage of the skin is preferable. For example, known ones such as plastic film, cloth, paper and the like can be mentioned.

The adhesive base constituting the transdermal patch comprises the active compound, the above-mentioned carriers and an adhesive. A tackifier and a softener may be added as necessary.

An adhesive base is appropriately selected from known ones in consideration of the skin safety, adhesion to the skin and the like. For example, an adhesive can be selected from acrylic type, rubber type, silicone type and the like.

As the acrylic type, for example, a (co)polymer mainly comprising (meth)acrylic acid alkyl ester can be mentioned. This (co)polymer may be a copolymer of two or more kinds of (meth)acrylic acid alkyl esters, or a copolymer of a functional monomer capable of copolymerization with (meth)acrylate alkyl ester and (meth)acrylic acid alkyl ester.

As the rubber type, for example, those comprising a rubber adhesive as a main component, such as natural rubber, polyisopropylene rubber, polyisobutylene rubber, styrene-isoprene-styrene block copolymer, styrene-butadiene-styrene block copolymer and the like can be mentioned.

As the silicone type, for example, those comprising a

silicone rubber as a main component, such as polydimethyl siloxane, diphenyl siloxane and the like can be mentioned.

As the tackifier, rosin, hydrogenated rosin, rosin ester, hydrogenated rosin ester, polyterpene resin, oil-soluble phenol resin and the like can be mentioned.

A softener plasticizes and softens the above-mentioned adhesive and tackifier to impart suitable adhesiveness to the skin. For example, almond oil, olive oil, camellia oil, persic oil, peanut oil, olefin acid, liquid paraffin and the like can be used.

A transdermal patch may contain conventionally known inorganic fillers, plasticizers, stabilizers, UV absorbers, preservatives, fragrances and the like as necessary.

In the present invention, the amount of the active compound to be contained in the above-mentioned ointment, salve, gel, cream or transdermal patch as an active ingredient is selected from the range of 0.01-10 w/w%, preferably 0.1-10 w/w%, more preferably 0.2-5 w/w%, and still more preferably 1-5 w/w%, of the entire amount of the composition.

The cosmetic composition of the present invention may contain various components generally used as cosmetic or skin external preparations as long as the effect the active compound of the present invention is not inhibited. Examples of such components include blood circulation enhancer, oily base, surfactant, polymeric substance, solvent, powder substance, antioxidant, anti-inflammatory agent, UV absorber, skin-lightening agent, cellular stimulant, moisturizing agent, metal chelating agent, dyes, flavor, transdermal absorption enhancer and the like.

Examples of the blood circulation enhancer include powdered capsicum, capsicum tincture, capsicum essence, capsaicin, homocapsaicin, homodihydrocapsaicin, vanillyl nonanamide and the like, capsaicin, ginger extract, capsicum extract, nicotinic acid, sophorae radix extract, Astragalus root extract, zingiber siccatum extract, safflower extract, Japanese pepper extract, Salvia miltiorrhiza extract, panacis japonici rhizoma extract, ginseng extract, γ-aminobutyric acid (GABA) and the like.

Examples of the oily base include hydrocarbons such as

squalane, liquid paraffin, light liquid isoparaffin, heavy liquid isoparaffin, microcrystalline wax, solid paraffin and the like, silicones such as dimethicone, phenyldimethicone, cyclomethicone, amodimethicone, polyether-modified silicones and the like, esters such as jojoba oil, carnauba wax, rhus succedanea fruit wax, beeswax, whale wax, octyldodecyl oleate, isopropyl myristate, neopentylglycol diisostearate, diisostearyl malate and the like, fatty acids such as stearic acid, lauric acid, myristic acid, palmitic acid, isostearic acid, isopalmitic acid, behenic acid, oleic acid and the like, acylamino acids such as acyl glutamate, acylglycine, acylalanine, acylsarcosine and the like, higher alcohols such as behenyl alcohol, cetyl alcohol, oleyl alcohol, octadecyl alcohol and the like, triglycerides such as castor oil, coconut oil, hydrogenated coconut oil, camellia Japonica oil, wheatgerm oil, glycelyl triisostearate, glycelyl isooctanoate, olive oil etc., and the like.

Examples of the surfactant include nonionic surfactants such as sorbitan sesquioleate, sorbitan monooleate, sorbitan trioleate, sorbitan sesquistearate, sorbitan monostearate, sorbitan polyoxyethylene monooleate, sorbitan polyoxyethylene monostearate, polyoxyethylene stearate, polyoxyethylene oleate, polyoxyethylene glycerol fatty acid ester, polyoxyethylene alkylether, polyoxyethylene hydrogenated castor oil and the like, anionic surfactants such as sodium lauryl stearate, polyoxyethylenealkyl sulfate, sulfosuccinate salt, acylglutamate salt, acylsarcosinate salt, acylglycinate salt, acylalaninate salt and the like, cationic surfactants such as quaternary alkylammonium salt and the like, amphoteric surfactants such as alkylbetaine and the like, emulsifiers, solubilizers and the like.

Examples of the solvent include lower alcohols such as ethanol and the like, polyvalent alcohols such as 1,2-pentanediol, 1,2-hexylene glycol, isoprene glycol and the like, ethers and the other organic solvents, water and the like.

Examples of the polymeric substance include polyamino acids such as polyaspartic acid, ε-polylysine, γ-polyglutamic acid and the like and derivatives thereof, natural polymeric

compounds such as collagen, elastin and the like, semisynthetic polymer compounds such as partially deacetylated chitin and the like, synthetic polymer compounds such as carboxymethylcellulose etc., and the like.

Examples of the powder substance include organic powders such as crystalline cellulose, crosslinking methylpolysiloxane, polyethylene powder, acrylic resin powder and the like, optionally surface-treated powders such as talc, mica, sericite, magnesium carbonate, calcium carbonate, titanium dioxide, iron oxide, iron blue, ultramarine blue, titanium mica, titanium sericite, silica and the like, pearlescent pigments such as hybrid fine powder, titanium dioxide-coated mica and the like, polymer powders such as photochromic pigment, nylon powder and the like, organic powders such as N-ε-lauroyllysine etc., and the like.

Examples of the dye include legal tar dye first category, legal tar dye second category, legal tar dye third category, hair dye, natural dye, mineral dye and the like.

Examples of the flavor include animal flavor such as musk and the like, plant flavors such as jasmine oil and the like, synthetic flavors such as α-amylcinnamaldehyde and the like, blended flavors and the like.

Examples of the transdermal absorption enhancer include urea, 2-pyrrolidone, 1-hexanol, 1-octanol, 1-decanol, 1-menthol, sodium lauryl sulfate, isopropyl myristate, n-hexyl acetate, oleic acid and the like.

The active compound of the present invention can be used as cosmetics for skin and hair by adding, where necessary, the aforementioned various other components according to a conventional method. The dosage form thereof is not particularly limited, and can take any dosage form such as solution state, paste state, gel state, solid state, powder state and the like. Examples thereof include oil, lotion, cream, emulsion, gel, shampoo, hair rinse, hair conditioner, enamel, foundation, lipstick, face powder, pack, ointment, granule, capsule, perfume, powder, cologne, toothpaste, soap, aerosol, cleansing foam and the like. Furthermore, the active compound of the present invention can also be used for pharmaceutical agents or quasi-drugs for the

prevention or improvement of various dermatic diseases, such as hair-growth medicine, an agent for antiaging and improving skin, skin essence, an agent for preventing and improving skin roughness due to capped skin crack and the like.

While the content of the active compound of the present invention in cosmetic compositions also varies depending on the kind of component, it only needs to be contained at a level permitting provision of a desired effect depending on the type of use, which is, for example, about 0.01 to 50 wt%, preferably about 0.01 to 10 wt%, more preferably about 0.01 to 5 wt% of the cosmetic composition.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It can be advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a 5 predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the

dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For instance, in certain embodiments, a pharmaceutical composition of the present invention is one suitable for oral administration in unit dosage form such as a tablet or capsule that contains from about 1 mg to about 1 g of the compound of this invention. In some other embodiments, a pharmaceutical composition of the present invention is one suitable for intravenous, subcutaneous or intramuscular injection. A patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of about 1 μg/kg to about 1g/kg of the compound of the present invention. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection or by continuous infusion over a period of time. Alternatively a patient will receive a daily oral dose approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

In one embodiment, the compound of the formula (I) of the present invention can be administered orally to mammals inclusive of human.

In the case, the dose is selected appropriately depending on various factors such as the body weight and/or age of patients, and/or the degree of the symptom and an administration route. For example, the dose of the compound of the formula (I) for oral administration is generally in the range of 1 to 10000 mg/day/kg body weight per day, preferably in the range of 1 to 5000 mg/day/kg body weight per day, and more preferably 10 to 5000 mg/day/kg body weight per day, once or in 2 to 3 divided portions daily.

Preferably, the compound of the formula (I) of the present invention can be administered oraly to mammals inclusive of human.

In the case, the dose is selected appropriately depending on various factors such as the body weight and/or age of patients, and/or the degree of the symptom and an administration route. For example, the dose of the compound of

the formula (I) for intravenous administration is generally in the range of 0.1 to 10000 mg/day/$m^2$ human body surface area, preferably in the range of 0.1 to 5000 mg/day/$m^2$ human body surface area, and more preferably 1 to 5000 mg/day/$m^2$ human body surface area by oral administration.

The pharmaceutical composition containing the compound of general formulae (I) can be used for treatment of disorders modulated by Wnt signaling pathway, especially cancer, more especially colorectal cancer.

In one aspect, the present invention provides methods for inhibiting tumor growth. Such methods comprise the step of administering to a subject (e.g., a mammalian subject) having a tumor a compound with general formula (I) in an amount effective to inhibit tumor growth. A compound or composition inhibits tumor growth if the tumor sizes are statistically significantly smaller in subjects with the treatment of the compound or composition than those without the treatment.

The inhibitory effect of a particular compound or composition of the present invention on tumor growth may be characterized by any appropriate methods known in the art. For instance, the effect of the compound or composition on survivin expression may be measured. Compounds or compositions down-regulate survivin expression are likely to have inhibitory effects on tumor growth. In addition, assays using tumor cell lines (e.g., soft agar assays using SW480 cells) and animal models for tumor growth (e.g., nude mice grafted with tumor cells and Min mouse model) may also be used to evaluate the inhibitory effect on tumor growth of a given compound or composition as described in detail in the examples. Other exemplary animal models or xenografts for tumor growth include those for breast cancer (Guo et al, Cancer Res. 62: 4678-84, 2002; Lu et al, Breast Cancer Res. Treat. 57: 183-92, 1999), pancreatic cancer (Bouvet et al, Cancer Res. 62: 1534-40, 2002), ovarian tumor (Nilsson et al, Cancer Chemother. Pharmacol. 49: 93- 100, 2002; Bao et al, Gynecol. Oncol. 78: 373-9, 2000), melanoma (Demidem et al, Cancer Res. 61: 2294-300, 2001), colorectal cancer (Brown et al, Dig. Dis. Sci. 45: 1578-84, 2000; Tsunoda et al, Anticancer Res. 19: 1149-52, 1999; Cao et al, Clin. Cancer Res. 5: 267-74, 1999; Shawler et

al, J. Immunother. Emphasis Tumor Immunol. 17: 201-8, 1995; McGregor et al, Dis. Colon. Rectum. 36: 834-9, 1993; Verstijnen et al, Anticancer Res. 8: 1193-200, 1988), hepatocellular cancer (Labonte et al, Hepatol. Res. 18: 72-85, 2000), and gastric cancer (Takahashi et al, Int. J. Cancer 85: 243-7, 2000).

The compound or composition that inhibits tumor growth may be administrated into a subject with a tumor via an appropriate route depending on, for example, the tissue in which the tumor resides. The appropriate dosage may be determined using knowledge and techniques known in the art as described above. The effect of the treatment of the compound or composition on tumor growth may also be monitored using methods known in the art. For instance, various methods may be used for monitoring the progression and/or growth of colorectal cancer, including colonoscopy, sigmoidoscopy, biopsy, computed tomograph, ultrasound, magnetic resonance imaging, and positron emission tomography. Methods for monitoring the progression and/or growth of ovarian cancer include, for example, ultrasound, computed tomography, magnetic resonance imaging, chest X-ray, laparoscopy, and tissue sampling.

In a related aspect, the present invention provides a method for treating or preventing cancer or fibrosis. Such methods comprise the step of administering to a subject in need thereof a compound or composition having general formula (I) in an amount effective to treat or prevent cancer or fibrosis in the subject. Treating cancer (or fibrosis) is understood to encompass reducing or eliminating cancer progression, e.g., cancer growth and metastasis (or fibrosis, as applicable). Preventing cancer (or fibrosis) is understood to encompass preventing or delaying the onset of cancer (or fibrosis, as applicable). Various types of cancer may be treated or prevented by the present invention. They include, but are not limited to, lung cancer, breast cancer, colorectal cancer, stomach cancer, pancreatic cancer, liver cancer, uterus cancer, ovarian cancer, gliomas, melanoma, lymphoma, and leukemia. A subject in need of treatment may be a human or non-human primate or other animal with various types of cancer.

A subject in need of prevention may be a human or non-human primate or other animal that is at risk for developing cancer or fibrosis. Methods for diagnosing cancer (or fibrosis) and screening for individuals with high risk of cancer (or fibrosis) are known in the art and may be used in the present invention. For instance, colorectal cancer may be diagnosized by fecal occult blood test, sigmoidoscopy, colonoscopy, barium enema with air contrast, and virtual colonoscopy. An individal with high risk of colorectal cancer may have one or more colorectal cancer risk factors such as a strong family history of colorectal cancer or polyps, a known family history of hereditary colorectal cancer syndromes, a personal history of adenomatous polyps, and a personal history of chronic inflammatory bowel disease.

A compound with general formula (I) useful in cancer (or fibrosis) treatment or prevention may be identified by appropriate methods known in the art. Methods that may be used to select compounds for inhibitory effect on tumor growth as described above may also be used. The route of administration, the dosage of a given compound, the effectiveness of the treatment may be determined using knowledge and techniques known in the art. Factors that may be considered in making such a determination include, for example, type and stage of the cancer (or fibrosis) to be treated.

The compound with general formula (I) useful in cancer treatment and prevention may be administered in combination with an other anti-neoplastic agent. The anti-neoplastic agent refers to a compound that inhibits tumor growth.

Specific examples of the other anti-neoplastic agent include alkylating agents such as thiotepa and CYTOXAN (RTM) cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic

analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammaI and calicheamicin omegaI1 (see, e.g., Agnew, Chem Intl. Ed. Engl. 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRLAMYCIN (RTM) doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU), tegafur, raltitrexed; folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine;

bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK (RTM) polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL (RTM) paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE (RTM) Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Illinois), and TAXOTERE (RTM) doxetaxel (Rhne-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR (RTM) gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE (RTM) vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

In addition, examples of the other anti-neoplastic agent also include anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX (RTM) tamoxifen), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON toremifene; aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE (RTM)

megestrol acetate, AROMASIN (RTM) exemestane, formestane, fadrozole, RIVISOR (RTM) vorozole, FEMARA (RTM) letrozole, and ARIMIDEX (RTM) anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in abherant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; ribozymes such as a VEGF expression inhibitor (e.g., ANGIOZYME (RTM) ribozyme) and a HER2 expression inhibitor; vaccines such as gene therapy vaccines, for example, ALLOVECTIN (RTM) vaccine, LEUVECTIN (RTM) vaccine, and VAXID (RTM) vaccine; PROLEUKIN (RTM) rIL-2; LURTOTECAN (RTM) topoisomerase 1 inhibitor; ABARELIX (RTM) rmRH; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Moreover, examples of the other anti-neoplastic agent also include a "growth inhibitory agent" referring to a compound or composition which inhibits growth of a cell in vitro and/or in vivo. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), TAXOL (RTM), and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C.

Furthermore, examples of the other anti-neoplastic agent also include a "molecular target drug" that blocks the proliferation and metastasis of cancer by interfering with specific molecules involved in carcinogenesis (the process by which normal cells become cancer cells), tumor growth, or tumor spread. Specific examples of the "molecular target drug" include kinase inhibitors that inhibit kinase activity on

tumors, including, for example, imatinib, erlotinib, gefitinib, sunitinib, sorafenib, dasatinib, nilotinib; antibodies that bind to the cell surface molecule on tumor cells or to the growth factor and the like such as, for example, ibritumomab, cetuximab, trastuzumab, panitumumab, bevacizumab, rituximab; and proteasome inhibitors that inhibit the proteasome which regulates protein expression and function by degradation of ubiquitinylated proteins, such as bortezomib; and pharmaceutically acceptable salts, acids or derivatives of any of above.

Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (W B Saunders: Philadelphia, 1995), especially p. 13.

A compound with general formula (I) administered in combination with an anti-neoplastic agent does not necessarily require that the compound and the anti-neoplastic agent be administered concurrently. The compound and the agent may be administered separately as long as at a time point, they both have effects on same cancer cells.

For example, the administration mode may be exemplified by (1) administration of a single preparation obtained by simultaneously formulating the compound of formula (I) and the other anti-neoplastic agent, (2) simultaneous administration through the same administration route of two preparations obtained by separately formulating the compound of formula (I) and the other anti-neoplastic agent, (3) administration with a time interval through the same administration route of two preparations obtained by separately formulating the compound of formula (I) and the other anti-neoplastic agent, (4) simultaneous administration through different administration routes of two preparations obtained by separately formulating the compound of formula (I) and the other anti-neoplastic agent, (5) administration with a time interval through different administration routes of two preparations obtained by separately formulating the compound of formula (I) and the other anti-neoplastic agent (e.g., administration in order of the compound of formula (I) and then the other anti-neoplastic

agent, or administration in the reverse order), or the like. The amount of the other anti-neoplastic agent to be administered can be appropriately selected with reference to the clinically used dosage. The mixing ratio of the compound of the compound of formula (I) and the other anti-neoplastic agent can be appropriately selected in accordance with the subject of administration, administration route, disease to be treated, symptoms, combination, and the like.

In addition, the compound of the present invention can be also used in combination with, for example, gene therapy involving VEGF, TNFα or the like, or therapeutic methods involving various antibody medicines or the like.

In a further related aspect, the present invention provides methods for promoting apoptosis in cancer cells. Such methods comprise the step of contacting cancer cells with a compound having general formula (I) in an amount effective to promote apoptosis in these cells. A compound promotes apoptosis if the number of cancer cells undergoing apoptosis is statistically significantly larger in the presence of the compound than that in the absence of the compound. Such compounds may be identified by methods known in the art (e.g., measuring caspase activities and/or cell death) using cultured cancer cell lines, xenografts, or animal cancer models. Preferably, the compound is more active in promoting apoptosis in cancer cells than in normal cells. Cancer cells treatable by the present method may be from various tissue origins.

In another aspect of the present invention, a method for treating a disorder modulated by Wnt signaling pathway in which the method comprises administering to a patient a safe and effective amount of the compounds having general formula (I) is disclosed. Pharmaceutical composition containing the compound of the present invention can be also used for this purpose. In this connection, it is found in the present invention that the compounds having general formula (I) or the pharmaceutical composition containing thereof can be useful for the treatment of disorder modulated by TCF4/β-catenin/CBP complex, which is believed to be responsible for initiating the overexpression of cancer cells related to Wnt signaling pathway. Thus, it is another aspect of the present invention

to provide a method for the treatment of disorder modulated by TCF4/β-catenin/CBP complex, using the compounds having the general formula (I).

The present invention also provides compounds and methods for inhibiting survivin expression. Survivin is a target gene of the TCF/β-catenin pathway, and more specifically is a target gene of the TCF/β-catenin/CBP pathway. It is a member of the IAP (Inhibitor of Apoptosis Protein) family of proteins. Biological activity associated with survivin includes: highly expressed at G2/M, regulating cell cycle entry and exit; associated with microtubule, centrosomes, centromeres and midbody depending upon the phases of the cell cycle; and anti-apoptosis via interacting directly or indirectly with caspases (e.g., caspase 3, 7 and 9). In connection with cancer, survivin is widely and highly expressed in tumor cells, but expressed to little or no extent in normal tissue cells. Also, it has been observed that cancer patients whose tumors expressed survivin had a decreased overall survival. Furthermore, the degree of survivin expression has been correlated with other cancer markers, e.g., Ki67, PNCA, p53, APC, etc.

The effect of a particular compound of the present invention on survivin expression may be characterized by methods known in the art. Such methods include methods for characterizing survivin expression at the transcriptional or translational level. Exemplary methods for characterizing survivin expression at the transcriptional level are: cDNA microarry, reverse transcription-polymerase chain reaction (RT-PCR), chromatin immunoprecipitation (ChIP), and assays for reporter activities driven by survivin promoter. Exemplary methods for characterizing survivin expression at the translational level are: Western blot analysis, immunochemistry and caspase activities. Detailed descriptions of the above exemplary methods may be found in the examples below.

As described above, the present invention provides methods for inhibiting survivin expression. Such methods comprise the step of contacting a survivin-expressing cell with a compound of the present invention in an amount

effective to inhibit survivin expression. A compound inhibits survivin expression if survivin expression in a cell is decreased in the presence of the compound compared to survivin expression in the absence of the compound. Survivin-expressing cells include tumor cells that express, such as cells in or from lung cancer, breast cancer, stomach cancer, pancreatic cancer, liver cancer, uterus cancer, ovarian cancer, gliomas, melanoma, colorectal cancer, lymphoma and leukemia. The step of contacting the survivin-expressing cells with the compound may be performed *in vitro*, *ex vivo*, or *in vivo*. A compound useful in inhibiting survivin expression may be identified, and the effects of a particular compound of the present invention may be characterized, by appropriate methods known in the art, as described in detail above.

Compounds of the present invention also may inhibit the expression of survivin. Blanc-Brude et al., Nat. Medicine 8:987 (2002), have shown that survivin is a critical regulator of smooth muscle cell apoptosis which is important in pathological vessel-wall remodeling. Accordingly, another aspect of the present invention provides a method of treating or preventing restenosis associated with angioplasty comprising administering to a subject in need thereof a safe and effective amount of an alpha-helix mimetic of the present invention. In one embodiment the invention treats the restenosis, i.e., administration of an alpha-helix mimetic of the present invention to a subject having restenosis achieves a reduction in the severity, extent, or degree, etc. of the restenosis. In another embodiment the invention prevents the restenosis, i.e., administration of an alpha-helix mimetic of the present invention to a subject that is anticipated to develop new or additional restenosis achieves a reduction in the anticipated severity, extent, or degree, etc. of the restenosis. Optionally, the subject is a mammalian subject.

Compounds of the present invention also may inhibit TCF/β-catenin transcription. Rodova et al., J. Biol. Chem. 277:29577 (2002), have shown that PKD-1 promoter is a target of the TCF/β-catenin pathway. Accordingly, another aspect of the present invention provides a method of treating or preventing polycystic kidney disease comprising administering

to a subject in need thereof a safe and effective amount of an alpha-helix mimetic of the present invention. In one embodiment the invention treats the polycystic kidney disease, i.e., administration of an alpha-helix mimetic of the present invention to a subject having polycystic kidney disease achieves a reduction in the severity, extent, or degree, etc. of the polycystic kidney disease. In another embodiment the invention prevents polycystic kidney disease, i.e., administration of an alpha-helix mimetic of the present invention to a subject that is anticipated to develop new or additional polycystic kidney disease achieves a reduction in the anticipated severity, extent, or degree, etc. of the polycystic kidney disease. Optionally, the subject is a mammalian subject.

Compounds of the present invention also may inhibit the expression of Wnt signaling. Hanai et al., J. Cell Bio. 158:529 (2002), have shown that endostatin, a known anti-angiogenic factor, inhibits Wnt signaling. Accordingly, another aspect of the present invention provides a method of treating or preventing aberrant angiogenesis disease comprising administering to a subject in need thereof a safe and effective amount of an alpha-helix mimetic of the present invention. In one embodiment the invention treats the aberrant angiogenesis disease, i.e., administration of an alpha-helix mimetic of the present invention to a subject having aberrant angiogenesis disease achieves a reduction in the severity, extent, or degree, etc. of the aberrant angiogenesis disease. In another embodiment the invention prevents aberrant angiogenesis disease, i.e., administration of an alpha-helix mimetic of the present invention to a subject that is anticipated to develop new or additional aberrant angiogenesis disease achieves a reduction in the anticipated severity, extent, or degree, etc. of the aberrant angiogenesis disease. Optionally, the subject is a mammalian subject.

Compounds of the present invention also may inhibit Wnt TCF/β-catenin signalling. Accordingly, another aspect of the invention provides a method of treating or preventing tuberous sclerosis complex (TSC) comprising administering to a subject in need thereof a safe and effective amount of an alpha-helix

mimetic the present invention. Subjects having TSC typically develop multiple focal lesions in the brain, heart, kidney and other tissues (see, e.g., Gomez, M. R. Brain Dev. 17(suppl): 55-57 (1995)). Studies in mammalian cells have shown that overexpression of TSC1 (which expresses hamartin) and TSC2 (which expresses tuberin) negatively regulates cell proliferation and induces G1/S arrest (see, e.g., Miloloza, A. et al., Hum. Mol. Genet. 9: 1721 -1727 (2000)). Other studies have shown that hamartin and tuberin function at the level of the β-catenin degradation complex, and more specifically that these proteins negatively regulate β-catenin stability and activity by participating in the β-catenin degradation complex (see, e.g., Mak, B.C., et al. J. Biol. Chem. 278(8): 5947-5951, (2003)). β-catenin is a 95-kDa protein that participates in cell adhesion through its association with members of the membrane-bound cadherin family, and in cell proliferation and differentiation as a key component of the Wnt/Wingless pathway (see, e.g., Daniels, D.L., et al., Trends Biochem. Sci 26: 672-678 (2001)). Misregulation of this pathway has been shown to be oncogenic in humans and rodents. The present invention provides compounds that modulate β-catenin activity, and particularly its interactions with other proteins, and accordingly may be used in the treatment of TSC. Thus, in one embodiment the invention treats TSC, i.e., administration of an alpha-helix mimetic of the present invention to a subject having TSC achieves a reduction in the severity, extent, or degree, etc. of the TSC. In another embodiment the invention prevents TSC, i.e., administration of an alpha-helix mimetic of the present invention to a subject that is anticipated to develop new or additional TSC achieves a reduction in the anticipated severity, extent, or degree, etc. of the TSC. Optionally, the subject is a mammalian subject.

Compounds of the present invention also may inhibit the expression of Wnt signalling. The Kaposi's sarcoma-associated herpesvirus (KSHV) latency-associated nuclear antigen (LANA) is expressed in all KSHV-associated tumors, including Kaposi's sarcoma (KS) and β-cell malignancies such as primary effusion lymphoma (PEL) and multicentric Castleman's disease. Fujimuro, M. et al., Nature Medicine 9(3):300-306 (2003), have shown

that LANA acts to stabilize β-catenin, apparently by redistribtution of the negative regular GSK-3β. The present invention provides compounds and methods for inhibiting β-catenin protein interactions, e.g., β-catenin/TCF complex formation. Thus, the compounds of the present invention thwart the LANA-induced accumulation of β-catenin/TCF complex and, at least in part, the consequences of KSHV infection. Accordingly, another aspect of the present invention provides a method of treating or preventing conditions due to infection by Kaposi's sarcoma-associated herpesvirus (KSHV). Such conditions include KSHV-associated tumors, including Kaposi's sarcoma (KS) and primary effusion lymphoma (PEL). The method comprises administering to a subject in need thereof a safe and effective amount of an alpha-helix mimetic the present invention. In one embodiment the invention treats the KSHV-associated tumor, i.e., administration of an alpha-helix mimetic of the present invention to a subject having a KSHV-associated tumor achieves a reduction in the severity, extent, or degree, etc. of the tumor. In another embodiment the invention prevents a KSHV-associated tumor, i.e., administration of an alpha-helix mimetic of the present invention to a subject that is anticipated to develop new or additional KSHV-associated tumors achieves a reduction in the anticipated severity, extent, or degree, etc. of the tumor. Optionally, the subject is a mammalian subject.

LEF/TCF DNA-binding proteins act in concert with activated β-catenin (the product of Wnt signaling) to transactivate downstream target genes. DasGupta, R. and Fuchs, E. Development 126(20):4557-68 (1999) demonstrated the importance of activated LEF/TCF complexes at distinct times in hair development and cycling when changes in cell fate and differentiation commitments take place. Furthermore, in skin morphogenesis, β-catenin has been shown to be essential for hair follicle formation, its overexpression causing the "furry" phenotype in mice (Gat, U., et al. Cell 95:605-614 (1998) and Fuchs, E. Harvey Lect. 94:47-48 (1999). See also Xia, X. et al. Proc. Natl. Aad. Sci. USA 98:10863-10868 (2001). Compounds of the present invention have been shown to inhibit the expression of Wnt signaling, and interfere with formation

of β-catenin complexes. Accordingly, the present invention provides a method for modulating hair growth comprising administering to a subject in need thereof a safe and effective amount of an alpha-helix mimetic the present invention, where the amount is effective to modulate hair growth in the subject. Optionally, the subject is a mammalian subject.

The present invention also provides compounds that may be useful in treating or preventing Alzheimer's disease. Alzheimer's disease (AD) is a neurodegenerative disease with progressive dementia. This disease is accompanied by three main structural changes in the brain, namely, i) intracellular protein deposits (also known as neurofibrillary tangles, or NFT), ii) extracellular protein deposits termed amyloid plaques that are surrounded by dystrophic neuritis, and iii) diffuse loss of neurons.

The compounds or compositions of the present invention may rescue defects in neuronal differentiation caused by a presenilin-1 mutation and may decrease the number, or rate at which neuronal precursor populations differentiate to neurons in Alzheimer's brains. Presenilins are transmembrane proteins whose functions are related to trafficking, turnover and cleavage of Notch and Amyloid Precursor Protein. Missense mutations in presenilin 1 (PS-1) are associated with early-onset familial Alzheimer's disease (Fraser et al, Biochem. Soc. Symp. 67, 89 (2001)). The compounds of the present invention may be applicable not only to individuals with PS-1 familial Alzheimer's mutations, but also to general Alzheimer's patients.

In addition, the present invention can provide a method for treating or preventing Alzheimer's disease comprising administering to a subject in need thereof a safe and effective amount of an alpha-helix mimetic of the present invention, where the amount is effective to treat or prevent Alzheimer's disease in the subject. Treating Alzheimer's disease is understood to encompass reducing or eliminating the manifestation of symptoms characteristic of Alzheimer's disease, or delaying the progression of this disease. Preventing Alzheimer's disease is understood to encompass

preventing or delaying the onset of this disease.

A subject in need of treatment may be a human or non-human primate or other animal that is at various stages of Alzheimer's disease. Methods for diagnosing Alzheimer's disease are known in the art (see, e.g., Dinsmore, J. Am. Osteopath. Assoc. 99.9, Suppl. S1-6, 1999; Kurz et al., J. Neural Transm. Suppl. 62: 127-33, 2002; Storey et al., Front Viosci. 7: e155-84, 2002; Marin et al., Geriatrics 57: 36-40, 2002; Kril and Halliday, Int. Rev. Neurobiol. 48: 167-217, 2001; Gurwitz, Trends Neurosci. 23: 386, 2000; Muller- Spahn and Hock, Eur. Arch. Psychiatry Clin. Neurosci. 249 Suppl. 3: 37-42; Fox and Rossor, Rev. Neuro. (Paris) 155 Suppl. 4: S33-7, 1999), including the use of neuropsychological measures, functional imaging measures, biological markers, and autopsy of brain tissue. A subject in need of prevention may be a human or non-human primate or other animal that is at risk for developing Alzheimer's disease, such as an individual having a mutation of certain genes responsible for this disease (e.g., genes encoding amyloid precursor protein, presenilin 1, and presenilin 2), and/or a gene involved in the pathogenesis of this disease (e.g., apolipoprotein E gene) (Rocchi et al., Brain Res. Bull. 61: 1- 24, 2003).

Compounds with structures as set forth in formula (I) may be screened for their activities in treating or preventing Alzheimer's disease by any appropriate methods known in the art. Such screening may be initially performed using in vitro cultured cells (e.g, PC-12 cells). Compounds capable of rescuing defects in neuronal differentiation caused by a presenilin 1 mutation may be further screened using various animal models for Alzheimer's disease. Alternatively, compounds with structures as set forth in formula (I) may be directedly tested in animal models for Alzheimer's disease. Many model systems are known in the art and may be used in the present invention (see, e.g., Rowan et al., Philos. Trans. R. Soc. Lond. B. Biol. Sci. 358: 821-8, 2003; Lemere et al., Neurochem. Res. 28: 1017- 27, 2003; Sant'Angelo et al., Neurochem. Res. 28: 1009-15, 2003; Weiner Harv. Rev. Psychiatry 4: 306-16, 1997). The effects of the selected compounds on treating or preventing Alzheimer's disease may be

characterized or monitored by methods known in the art for evaluating the progress of Alzheimer's disease, including those described above for diagnosing this disease.

The present invention also provides methods for promoting neurite outgrowth. Such methods comprise the step of contacting a neuron with a compound according to formula (I) in an amount effective to promote neurite outgrowth. These methods are useful in treating neurodegenerative diseases (e.g., glaucoma, macular degeneration, Parkinson's Disease, and Alzheimer's disease) and injuries to nervous system. A compound promotes neurite outgrowth if the neurite lengths of neurons are statistically significantly longer in the presence of the compound than those in the absence of the compound. Such a compound may be identified using in vitro cultured cells (e.g, PC-12 cells, neuroblastoma B104 cell) (Bitar et al., Cell Tissue Res. 298: 233-42, 1999; Pellitteri et al., Eur. J. Histochem. 45: 367-76, 2001; Satoh et al., Biochem. Biophys. Res. Commun. 258: 50-3, 1999; Hirata and Fujisawa, J. Neurobiol. 32:415-25, 1997; Chauvet et al., Glia 18: 211-23, 1996; Vetter and Bishop, Curr. Biol. 5: 168-78, 1994; Koo et al., Proc. Natl. Acad. Sci. USA 90: 4748-52, 1993; Skubitz et al., J. Cell Biol. 115: 1137-48, 1991; O'Shea et al., Neuron 7: 231-7, 1991; Rydel and Greene, Proc. Natl. Acad. Sci. USA 85: 1257-61, 1988) or using explants (Kato et al., Brain Res. 31: 143-7, 1983; Vanhems et al., Eur. J. Neurosci. 2: 776-82, 1990; Carri et al., Int. J. Dev. Neurosci. 12: 567-78, 1994). Contacting a neuron with a compound according to the present invention may be carried out in vitro or in vivo. The resulting treated neuron, if generated in vitro, may be transplanted into a tissue in need thereof (Lacza et al., Brain Res. Brain Res. Protoc. 11: 145-54, 2003; Chu et al., Neurosci. Lett. 343: 129-33, 2003; Fukunaga et al., Cell Transplant 8: 435-41, 1999).

The present invention also provides methods for promoting differentiation of a neural stem cell comprising contacting a neural stem cell with a compound according to formula (I) in an amount effective to promote differentiation of a neural stem cell. Such methods are also useful in treating neurodegenerative diseases (e.g., glaucoma, macular

degeneration, Parkinson's Disease, and Alzheimer's disease) and injuries to nervous system. "Neural stem cell" refers to a clonogenic, undifferentiated, multipotent cell capable of differentiating into a neuron, an astrocyte or an oligodendrocyte under appropriate conditions. A compound promotes differentiation of neural stem cells if neural stem cells exhibit a statistically significantly higher degree of differentiation in the presence of the compound than in the absence of the compound. Such a compound may be identified using assays involving in vitro cultured stem cells or animal models (Albranches et al., Biotechnol. Lett. 25: 725-30, 2003; Deng et al., Exp. Neurol. 182: 373-82, 2003; Munoz-Elias et al., Stem Cells 21: 437-48, 2003; Kudo et al, Biochem. Pharmacol. 66: 289-95, 2003; Wan et al., Chin. Med. J. 116: 428-31, 2003; Kawamorita et al., Hum. Cell 15: 178-82, 2002; Stavridis and Smith, Biochem. Soc. Trans. 31: 45-9, 2003; Pachenik et al., Reprod. Nutr. Dev. 42: 317-26, 2002; Fukunaga et al., supra). The neural stem cell may be a cultured stem cell, a stem cell freshly isolated from its source tissue, or a stem cell within its source organism. Thus, contacting the neural stem cell with a compound according to the present invention may be carried out either in vitro (for a cultured or freshly isolated stem cell) or in vivo (for a stem cell within its source organism). The resulting differentiated neural cell, if generated in vitro, may be transplanted into a tissue in need thereof (Lacza et al., supra; Chu et al., supra; Fukunaga et al., supra). Such a tissue includes a brain tissue or other nervous tissue that suffers from a trauma or a neurodegenerative disease.

In an embodiment of the present invention, the compound(s) of the present invention or pharmaceutical formulations containing one or more compounds of the present invention are useful in the treatment and/or prevention of fibrosis in general. Below is a further description of examples of various types/forms of fibrosis that are treatable with the compounds of the present invention.

Transforming growth factor β (TGF-β), a key mediator in the development of fibrosis, is important in cell proliferation and differentiation, apoptosis, and deposition

of extracellular matrix (ECM). TGF-β signaling activates both the Smad and AP-1 transcription pathways. TGF-β in the airways of patients with pulmonary fibrosis (PF) may function initially as a "healing molecule" involved in the diminution of initial airway inflammation and in tissue repair. However, with continued inflammatory response such as may occur in PF, the balance may be shifted, to excessive ECM deposition and development of airway fibrosis.

Fibroproliferative diseases are generally caused by the activation of resident stellate cells which are found in most organs. This activation of stellate cells leads to their conversion to myofibroblasts which display characteristics of muscle and non-muscle cells. Activated stellate cells initiate inflammatory signals, principally mediated through TGF-β. Inflammatory cytokines and mediators in addition to TGF-β, lead to proliferation of myofibroblasts. Stellate-derived myofibroblasts proliferate and replace healthy, functional organ cells with extra-cellular matrix that exhibit muscle and connective tissue traits. Ultimately, organ failure results when the nonfunctional fibrotic honeycomb matrix replaces a critical number of healthy cells.

The initial cause of fibrosis is believed to be the result of injury or insult to organ tissues. This cellular injury to organ tissues can often be traced to toxic or infectious agents. Pulmonary fibrosis, or interstitial lung disease, is often the result of smoking, chronic asthma, chronic obstructive pulmonary disease (COPD) or pneumonia. Fibrosis affects nearly all tissues and organ systems. Non-limiting examples of disorders in which fibrosis is a major cause of morbidity and mortality are listed below.

Major-organ fibrosis

Interstitial lung disease (ILD) includes a wide range of distinct disorders in which pulmonary inflammation and fibrosis are the final common pathway of pathology. There are more than 150 causes of ILD, including sarcoidosis, silicosis, adverse drug reactions, infections and collagen vascular diseases and systemic sclerosis (scleroderma).

Idiopathic pulmonary fibrosis (IPF) is the most common

type of ILD. Liver cirrhosis has similar causes to ILD, with viral hepatitis, schistosomiasis and chronic alcoholism being the major causes worldwide.

Kidney disease including diabetes can damage and scar the kidneys, which leads to progressive loss of function. Untreated hypertension can also contribute to the fibroproliferation of the kidneys.

Heart disease associated with scar tissue can impair the heart's pumping ability.

Eye Disease including macular degeneration and retinal and vitreal retinopathy can impair vision.

Chronic pancreatitis is an irreversible disease of the pancreas characterized by chronic inflammation and fibrosis which leads to the loss of endocrine and exocrine function.

Fibroproliferative disorders include systemic and local scleroderma. Scleroderma is a chronic connective tissue disease that may be localized or systemic, and may have an affect in many organs and tissues of the body.

Keloids and hypertrophic scars, which can occur after surgery, traumatic wounds, burns, or even scratches. They manifest as an overgrowth of scar tissue at the site of injury.

Atherosclerosis and restenosis. Restenosis refers to the re-narrowing of a coronary artery after angioplasty to treat atherosclerosis. Scarring associated with trauma can be associated with overgrowth of scar tissue at the site of the trauma-related injury. Surgical complications can lead to fibrosis in any organ in which scar tissue and fibroproliferation result from the surgical procedures.

Chemotherapy induced fibrosis can occur in, for example, the lungs following chemotherapy, manifests as pulmonary fibrosis, and can be severe enough to require lung transplant, even in cases where the underlying malignancy did not affect the lungs.

Radiation-induced fibrosis (RIF) is a serious and common complication of radiation therapy that may cause chronic pain, neuropathy, limited movement of joints, and swelling of the lymph nodes. It occurs most often in breast, head, neck, and connective tissues. RIF may develop from 4-6 months to 1-2 years following exposure to radiation therapy, and it becomes

more severe over time. Risk factors for developing RIF include high radiation dose, large volumes of tissue exposed to radiation, and radiation combined with surgery, chemotherapy, or both.

Burns can lead to fibrosis when there is an overproduction of ECM proteins. Excessive ECM deposition causes the tissue to become fibrotic.

Pulmonary Fibrosis

Pulmonary fibrosis destroys the lung's ability to transport oxygen and other gases into or out of the blood. This disease modifies the delicate and elastic tissues of the lung, changing these tissues into thicker, stiff fibrous tissue. This change or replacement of the original tissue is similar to the permanent scarring that can occur to other damaged tissues. Scarring of the lung reduces the lung's ability to allow gases (i.e. oxygen, carbon dioxide) to pass into or out of the blood. Gradually, the air sacs of the lungs become replaced by fibrotic tissue. When the scar forms, the tissue becomes thicker causing an irreversible loss of the tissue's ability to transfer oxygen into the bloodstream. Symptoms include shortness of breath, particularly with exertion; chronic dry, hacking cough; fatigue and weakness; discomfort in the chest; loss of appetite; and rapid weight loss.

Several causes of pulmonary fibrosis are known and they include occupational and environmental exposures. Many jobs, particularly those that involve mining or that expose workers to asbestos or metal dusts, can cause pulmonary fibrosis. Workers doing these kinds of jobs may inhale small particles (like silica dusts or asbestos fibers) that can damage the lungs, especially the small airways and air sacs, and cause the scarring associated with fibrosis. Agricultural workers also can be affected. Some organic substances, such as moldy hay, cause an allergic reaction in the lung. This reaction is called Farmer's Lung and can cause pulmonary fibrosis. Other fumes found on farms are directly toxic to the lungs.

Another cause is Sarcoidosis, a disease characterized by the formation of granulomas (areas of inflammatory cells),

which can attack any area of the body but most frequently affects the lungs.

Certain medicines may have the undesirable side effect of causing pulmonary fibrosis, as can radiation, such as treatment for breast cancer. Connective tissue or collagen diseases such as systemic sclerosis are also associated with pulmonary fibrosis. Although genetic and familial factors may be involved, this cause is not as common as the other causes listed above.

In Chronic Obstructive Pulmonary Disease (COPD), connective tissue proliferation and fibrosis can characterize severe COPD. COPD can develop as a result of smoking or chronic asthma.

Idiopathic Pulmonary, Fibrosis (IPF)

When all known causes of interstitial lung disease have been ruled out, the condition is called "idiopathic" (of unknown origin) pulmonary fibrosis (IPF). Over 83,000 Americans are living with IPF, and more than 31,000 new cases develop each year. This debilitating condition involves scarring of the lungs. The lungs' air sacs develop scar, or fibrotic tissue, which gradually interferes with the body's ability to transfer the oxygen into the bloodstream, preventing vital organs and tissue from obtaining enough oxygen to function normally.

There are several theories as to what may cause IPF, including viral illness and allergic or environmental exposure (including tobacco smoke). These theories are still being researched. Bacteria and other microorganisms are not thought to be the cause of IPF. There is also a familial form of the disease, known as familial idiopathic pulmonary fibrosis. Additional research is being done to determine whether there is a genetic tendency to develop the disease, as well as to determine other causes of IPF.

Patients with IPF suffer similar symptoms to those with pulmonary fibrosis when their lungs lose the ability to transfer oxygen into the bloodstream. The symptoms include shortness of breath, particularly during or after physical activity; spasmodic, dry cough; gradual, unintended weight

loss; fatigue and weakness; chest discomfort; clubbing, or enlargement of the ends of the fingers (or sometimes the toes) due to a buildup of tissue. These symptoms can greatly reduce IPF patients' quality of life. Pulmonary rehabilitation, and oxygen therapy can reduce the lifestyle-altering effects of IPF, but do not provide a cure.

In order to develop a treatment for fibrotic disease, it is important to focus on the common pathway to the ultimate pathology that is shared by the disease states, regardless of cause or of tissue in which it is manifested. Several components of the causative pathway are discussed below, particularly in relation to the role of β-catenin.

Other Pathological Conditions

Survivin, an inhibitor of apoptosis, is implicated in pulmonary hypertension. CK2 kinase activity has been shown to promote cell survival by increasing survivin expression via β-catenin Tcf/ Lef-mediated transcription. Tapia, lC. et al., Proc. Nat. Acad. Sci. U.S.A. 103: 15079-84 (2006). This pathway therefore provides another opportunity to utilize the present compounds to alter the β-catenin-mediated gene transcription processes.

McMurtry, M.S. et al., J. Clin. Invest. 115:1461-1463 (2005) reported that survivin was expressed in the pulmonary arteries of patients with pulmonary arterial hypertension, but not in the pulmonary arteries of patients without pulmonary arterial hypertension. Comparable results were found in rats treated with monocrotaline to induce pulmonary arterial hypertension. In the rats, survival was prolonged and the pulmonary arterial hypertension was reversed by gene therapy with inhalation of an adenovirus carrying a survivin mutant with dominant-negative properties.

Survivin expression is upregulated in hyperproliferative neovasculature (Simosa, H.F. et al., l Vase. Curg. 41:682-690,2005). Survivin was specifically expressed in human atherosclerotic plaque and stenotic vein grafts. In a rabbit model of hyperplasia after balloon injury of iliofemoral arteries, treatment with a phosphorylation-defective survivin mutant vector reduced the neointimal area. The correlation

between survinin expression and regulation of a smooth muscle cell phenotype after vascular injury points to survivin as a target for therapy in treating vascular disease.

Survivin is amenable to targeting by administration of a compound disclosed herein via one or more of the routes as described herein. Without being bound by a particular mode of action, the compounds disclosed herein can be administered in the form of coated stents, for example in connection with angioplasty. The methods for preparing coated stents are described in the art and would be modified as needed for use with the compounds of the invention. For example, U.S. Patent No. 7,097,850 discloses and teaches methods of coating a stent with a variety of bioactive compounds. U.S. Patent No. 7,087,078 discloses methods of preparing a stent with at least one active ingredient. Both coronary and peripheral stents are amenable to incorporating one or more compounds disclosed herein. Further teachings regarding drug- coated stents is available in Grube, E. et al., Herz 29:162-6 (2004) and W.L. Hunter, Adv. Drug Deliv. Rev. 58:347-9 (2006).

Bone marrow cells contribute to transplant-associated atherosclerosis (Sata, M., Trends Cardiovasc. Med. 13:249-253,2003). Bone marrow cells also contribute to the pathogenesis of lesion formation after mechanical vascular injury (Sata, M. et al., Nat. Med. 8:403-409, 2002). Thus, by treating atherosclerosis and vascular damage with one of more compounds of the invention, reduction in vascular lesion formation can be accomplished.

Survivin also plays a role in vein graft hyperplasia (Wang, G.J. et al., Arterioscler. Thromb. Vase. Biol. 25:2091-2087, 2005). Bypass grafts often develop intimal hyperplasia, a fibroproliferative lesion characterized by intimal thickening. Rabbit vein grafts were treated with adenoviral survivin constructs. Transgene expression was demonstrated in all the adenovirus-treated grafts. Treatment with a dominant negative mutant adenovirus decreased cellular proliferation in the early phase of graft remodeling. The data provide evidence for an important role of survivin in the regulation of vein graft remodeling in this system as well, and further support a role for the compounds of the invention in conjunction with

bypass grafts.

Lymphangioleiomyomatosis (LAM) is a disease that occurs in some patients with tuberous sclerosis complex (Moss, *J. et al.*, Am. J. Respir. Crit Care Med. 163:669-671,2001).

Cystic lung disease in LAM is characterized by abnormal smooth muscle cell proliferation. Compounds disclosed herein are expected to find use in regulating and alleviating the cell proliferation, thus moderating the clinical symptoms.

The Role of TGF-β

In pulmonary fibrosis, the normally thin lung tissue is replaced with thick, coarse scar tissue that impairs the flow of oxygen into the blood and leads to a loss of lung function. A growing body of research suggests that excess TGF-β is the immediate cause of the fibrosis. This over-expression of TGF-β has been shown to cause pulmonary fibrosis in mice. An abnormally high TGF-β signal causes healthy epithelial cells in the lung to die via apoptosis. Cell death leads to the replacement of healthy lung tissue by thick, poor functioning scar tissue. Apoptosis of healthy epithelial cells is required prior to the development of pulmonary fibrosis (Elias et al). One form of treatment of fibrotic lung disorders involves administering drugs that specifically inhibit TGF-β, which in turn blocks apoptosis, preventing the formation of fibrotic tissue in the lung. However, for reasons discussed below, TGF-β itself may not be an ideal therapeutic target.

TGF-β is a member of the transforming growth factor-superfamily which consists of secreted polypeptide signaling molecules involved in cell proliferation and differentiation, apoptosis, deposition of extracellular matrix (ECM) and cell adhesion. TGF-β is a potent inhibitor of cell growth, and has immunosuppressive properties. However, TGF-β also causes the deposition of ECM components leading to fibrosis. A role for TGF-β as a key mediator in the development of fibrosis relates to its ability to act as a chemoattractant for fibroblasts, stimulate fibroblast procollagen gene expression/collagen protein synthesis, and inhibit collagen breakdown. TGF-β further stabilizes the ECM by inhibiting the expression of ECM proteases and stimulating the expression of ECM protease

inhibitors. The fibrinolysis system is essential in ECM accumulation and fibrosis. Inhibition of fibrinolysis results in the accumulation of fibrin and ECM. Plasminogen activator inhibitor-1 (PAI-1) is the key inhibitor of fibrinolysis. The PAI-promoter contains several transcription factor binding sites including an AP-1 and Smad binding elements that promote PAI-1 induction by TGF-β. PAI-1 is the primary inhbitor of both tissue-type (TPA) and urokinase-type plasminogen (uPA) activator. Thus, TGF-β and PAI-1 work in tandem to produce the characteristic tissue of fibrosis.

In the bleomycin-induced model of pulmonary fibrosis (PF), mice in which the PAI-1 gene is deleted are protected from developing PF. Additionally, adenovirus-mediated transfer of the uPA gene to the lung significantly reduces the production of lung hydroxyproline and attenuated the bleomycin-induced increase in lung collagen, both hallmarks of fibrosis. The TGF-β signaling pathway is complex. TGF-β family members bind to specific pairs of receptor serine/threonine kinases. Upon binding, the ligand acts to assemble two type I and two type II receptors into a complex. The type II receptor phosphorylates the type I receptor that subsequently phosphorylates the intracellular substrates Smad 2 and Smad 3. This complex then binds Smad 4 and translocates to the nucleus for signal propagation. TGF-β can also activate AP-1 transcription via the MAPK pathway. TGF-β may originally act as a "healing molecule" in the lung or liver after initial inflammation and injury to the tissue. However, with continued inflammation/injury the balance may be shifted to excessive fibroproliferation and ECM deposition, leading to an "endless healing" process and development of fibrosis. Thus, complete inhibition of TGF-β could initially undermine the healing process.

TGF-β is highly expressed in airway epithelium and macrophages of small airways in patients with COPD. Using anti-inflammatory therapies, such as corticosteroids and interferon-γ, to treat PF has been disappointing due to variable efficacy and significant adverse effects. Therefore, an important goal is to identify small molecules that interact with previously identified molecular pathways (i.e. TGF-β

signaling) involved in the development of fibrosis to prevent the progression or reverse the fibrosis seen in patients.

Wnt Signaling and Human Disease

Vertebrate Wnt proteins are homologues of the Drosophila wingless gene and have been shown to play important roles in regulating cell differentiation, proliferation, and polarity. Cadijan, K.M. et al., Genes Dev. 11 :3286-3305 (1997); Parr, B.A. et al., Curr. Opin. Genet. Dev. 4:523-528 (1994); Smalley, M. J. et al., Cancer Met. Rev. 18:215-230 (1999); and Willert, K. et al., Curr. Opin. Genet. Dev. 8:95-102 (1998). Wnt proteins are cysteine-rich secreted glycoproteins that signal through at least three known pathways. The best understood of these, commonly called the canonical pathway, involves binding of Wnt proteins to frizzled cell surface receptors and low-density lipoprotein cell surface co-receptors, thereby inhibiting glycogensynthase kinase 313 (GSK-313) phosphorylation of the cytoskeletal protein β-catenin. This hypophosphorylated β-catenin is then translocated to the nucleus, where it binds to members of the LEF/TCF family of transcription factors. Binding of β-catenin converts LEF/TCF factors from repressors to activators, thereby switching on cell-specific gene transcription. The other two pathways that Wnt proteins can signal through either activate calmodulin kinase II and protein kinase C (known as the Wnt/Ca++ pathway) or jun N-terminal kinase (also known as the planar cell polarity pathway).

Several components of the Wnt pathway have been implicated in tumorigenesis in humans and mice, and studies of those have in turn identified a role for β-catenin. Wnt1 was first identified from a retroviral integration in mice that caused mammary tumors. Tsukamoto, A.S. et al., Cell 55:619-625 (1988); and Jue, S.F. et al., Mol. Cell. Biol. 12:321-328 (1992). Overexpression of protein kinase CK2 in the mammary gland, which potentiates β-catenin-dependent Wnt signaling, also increases the incidence of mammary tumors in transgenic mice. Landesman-Bollag, E. et al., Oncogene 20:3247-3257 (2001); and Song, D. H. et al., J. Biol. Chem. 275:23790-23797 (2000). Gut epithelia has revealed the most extensive

correlation between Wnt signaling and tumorigenesis. Several reports have described mutations in β-catenin itself in some colon tumors and these mutations occur in or near the GSK-313 phosphorylation sites. Polakis, P. et al., Adv. Exp. Med. Biol. 470:23-32 (1999); and Morin, P.J. et al., Science 275:1787-1790 (1997). Chilosi and colleagues (Chilosi, M. et al., Am. J. Pathol. 162:1497-1502, 2003) investigated β-catenin mutations in IPF patients but did not identify any. This is consistent with a mechanism in which the aberrant activation of the Wnt pathway is a response and not a cause of IPF.

Lung Development and Wnt Signaling

In the mouse, the lung arises from the primitive foregut endoderm starting at approximately E9.5 during mouse development (Warburton, D. et al., Mech. Dev. 92:55-81, 2000). This primitive epithelium is surrounded by mesodermally derived multipotent mesenchymal cells, which in time will differentiate into several cell lineages including bronchial and vascular smooth muscle, pulmonary fibroblasts, and endothelial cells of the vasculature. During gestation, the airway epithelium evolves and grows through a process termed branching morphogenesis. This process results in the three-dimensional arborized network of airways required to generate sufficient surface area for postnatal respiration. Mouse embryonic lung development can be divided into at least four stages: embryonic (E9.5 to E12.5), pseudoglandular (EI2.5 to E16.0), canalicular (EI6.0 to EI7.5), and saccular/alveolar (EI7.5 to postnatal).

During development, epithelial-mesenchymal signaling plays an important role in the regulation of both epithelial and mesenchymal cell differentiation and development. Several important signaling molecules are expressed in the airway epithelium and signal to the adjacent mesenchyme including members of the bone morphogenetic family (BMP-4), transforming growth factor family (TGF-β1, -2), and sonic hedgehog (SHH). In turn, the mesenchyme expresses several signaling molecules such as FGF-7, -9, and -10, important for lung epithelial development and proliferation. Gain of function and loss of function experiments in mice have demonstrated an important

role for each of these factors in regulating lung epithelial and mesenchymal proliferation and differentiation. Bellusci, S., et al., Development 1997, 124:4867-4878; Simonet, W.S., et al., Proc. Nat. Acad. Sci. USA 1995,92:12461-12465; Clark, JC., et al., Am. J. Physiol. 2001, 280:L705-L715; Min, R., et al., Genes Dev. 1998, 12:3156-3161; Motoyama, et al., Nat. Genet. 1998,20:54-57; Litingtung, Y, et al., Nat. Genet. 1998,20:58-61; Pepicelli, C.V., et al., Curr. Biol. 1998, 8:1083-1086; Weaver, M., et al., Development 1999, 126:4005-4015.

Wnt signaling also plays a role during lung development. Several Wnt genes are expressed in the developing and adult lung including Wnt2, Wnt2b/13, Wnt7b, Wnt5a, and Wntll. Kispert, A., et al., Development 1996, 122:3627-3637; Lin, Y., et al., Dev. Dyn. 2001, 222:26-39; Monkley, S.l., et al., Development 1996, 122:3343-3353; Yamaguchi, T.P., et al., Development 1999, 126:1211-1223; Weidenfeld, J., et al., J. Biol. Chem. 2002, 277:21061-21070. Of these, Wnt5a and Wnt7b are expressed at high levels exclusively in the developing airway epithelium during lung development. Wnt2, Wnt5a, and Wnt7b have been inactivated through homologous recombination in mice. Wnt2-null mice do not display an overt lung phenotype and Wnt5a null mice have late-stage lung maturation defects, corresponding to expression of Wnt5a later in lung development. (Monkley, (1996); Li, C. et al., Dev. Biol. 248:68-81 (2000). Inactivation of Wnt7b results in either early embryo demise because of defects in extra-embryonic tissues or perinatal demise because of defects in lung development. Parr, B.A., et al., Dev. Biol. 237:324-332 (2001); Shu, W. et al., Development 129:4831-4842 (2002)). These lung defects include decreased mesenchymal proliferation, lung hypoplasia caused by reduced branching, and pulmonary vascular smooth muscle defects leading to blood vessel hemorrhage in the lung (Shu, W. (2002)). Thus, Wnt signaling regulates important aspects of both epithelial and mesenchymal development during gestation, likely through both autocrine and paracrine signaling mechanisms.

Accumulation of nuclear β-catenin has been observed in both epithelial and mesenchymal (myofibroblasts) cell lineages in adult human lung. Other reports support these observations

during mouse lung development. (Tebar, R., et al., Mech. Dev. 109:437-440 (2001)). Type 2 pneumocytes appear to express high levels of β-catenin both in the embryo and in the adult. (Tebar, 2001). Type 2 cells are precursors of type 1 cells, which form the thin diffusible stratum important for gas exchange in the lung. Type 2 cells have been shown to re-enter the cell cycle, grow, and differentiate into type 1 cells in some models of lung re-epithelialization. (Borok, Z. et al., Am. J. Respir. Cell Mol. Biol. 12:50-55 (1995); Danto, S.I. et al., Am. J. Respir. Cell Mol. Biol. 12:497-502 (1995)).

Importantly, type 2 cells proliferate excessively during idiopathic fibrosis (IPF) and other proliferative lung diseases, and increased nuclear β-catenin in these cells suggests that Wnt signaling regulates this proliferation. (Kawanami, O., et al., Lab. Invest. 46:39-53 (1982); Kasper, M. et al., Histol. Histopathol. 11:463-483 (1996)). Increased proliferation of type 2 cells in IPF may also inhibit their differentiation into type 1 cells because excessive proliferation is often antagonistic to cellular differentiation. In this context, it is important to note that expression of certain important transcriptional and signaling regulators in the lung decreases with gestational age. Forced overexpression of some of these such as BMP-4, GATA6, and Foxa2 results in aberrant lung development that exhibits many aspects of arrested lung epithelial maturity (Weaver, 1999; Koutsourakis, M. et al., Mech. Dev. 105: 105-114,2001; Zhou, L. et al., Dev. Dyn. 210:305-314, 1997). Thus, a careful balance of the correct spatial and temporal expression of certain regulatory genes is required for normal lung development, and improper activation of these pathways can result in severe defects in epithelial differentiation.

Nuclear β-catenin is found in the mesenchyme adjacent to the airway epithelium (Chilosi, 2003), and this is significant especially because these cells appear to be myofibroblastic in nature and may contribute to bronchial and vascular smooth muscle in the lung. Although Wnt signals in these mesenchymal cells could be autocrine in nature, it is just as likely that the mesenchymal cells are responding to a paracrine signal

from the airway epithelium where Wnts such as Wnt5a and Wnt7b are expressed. In this way, the epithelium may be responsible for causing the aberrant activation of Wnt signaling in adjacent mesenchyme, leading to increased fibrosis and damage to the lung. This is particularly relevant because of the increase in the number of type 2 cells in the airways of IPF patients. This may also be reflective of a switch to an embryonic phenotype in the alveolus, where type 1 cells are rare. In turn, this would result in an increase in expression of several genes, including Wnts such as Wnt7b, whose expression is dramatically down-regulated in postnatal development (Weidenfeld, 2002; Shu, 2002). The increased level of Wnts may inhibit the proper differentiation of more mature alveolar cells such as type 1 cells, impairing the repair process.

Because nuclear translocation of β-catenin is a result of Wnt signaling activity, its presence in cells such as distal airway epithelium and in mesenchyme adjacent to airway epithelium suggests that epithelial-mesenchymal Wnt signaling is active and likely plays an important role during both lung development and disease states such as IPF.

Regulation of Cell-Matrix Interactions by Wnt Signaling

A link has been shown between Wnt signaling and regulation of cell-matrix interactions including cell adhesion and migration. In particular, Wnt signaling has been shown to affect cell motility and invasiveness of melanoma cells (Weeraratna, A.T. et al., Cancer Cell 1:279-288 (2002)). In this system, melanoma cells overexpressing Wnt5a displayed increased adhesiveness, which correlated to a reorganized actin cytoskeleton (Weer, 2002). These data suggest that Wnt5a expression correlates directly with the metastatic ability of melanoma tumors. In IPF lung tissue (Chilosi, 2003), the important extracellular matrix metalloproteinase matrilysin was overexpressed in some of the cells containing high levels of nuclear β-catenin. This is supported by previous studies showing that matrilysin is a molecular target of Wnt signaling (Crawford, H.C., Oncogene 18:2883-2891, 1999). Matrilysin has been linked to a role in carcinogenesis both in intestinal and

endometrial tumors. Increased matrilysin expression strongly correlates with increased nuclear β-catenin expression and inhibition of this nuclear translocation results in decreased matrilysin expression (Crawford, 1999). Without being bound by a specific hypothesis, the mechanism may involve increased degradation of the extracellular matrix from increased matrilysin expression, leading to decreased cell adhesion and increased cell motility. In IPF, this might reduce the ability of both epithelial and mesenchymal cells to properly restructure the alveolar architecture after injury. In addition, extracellular matrix integrity may be required for type 1 cell differentiation, because of their flattened morphology and the very large surface area that they cover in the alveolus. This process may contribute to an increase in type 2 cell proliferation, which in turn could decrease type 1 cell differentiation.

Wnt Signaling and IPF

Without being bound by a specific hypothesis, several models could explain the finding that Wnt signaling is aberrantly activated in IPF. First, unregulated activation of the Wnt signaling pathway could be a physiological response to either lung injury or the repair process, possibly because of the requirement of the Wnt pathway for proliferation in cells such as type 2 alveolar epithelium and adjoining myofibroblasts. In this model, Wnt signaling should deactivate once the repair process is complete, leading to a return to normal proliferation. In the second model, aberrant Wnt signaling is the initiating event leading to increased cell proliferation in type 2 cells, which may inhibit their ability to differentiate into type 1 cells and restructure the alveolar architecture properly. Either injury-induced or spontaneous mutations in certain components of the canonical Wnt pathway or in regulatory molecules that regulate this pathway may result in this dysregulation of cell proliferation. The fact that nuclear β-catenin is up-regulated in other lung proliferative diseases suggests that the previous data (Chilosi, 2003) may be a response and not a primary causative event in IPF. Moreover, the unregulated proliferation in type

2 cells and mesenchymal fibroblasts along with the increased presence of nuclear β-catenin suggests that the Wnt pathway is continuously stimulated in lung diseases such as IPF and that inhibitors of Wnt signaling may provide a means to control this proliferation. Increased nuclear β-catenin was detected in the mesenchyme adjacent to the airway epithelium, described as myofibroblasts (Chilosi, 2003). These myofibroblasts can induce apoptosis in neighboring epithelial cells *in vitro* and *in vivo,* probably through degradation of the extracellular matrix (Ubal, B.D. et al., Am. J. Physiol. 275:L1192-L1199, 1998; Dhal, B.D.et al., Am. J. Physiol. 269:L819-L822, 1995; Selman, M. et al., Am. J. Physiol. 279:L562-L574, 2000). In addition, in IPF there appears to be either a lack of re-epithelialization or an increase in type 2 cells with little if any maturation of type 1 cells, leading to injured areas with exposed mesodermal components or re-epithelialized with immature type 2 cells. Since it has been demonstrated that type 2 cells express high levels of TGF-β1, which is a profibrotic cytokine, in IPF either scenario would inhibit the proper re-epithelialization of these injured areas, causing more fibrosis (Kapanci, Y., et al., Am. J. Respir. Crit. Care Med. 152:2163-2169, 1995; Khalil, N., et al., Am. 1. Respir. Cell Mol. Biol. 5: 155-162, 1991). This process could go unchecked and eventually lead to massive changes in tissue architecture, eventual tissue destruction, and loss of lung function.

Connective tissue growth factor (CTGF) is a 36 to 38 kD cysteine-rich peptide containing 349 amino acids. It belongs to the CCN (CTGF, cyr 61/cef 10, nov) family of growth factors. The gene for CTGF was originally cloned from a human umbilical endothelial cell cDNA library. CTGF has been detected in endothelial cells, fibroblasts, cartilaginous cells, smooth muscle cells, and some cancer cell lines. Earlier studies revealed that TGF-β1 increases CTGF mRNA markedly in human foreskin fibroblasts. PDGF, EGF, and FGF were also shown to induce CTGF expression, but their effects were only transient and weak.

Connective tissue growth factor has diverse bioactivities. Depending on cell types, CTGF was shown to

trigger mitogenesis, chemotaxis, ECM production, apoptosis, and angiogenesis. In earlier studies, CTGF was noted to have mitogenic and chemotactic effects on fibroblasts. CTGF was also reported to enhance the mRNA expression of a1(I) collagen, fibronectin, and as integrin in fibroblasts. The finding that TGF-β increases CTGF synthesis and that TGF-β and CTGF share many functions is consistent with the hypothesis that CTGF is a downstream mediator of TGF-β.

The mechanism by which CTGF exerts its effects on cells, especially its signal transduction, is still unclear. CTGF was reported to bind to the surface of fibroblasts with high affinity, and this binding was competed with recombinant PDGF BB. This suggests that CTGF binds to a certain class of PDGF receptors, or that there is some cross reactivity of PDGF BB with CTGF receptors.

Connective tissue growth factor mRNA has been detected in fibroblasts of sclerotic lesions of patients with systemic sclerosis. In patients with localized scleroderma, CTGF mRNA was detected in fibroblasts in tissues from sclerotic stage more than the inflammatory stage, which suggests a close correlation between CTGF and fibrosis. Similar results were also obtained in keloid and other fibrotic diseases. Subsequently, expression of CTGF has been reported in a variety of fibrosis, such as liver fibrosis, pulmonary fibrosis, and heart fibrosis.

CTGF is also implicated in dermal fibrosis of scleroderma. However, the detailed role of CTGF in fibrosis is still unclear. Further studies are needed to clarify this point.

The CCN family comprises cysteine-rich 61 (CYR61/CCN1), connective tissue growth factor (CTGF/CCN2), nephroblastoma overexpressed (NOV/CCN3), and Wnt-induced secreted proteins-1 (WISP-1/CCN4), -2 (WISP-2/CCN5) and -3 (WISP-3/CCN6). These proteins stimulate *mitosis,* adhesion, apoptosis, extracellular matrix production, growth arrest and migration of multiple cell types. Many of these activities probably occur through the ability of CCN proteins to bind and activate cell surface integrins.

Connective tissue growth factor (CTGF) has been

identified as a potential target of Wnt and BMP signaling. It has been confirmed by microarray results, and demonstrated that CTGF was up-regulated at the early stage of B:MP~9 and Wnt3A stimulations and that Wnt3A-regulated CTGF expression was β-catenin-dependent.

Each of the above conditions can benefit from treatment with one or more compounds of the present invention. Each of the types of fibrosis described above can be treated with one or more compounds of the present invention.

The following non-limiting examples illustrate the compounds, compositions, and methods of use of this invention.

**Examples**

The present invention will be further specifically explained with reference to examples. However, the scope of the present invention is not limited to the following examples. In the examples, for thin layer chromatography (TLC), Precoated Silica Gel 60 F254 (produced by Merck, product number: 5715-1M)) was used. After development with chloroform:methanol (1:0 to 1:1) or ethyl acetate:hexane (1:0 to 0:1), spots were observed by UV irradiation (254 nm) or color development with ninhydrine or phosphomoribdic acid solution in ethanol. For drying organic solvent, anhydrous magnesium sulfate or anhydrous sodium sulfate was used. As for column chromatography, the indication of "Buch" means use of Buch sepacore preparative chromatography system (produced by Buch), and one or several columns selected from cartridge columns Si6M-12x75mm, 12x150mm, 40x75mm and 40x150mm produced by the same manufacturer were used depending on the amount of sample. As for column chromatography, the indication of "Purif" means use of Moritex Purif preparative chromatography system (produced by Moritex), and one or several columns selected from cartridge columns 20, 35, 60, 200 and 400 produced by the same manufacturer were used depending on the amount of sample. For flash column chromatography, Silica gel 60N (spherical shape, neutral, 40 to 100 μm, produced by Kanto Chemicals) was used. Preparative thin layer chromatography (hereinafter abbreviated as "PTLC") was performed by using one

or several plates of PLC Plate Silica Gel 60 F254 (20 x 20 cm, thickness: 2 mm, concentration zone: 4 cm, produced by Merck, product number: 13793-1M) depending on the amount of sample.

The indication of "LCMS" means that mass spectrum was measured by liquid chromatography-mass spectrometry (LC/MS). Platform-LC type mass spectrometry apparatus ZQ2000 (produced by Micromass) was used as the mass spectrometer, and the measurement was performed by the electrospray ionization (ESI) method. As a liquid chromatography apparatus, an apparatus produced by waters was used. As a separation column, Develosil C30-UG-5 (50 x 4.6 mm, Nomura Kagaku Co., Ltd.) for method "A" and "B" in the tables mentioned below was used. Elution was performed at a flow rate of 1 ml/minute, and Solution A = water [containing 0.1% (v/v) formic acid] and Solution B = acetonitrile [containing 0.1% (v/v) formic acid].

In the tables mentioned below, data indicated by "RT" mean data of liquid chromatography retention time. In the columns of "Mass", data of mass spectrometry were shown (the indication "N.D" means that no molecular ion peak was detected). In the columns of "method", elution conditions of the liquid chromatography are described. For the indication of retention time in the liquid chromatography, the indication "A" for elution condition means that measurement was performed by elution with a linear gradient of 5 to 100% (v/v) Solution B from 0 minute to 5 minutes and then with 100% Solution B until 6 minutes. Another indication "B" for elution condition means that measurement was performed by elution with a linear gradient of 30 to 100% (v/v) Solution B from 0 minute to 5 minutes and then with 100% Solution B until 6 minutes

In the tables mentioned below, data indicated by "1/2t" means data of plasma half-life (minutes) is determined by plasma stability test that mentioned below.

**Plasma stability test**

Determination of Plasma half life was carried out according to the following procedure using the fresh plasma.

1. 0.025 mg/mL spiking solution A: add 10 μL of 0.5 mg/mL

stock solution to 190 µL of DMSO.

2. Add 90 µL of plasma into the wells designated for all the time points (0, 5, 10, 30, 60, 90, 120, 240 min).

3. Add 10 µL of pre-warmed spiking solution A into the wells designated for all the time points (0, 5, 10, 30, 60, 90, 120, 240 min). Immediately, add 400 µL of ACN containing IS into the wells designated for 0 min, then start timing.

4. At 5, 10, 30, 60, 90, 120, 240 min, add 400 µL of ACN containing IS into the wells, respectively.

5. Protein is precipitated by centrifugation (4000 rpm, 15 min).

6. Transfer 50 µL of supernatant into 50 µL of ultra-pure water (Millipore) in a 96-well sample plate for LC-MS/MS analysis.

Syntheses of compounds of general formula (I') and (II) were performed by using genaral synthesis method as described herein or in WO2009/148192.

[Example I-1]
Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in pyridine 10 ml, acetic anhydride 10 ml (945 mmol) was added and stirred at room temperature for 24 hr. The reaction mixture was diluted with ethyl acetate 100 ml and washed with 10% citric acid 100 ml 3 times and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (hexane:ethyl acetate=9:1 to 0:10) to obtain title compound

672.5 mg (101%).

[Example I-2]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in dry-THF 20 ml, valeroyl chloride 0.363 ml (3 mmol) and then triethylamine 0.417 ml (3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 100 ml and washed with water 100 ml, saturated sodium bicarbonate 100 ml, water 100 ml, and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (hexane:ethyl acetate=9:1 to 0:10) to obtain title compound 597.1 mg (90%).

[Example I-3]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in dry-THF 20 ml, nonanoyl chloride 0.541 ml (3 mmol) and then triethylamine 0.418 ml (3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 100 ml and washed with water 100 ml, saturated sodium bicarbonate 100 ml, water 100 ml, and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (hexane:ethyl acetate=9:1 to 0:10) to obtain title compound 671.7 mg (93%).

[Example I-4]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl dodecanoate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in dry-THF 20 ml, dodecanoyl chloride 0.719 ml (3 mmol) and then triethylamine 0.418 ml (3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 100 ml and washed with water 100 ml, saturated sodium bicarbonate 100 ml, water 100 ml, and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (hexane:ethyl acetate=9:1 to 0:10) to obtain title compound 684.8 mg (90%).

[Example I-5]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in dry-THF 20 ml, tridecanoyl chloride 0.764 ml (3 mmol) and then triethylamine 0.418 ml (3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 100 ml and washed with water 100 ml, saturated sodium bicarbonate 100 ml, water 100 ml, and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (hexane:ethyl acetate=9:1 to 0:10) to obtain title compound 701.4 mg (90%).

[Example I-6]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 579 mg (1 mmol) in dry-THF 20 ml, palmitoyl chloride 0.764 ml (3 mmol) and then triethylamine 0.418 ml (3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 100 ml and washed with water 100 ml, saturated sodium bicarbonate 100 ml, water 100 ml, and brine 100 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 90:10) to obtain title compound 578.5 mg (70%).

[Examples I-7 to 12]

By reaction and purification in the same manner as in the method described in Examples I-1 to 6 and using (6S)-N-benzyl-6-(4-hydroxybenzyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide, the compounds of Examples I-7 to 12 were obtained, respectively.

[Examples I-13 to 18]

By reaction and purification in the same manner as in the method described in Examples I-1 to 6 and using (6S)-N-benzyl-6-(4-hydroxybenzyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidine-1-carboxamide, the compounds of Examples I-13 to 18 were obtained, respectively.

[Examples I-19 to 22]

By reaction and purification in the same manner as in the method described in Examples I-1, 2, 4 and 6 and using (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-9-methyl-4,7-dioxo-8-(naphthalen-1-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-1-carboxamide, the compounds of Examples I-19 to 22 were obtained, respectively.

[Examples I-23 to 26]

By reaction and purification in the same manner as in the

method described in Examples I-1, 2, 4 and 6 and using (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-1-carboxamide, the compounds of Examples I-23 to 26 were obtained, respectively.

[Example I-27]

Synthesis of 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid

To the solution of valine tert-butyl ester 419.4 mg (2 mmol) in DCM 14 ml, triphosgene 1.78 g (6 mmol) and triethylamine 2.8 ml (20 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain tert-butyl 2-isocyanato-3-methylbutanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 964.4 mg (1 mmol) in DCM 12 ml, triethylamine 0.07 ml (0.5 mmol) and tert-butyl 2-isocyanato-3-methylbutanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 98:2) to obtain tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate 787 mg (61%).

To the tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate 787 mg (1 mmol), trifluoroacetic acid 6 ml and DCM 6 ml were added and

stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 30 ml and washed with water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain title compound 705mg (96 %).

[Example I-28]

Synthesis of tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate

To the solution of valine tert-butyl ester 419.4 mg (2 mmol) in DCM 14 ml, triphosgene 1.78 g (6 mmol) and triethylamine 2.8 ml (20 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain tert-butyl 2-isocyanato-3-methylbutanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 964.4 mg (1 mmol) in DCM 12 ml, triethylamine 0.07 ml (0.5 mmol) and tert-butyl 2-isocyanato-3-methylbutanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 98:2) to obtain title compound 787 mg (61%).

[Example I-29]

Synthesis of benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate

To the solution of valine benzyl ester 243.7 mg (1 mmol) in DCM 14 ml, triphosgene 0.89 g (3 mmol) and triethylamine

1.4 ml (10 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 20 ml, water 20 ml, and brine 20 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain benzyl 2-isocyanato-3-methylbutanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 482.2 mg (0.83 mmol) in DCM 12 ml, triethylamine 0.03 ml (0.25 mmol) and benzyl 2-isocyanato-3-methylbutanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 98:2) to obtain title compound 517 mg (76%).

[Example I-30]

Synthesis of 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid

To the solution of leucine tert-butyl ester 447.5 mg (2 mmol) in DCM 14 ml, triphosgene 1.78 g (6 mmol) and triethylamine 2.8 ml (20 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain tert-butyl 2-isocyanato-4-methylpentanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 964.4 mg (1 mmol) in DCM 12ml, triethyl amine 0.07 ml (0.5 mmol) and tert-butyl 2-isocyanato-4-methylpentanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30

ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 98:2) to obtain tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate 909 mg (69%).

To the tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate 909 mg (1 mmol), trifluoroacetic acid 6 ml and DCM 6 ml were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 30 ml and washed with water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain title compound 805 mg (95%).

[Example I-31]

Synthesis of tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate

To the solution of leucine tert-butyl ester 447.5 mg (2 mmol) in DCM 14 ml, triphosgene 1.78 g (6 mmol) and triethylamine 2.8 ml (20 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain tert-butyl 2-isocyanato-4-methylpentanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 964.4 mg (1 mmol) in DCM 12 ml, triethylamine 0.07 ml (0.5 mmol) and tert-butyl 2-isocyanato-4-methylpentanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30

ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chroloform:methanol=100:0 to 98:2) to obtain tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate 909 mg (69%).

[Example I-32]

Synthesis of benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate

To the solution of leucine benzyl ester 257.8 mg (1 mmol) in DCM 14 ml, triphosgene 0.89 g (3 mmol) and triethylamine 1.4 ml (10 mmol) were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 20 ml, water 20 ml, and brine 20 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to obtain benzyl 2-isocyanato-4-methylpentanoate.

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 482.2 mg (0.83 mmol) in DCM 12 ml, triethylamine 0.03 ml (0.25 mmol) and benzyl 2-isocyanato-4-methylpentanoate were added and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate 30 ml, water 30 ml, and brine 30 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 98:2) to obtain title compound 405 mg (58.8%).

[Examples I-33 to 38]

By reaction and purification in the same manner as in the method described in Examples I-27 to 32 and using (6S)-N-benzyl-6-(4-hydroxybenzyl)-2-methyl-4,7-dioxo-8-(quinolin-8-

ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide, the compounds of Examples I-33 to 38 were obtained, respectively.

[Examples I-39 to 44]

By reaction and purification in the same manner as in the method described in Examples I-27 to 32 and using (6S)-N-benzyl-6-(4-hydroxybenzyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidine-1-carboxamide, the compounds of Examples I-39 to 44 were obtained, respectively.

[Example I-45]

Synthesis of 1-(4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)ethyl ethyl carbonate

To a suspension of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 200 mg (0.345 mmol), sodium iodide 104 mg (0.69 mmol), potassium carbonate 95.5 mg (0.69 mmol) in acetone 6 ml, 1-chlorodiethyl carbonate 93 μL (0.69 mmol) was added and refluxed for 3 days. After evaporation of the solvent, ethyl acetate 35 ml and water 15 ml were added to the residue. The organic layer was washed with brine 15 ml, dried with magnesium sulfate, and then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=10:0 to 9:1) to obtain title compound 12 mg (5%).

[Example I-46]

Synthesis of (6S,9S)-N-benzyl-6-(4-(3-methoxypropoxy)benzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 200 mg (0.345 mmol)in dryTHF 6 ml, 3-methoxy-1-propanol 40 μL (0.415 mmol), tributylphosphine 84 mg (0.415 mmol) and then 1,1'-

(azodicarbonyl)dipiperidine 105 mg (0.415 mmol)were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 35 ml and washed with water 15 ml, saturated sodium bicarbonate 15 ml, water 15 ml, and brine 15 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 90:10) to obtain title compound 214 mg (95%).

[Example I-47]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl isobutyrate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 200 mg (0.345 mmol)in dryTHF 6 ml, isobutyryl chloride 109 μL (1.04 mmol) and then triethylamine 145 μL (1.04 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 35 ml and washed with water 15 ml, saturated sodium bicarbonate 15 ml, water 15 ml, and brine 15 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=100:0 to 90:10) to obtain title compound 218 mg (97%).

[Example I-48]

Synthesis of 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl ethyl carbonate

To the solution of (6S,9S)-N-benzyl-6-(4-hydroxybenzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide 60 mg (0.1 mmol)in dryTHF 2 ml, ethyl chloroformate 30 μL (0.3 mmol) and then triethylamine 43 μL (0.3 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate 10 ml and washed with water 10 ml,

saturated sodium bicarbonate 10 ml, water 10 ml, and brine 10 ml. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Büchi silica gel column chromatography (chloroform:methanol=99:1 to 95:5) to obtain title compound 55.4 mg (82%).

The above-mentioned compounds are shown in Table 1.

Typical examples of the compounds of the present invention that can be given by reacting and treating corresponding starting compounds using any of the methods described in the present specification are shown in Table 1.

Table 1

| EX No. | chemical name | method | R.T. | Mass |
|---|---|---|---|---|
| I-1 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate | A | 4.65 | 621 |
| I-2 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate | A | 5.37 | 663 |
| I-3 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate | A | 6.38 | 719 |
| I-4 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl dodecanoate | A | 6.82 | 761 |
| I-5 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate | A | 7.68 | 775 |
| I-6 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate | B | 7.15 | 817 |
| I-7 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate | A | 4.3 | 607 |
| I-8 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate | A | 5.05 | 649 |
| I-9 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate | A | 6.07 | 705 |
| I-10 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl dodecanoate | A | 6.51 | 747 |
| I-11 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate | A | 7.34 | 761 |
| I-12 | 4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate | B | 6.82 | 803 |
| I-13 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate | A | 4.8 | 591 |
| I-14 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate | A | 5.5 | 633 |
| I-15 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl nonanoate | A | 6.41 | 689 |
| I-16 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate | A | 6.97 | 731 |

Table 1 (continued)

| EX No. | chemical name | method | R.T. | Mass |
|---|---|---|---|---|
| I-17 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl tridecanoate | A | 7.81 | 745 |
| I-18 | 4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate | B | 7.3 | 787 |
| I-19 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate | A | 4.9 | 604 |
| I-20 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate | A | 5.83 | 660 |
| I-21 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate | A | 7.29 | 744 |
| I-22 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate | B | 9.45 | 800 |
| I-23 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate | A | 4.37 | 605 |
| I-24 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate | A | 5.39 | 661 |
| I-25 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate | A | 7.09 | 745 |
| I-26 | 4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate | B | 9.19 | 801 |
| I-27 | 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid | A | 4.43 | 722 |
| I-28 | tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.52 | 778 |
| I-29 | benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.49 | 812 |
| I-30 | 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid | A | 4.65 | 736 |

Table 1 (continued)

| EX No. | chemical name | method | R.T. | Mass |
|---|---|---|---|---|
| I-31 | tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.64 | 792 |
| I-32 | benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.61 | 826 |
| I-33 | 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid | A | 4.13 | 708 |
| I-34 | tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.23 | 764 |
| I-35 | benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.18 | 798 |
| I-36 | 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid | A | 4.35 | 722 |
| I-37 | tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.32 | 778 |
| I-38 | benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.3 | 812 |
| I-39 | 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid | A | 4.57 | 693 |
| I-40 | tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.64 | 749 |
| I-41 | benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate | A | 5.63 | 783 |
| I-42 | 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid | A | 4.8 | 707 |

Table 1 (continued)

| EX No. | chemical name | method | R.T. | Mass |
|---|---|---|---|---|
| I-43 | tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.78 | 763 |
| I-44 | benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate | A | 5.75 | 797 |
| I-45 | 1-(4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)ethyl ethyl carbonate | A | 5.08 | 694 |
| I-46 | (6S,9S)-N-benzyl-6-(4-(3-methoxypropoxy)benzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide | A | 4.93 | 650 |
| I-47 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl isobutyrate | A | 5.15 | 648 |
| I-48 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl ethyl carbonate | A | 4.88 | 650 |

In the Table 2, the plasma half life of the compounds determined by plasma stability test are shown below.

Table 2

| EX No. | chemical name | Animal | 1/2t (min) |
|---|---|---|---|
| I-1 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate | human | 44 |
| I-2 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate | human | 165 |
| I-3 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate | human | 166 |
| I-4 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate | human | 990 |
| I-5 | 4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate | human | 318 |
| I-16 | 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid | human | 630 |
| I-19 | 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid | human | 990 |

## Industrial Applicability

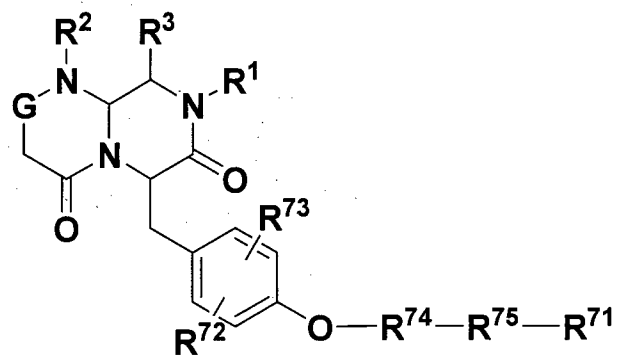
The compound of the formula (I) in the present invention can allow subatainable release of an active form which blocks TCF4/β-catenin transcriptional pathway by inhibiting CBP, and therefore can be used for treatment of cancer, especially colorectal cancer, and fibrotic diseases.

This application is based on provisional application No. 61/446,801 filed in U.S.A., the contents of which are hereby incorporated by reference.

Although only some exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention.

## CLAIMS

1. A compound having the following general formula (I):



wherein

$R^{71}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are independently selected from hydrogen or halogen;

$R^{74}$ is a bond or optionally substituted lower alkylene;

$R^{75}$ is -O-, -(CO)-, -(CO)-O-, or -O-(CO)-O-;

provided that when $R^{74}$ is a bond, then $R^{75}$ is -(CO)- or -(CO)-O-;

G is -NH-, $-NR^6-$, -O-, $-CH_2-$, $-CHR^6-$ or $-C(R^6)_2-$, wherein $R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

$R^1$ is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted cycloalkylalkyl or optionally substituted heterocycloalkylalkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)- or $-(SO_2)-$; $W^{22}$ is a bond, -O-, -NH- or optionally substituted lower alkylene; Rb is a bond or optionally substituted lower alkylene; and $R^{20}$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl; and

$R^3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1,
wherein
$R^{74}$ is a bond; and
$R^{75}$ is -(CO)-.

3. The compound of claim 1,
wherein
$R^{74}$ is a bond; and
$R^{75}$ is -(CO)-O-.

4. The compound of claim 1,
wherein
$R^{74}$ is optionally substituted lower alkylene; and
$R^{75}$ is -O-.

5. The compound of claim 1,
wherein
$R^{74}$ is optionally substituted lower alkylene; and
$R^{75}$ is -O-(CO)-O-.

6. The compound of any one of claims 1-5,
wherein
G is -NH-, $-NR^6$-, -O-, or $-CH_2$-;
wherein
$R^6$ is independently selected from optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;
$R^1$ is $-Ra-R^{10}$;
wherein
Ra is optionally substituted lower alkylene and
$R^{10}$ is optionally substituted aryl or optionally substituted heteroaryl.

7. The compound of claim 6,
wherein

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety.

8. The compound of claim 6,
wherein
$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$,
wherein
$W^{21}$ is $-(CO)-$;
$W^{22}$ is $-NH-$;
Rb is a bond or optionally substituted lower alkylene; and
$R^{20}$ is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycloalkyl.

9. The compound of claim 6,
wherein
$R^3$ is hydrogen or $C_{1-4}$ alkyl.

10. The compound of claim 6 or 9,
wherein
G is $-NR^6-$ wherein $R^6$ is lower alkyl or lower alkenyl.

11. The compound of claim 6 or 9,
wherein
G is $-CH_2-$.

12. The compound of any one of claim 6-11,
wherein
Ra is optionally substituted lower alkylene and
$R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally

substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl.

13. The compound of claim 6,
wherein
$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and
$R^{72}$ and $R^{73}$ are hydrogen;
$R^1$ is -Ra-$R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted

isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen or $C_{1-4}$ alkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

14. The compound of claim 6,

wherein

$R^{71}$ is optionally substituted alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl,

optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is $C_{1-4}$ alkyl;

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

15. The compound of claim 10,

wherein

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety; and

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted

pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is -(CO)-; $W^{22}$ is -NH-; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

16. The compound of claim 11,

wherein

$R^{71}$ is $C_{1-20}$ alkyl or optionally substituted amino acid moiety;

$R^{72}$ and $R^{73}$ are hydrogen

$R^1$ is $-Ra-R^{10}$; wherein Ra is optionally substituted lower alkylene and $R^{10}$ is optionally substituted benzhydryl, optionally substituted biphenyl, optionally substituted

phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazinyl, optionally substituted pyrrolyl, optionally substituted thienyl, optionally substituted furanyl, optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted imidazolyl, optionally substituted naphthyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted quinoxalinyl, optionally substituted cinnolinyl, optionally substituted naphthyridinyl, optionally substituted benzotriazinyl, optionally substituted pyridopyrimidinyl, optionally substituted pyridopyrazinyl, optionally substituted pyridopyridazinyl, optionally substituted pyridotriazinyl, optionally substituted indenyl, optionally substituted benzofuryl, optionally substituted benzothienyl, optionally substituted indolyl, optionally substituted indazolyl, optionally substituted benzoxazolyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted benzothiadiazolyl, optionally substituted furopyridinyl, optionally substituted thienopyridinyl, optionally substituted pyrropyridinyl, optionally substituted oxazolopyridinyl, optionally substituted thiazolopyridinyl or optionally substituted imidazopyridinyl;

$R^3$ is hydrogen; and

$R^2$ is $-W^{21}-W^{22}-Rb-R^{20}$, wherein $W^{21}$ is $-(CO)-$; $W^{22}$ is $-NH-$; Rb is a bond or optionally substituted lower alkylene; $R^{20}$ is optionally substituted aryl or optionally substituted heteroaryl.

17. The compound of claim 1 selected from
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-

(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl dodecanoate,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl acetate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl pentanoate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl nonanoate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl dodecanoate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl tridecanoate,
4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl palmitate,
4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate,
4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate,
4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-

dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl nonanoate,

4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate,

4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl tridecanoate,

4-(((6S)-1-(benzylcarbamoyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-8-(naphthalen-1-ylmethyl)-4,7-dioxooctahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl acetate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl pentanoate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl dodecanoate,

4-(((6S,9S)-1-(benzylcarbamoyl)-9-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenyl palmitate,

2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid,

tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,

benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,

2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid,

tert-butyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate,

benzyl 2-((4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate,

2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid,

tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,

benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,

2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid,

tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-

methylpentanoate,
benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-2-methyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate,
2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoic acid,
tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,
benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-3-methylbutanoate,
2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoic acid,
tert-butyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate,
benzyl 2-((4-(((6S)-1-(benzylcarbamoyl)-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[1,2-a]pyrimidin-6-yl)methyl)phenoxy)carbonylamino)-4-methylpentanoate,
1-(4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenoxy)ethyl ethyl carbonate,
(6S,9S)-N-benzyl-6-(4-(3-methoxypropoxy)benzyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazine-1-carboxamide,
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl isobutyrate, and
4-(((6S,9S)-1-(benzylcarbamoyl)-2,9-dimethyl-4,7-dioxo-8-(quinolin-8-ylmethyl)octahydro-1H-pyrazino[2,1-c][1,2,4]triazin-6-yl)methyl)phenyl ethyl carbonate.

18. A pharmaceutical composition comprising a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically

acceptable carrier.

19. A pharmaceutical composition of claim 18, wherein the composition comprising an effective amount of the compound.

20. A method of treating or preventing cancer comprising administering to a subject in need thereof a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition according to any one of claims 18 and 19, in an amount effective to treat or prevent the cancer.

21. A method of treating or preventing fibrosis comprising administering to a subject in need thereof a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition according to any one of claims 18 and 19, in an amount effective to treat or prevent the fibrosis.

22. A method of treating or preventing a disease or condition selected from the group consisting of cancer, fibrosis, restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, tuberous sclerosis complex (TSC), KSHV-associated tumor, hair loss, and Alzheimer's disease, comprising administering to a subject in need thereof a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition of any one of claims 18 and 19, in an amount effective to treat or prevent said disease or condition.

23. An agent for treating or preventing cancer comprising a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof.

24. An agent for treating or preventing fibrosis comprising a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof.

25. An agent for treating or preventing a disease or

condition selected from the group consisting of cancer, fibrosis, restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, tuberous sclerosis complex (TSC), KSHV-associated tumor, hair loss, and Alzheimer's disease comprising a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof.

26. A compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition according to any one of claims 18 and 19 for use in treating or preventing cancer.

27. A compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition according to any one of claims 18 and 19 for the use in treating or preventing fibrosis.

28. A compound according to any one of claims 1-17 or a pharmaceutically acceptable salt thereof, or a composition according to any one of claims 18 and 19 for use in treating or preventing a disease or condition selected from the group consisting of cancer, fibrosis, restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, tuberous sclerosis complex (TSC), KSHV-associated tumor, hair loss, and Alzheimer's disease.

FIG. 1

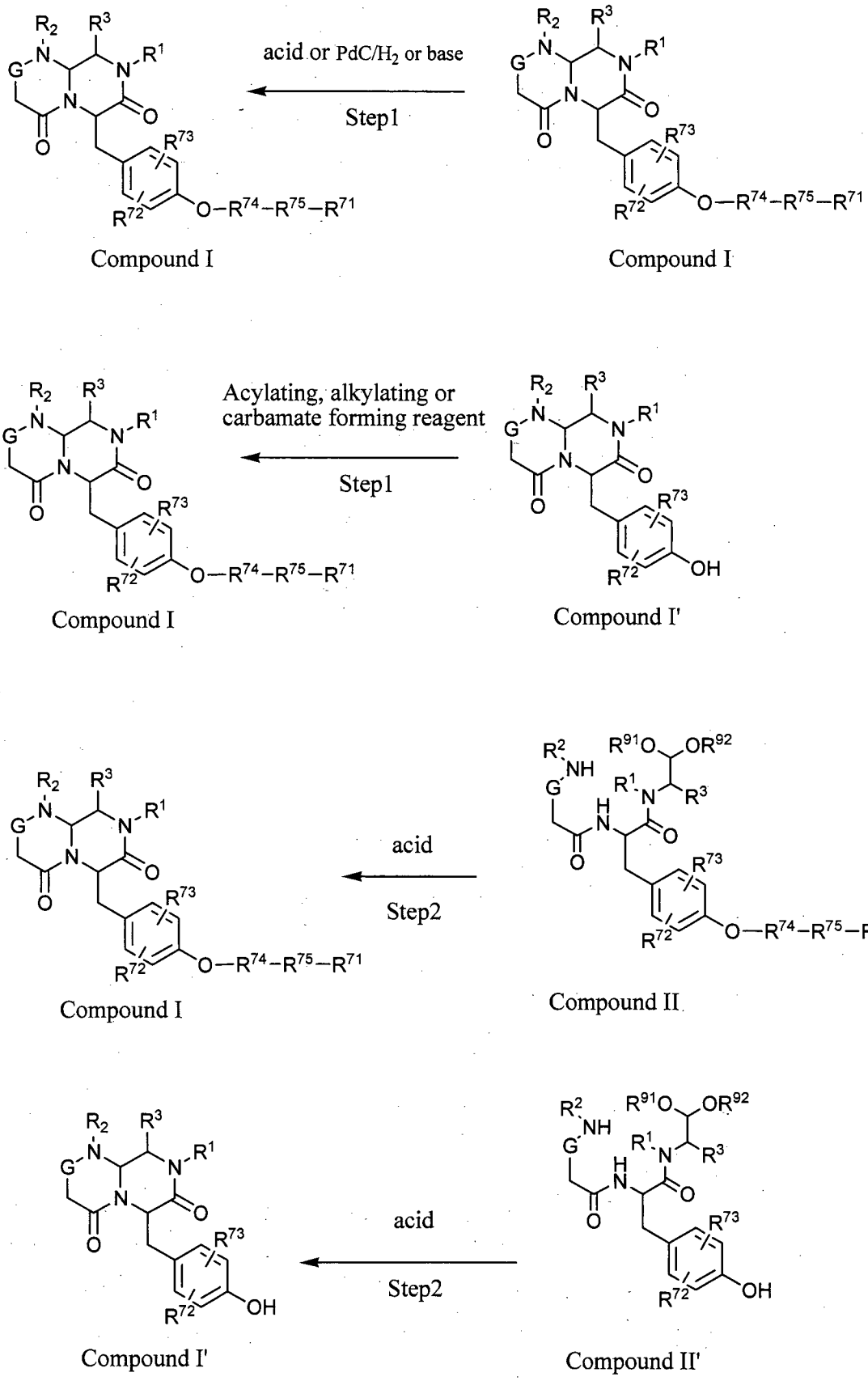

acid or PdC/H2 or base
Step1
Compound I
Compound I
Acylating, alkylating or carbamate forming reagent
Step1
Compound I
Compound I'
acid
Step2
Compound I
Compound II
acid
Step2
Compound I'
Compound II'

FIG. 2

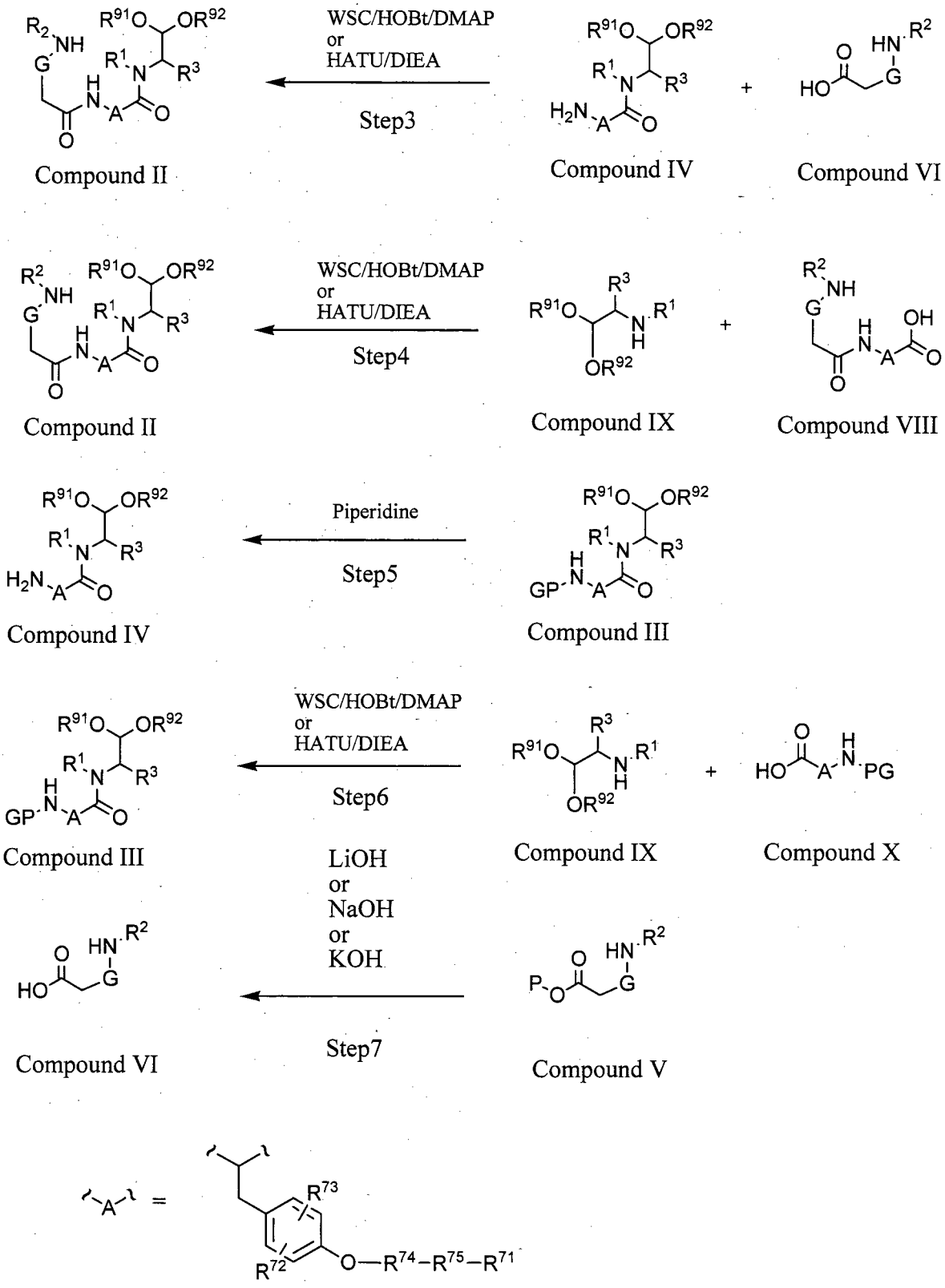

WSC/HOBt/DMAP
or
HATU/DIEA
Step3
Compound II
Compound IV
Compound VI
WSC/HOBt/DMAP
or
HATU/DIEA
Step4
Compound II
Compound IX
Compound VIII
Piperidine
Step5
Compound IV
Compound III
WSC/HOBt/DMAP
or
HATU/DIEA
Step6
Compound III
Compound IX
Compound X
LiOH
or
NaOH
or
KOH
Step7
Compound VI
Compound V

FIG. 3

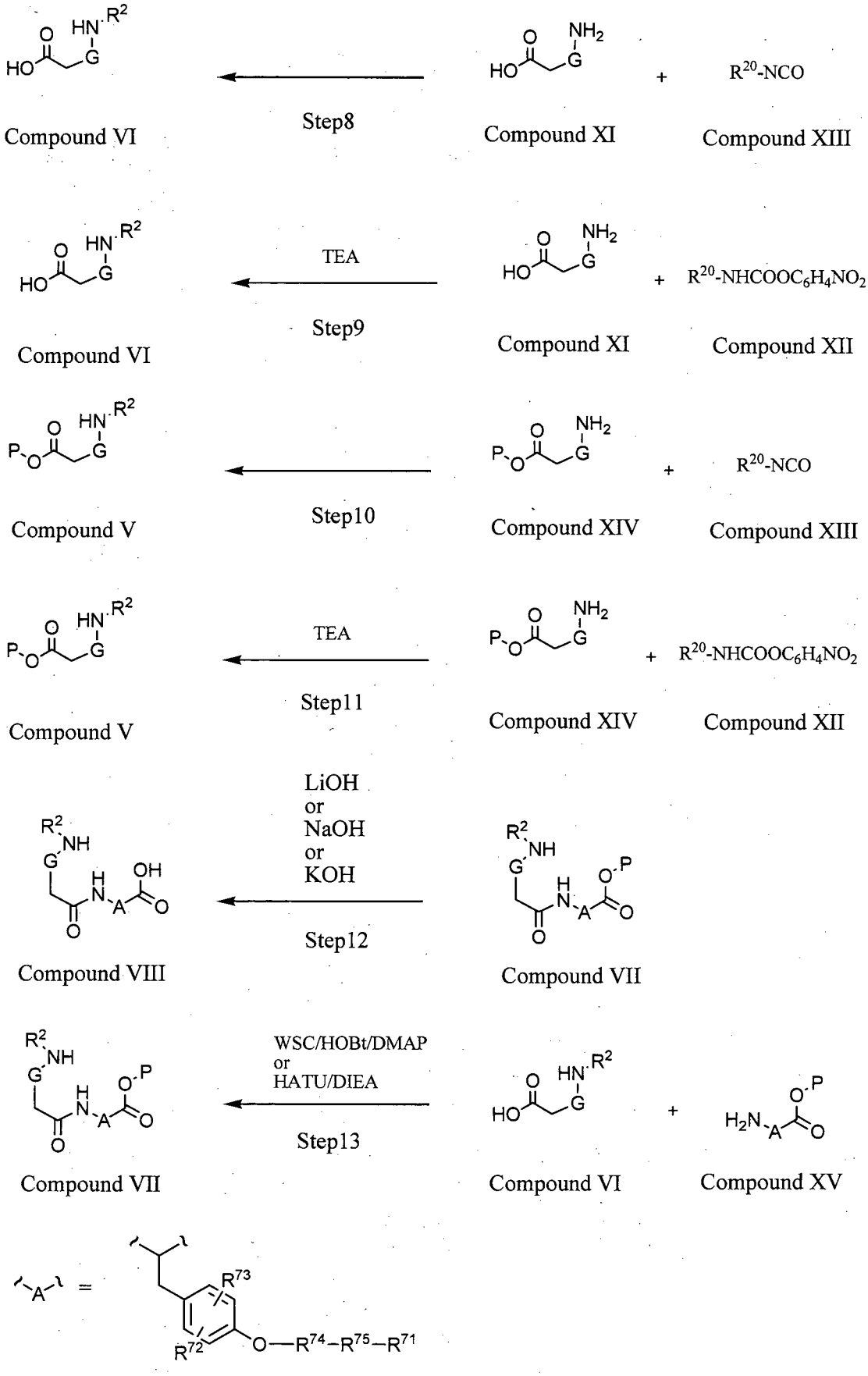
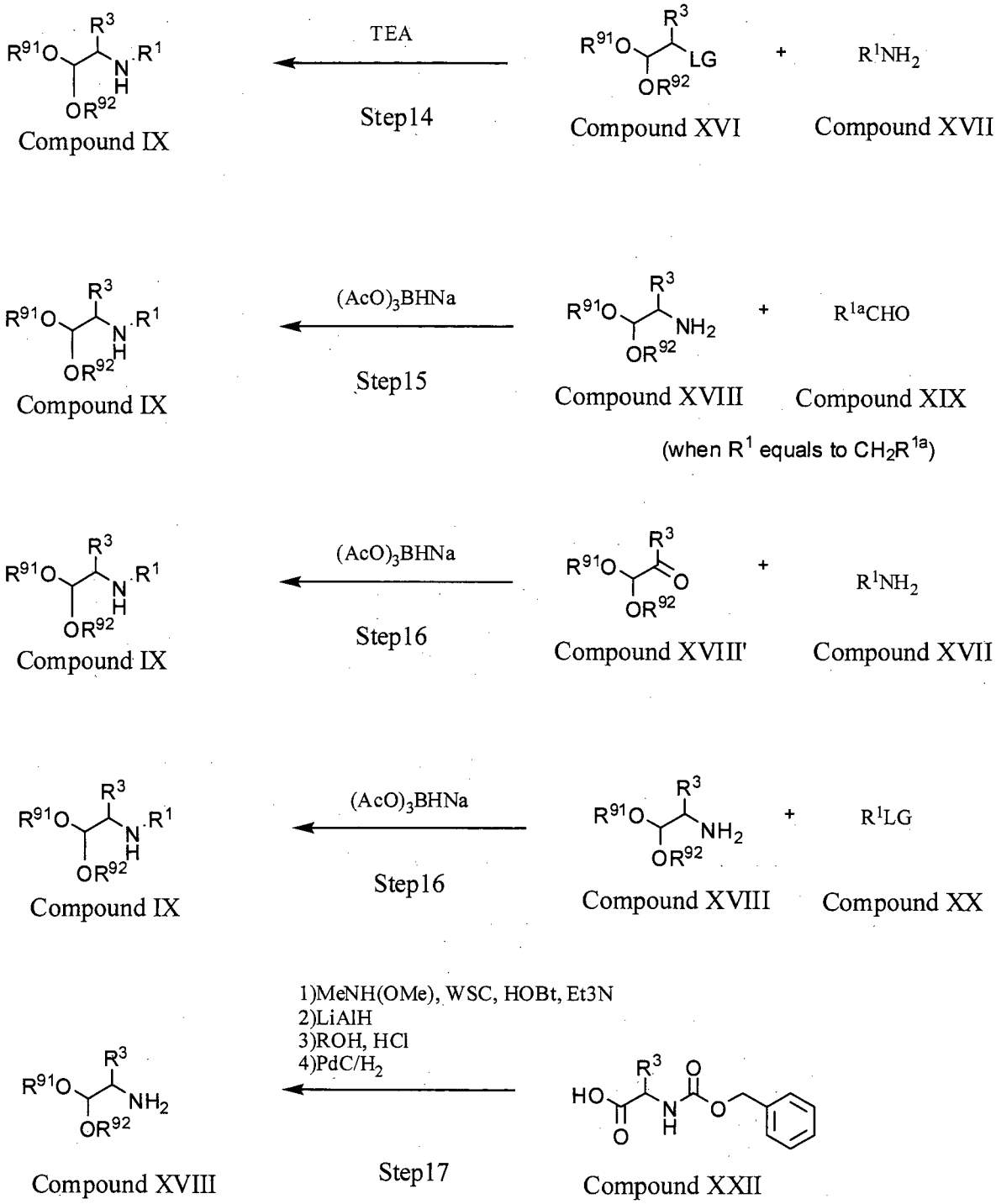

Compound VI
Step8
Compound XI
+ R20-NCO
Compound XIII
Compound VI
TEA
Step9
Compound XI
+ R20-NHCOOC6H4NO2
Compound XII
Compound V
Step10
Compound XIV
+ R20-NCO
Compound XIII
Compound V
TEA
Step11
Compound XIV
+ R20-NHCOOC6H4NO2
Compound XII
Compound VIII
LiOH
or
NaOH
or
KOH
Step12
Compound VII
Compound VII
WSC/HOBt/DMAP
or
HATU/DIEA
Step13
Compound VI
+
Compound XV
A = R73 R72 O—R74–R75–R71

FIG. 4


TEA
Step14
Compound IX
Compound XVI
Compound XVII
(AcO)3BHNa
Step15
Compound IX
Compound XVIII
Compound XIX
(when R1 equals to CH2R1a)
(AcO)3BHNa
Step16
Compound IX
Compound XVIII'
Compound XVII
(AcO)3BHNa
Step16
Compound IX
Compound XVIII
Compound XX
1)MeNH(OMe), WSC, HOBt, Et3N
2)LiAlH
3)ROH, HCl
4)PdC/H2
Step17
Compound XVIII
Compound XXII

# INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2012/055489

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61K31/53 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| | -/-- | |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 2 May 2012 | 08/05/2012 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Koch, Kristian |

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Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2012/055489

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/JP2012/055489

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