

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 199729988 B2**
(10) Patent No. **726784**

(54) Title
Inhibitors of prenyl transferases

(51)⁶ International Patent Classification(s)
C07D 277/02 C07D 277/04

(21) Application No: **199729988** (22) Application Date: **1997.05.06**

(87) WIPO No: **W098/00409**

(30) Priority Data

(31) Number	(32) Date	(33) Country
08/672474	1996.06.28	US

(43) Publication Date : **1998.01.21**

(43) Publication Journal Date : **1998.03.19**

(44) Accepted Journal Date : **2000.11.23**

(71) Applicant(s)
Biomeasure Incorporated

(72) Inventor(s)
Zheng Xin Dong; Sun H. Kim

(74) Agent/Attorney
GRIFFITH HACK,GPO Box 3125,BRISBANE QLD 4001

OPI DATE 21/01/98 APPLN. ID 29988/97
AOJP DATE 19/03/98 PCT NUMBER PCT/US97/07711



AU9729988

PCT)

(51) International Patent Classification 6 : C07D 277/02, 277/04		A1	(11) International Publication Number: WO 98/00409
			(43) International Publication Date: 8 January 1998 (08.01.98)
(21) International Application Number: PCT/US97/07711		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 6 May 1997 (06.05.97)		Published With international search report.	
(30) Priority Data: 08/672,474 28 June 1996 (28.06.96) US			
(71) Applicant (for all designated States except US): BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Milford, MA 01757 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): DONG, Zheng, Xin [CN/US]; 40 Angelica Drive, Framingham, MA 01701 (US). KIM, Sun, H. [US/US]; 423 Deedham Avenue, Needham, MA 02192 (US).			
(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).			
(54) Title: INHIBITORS OF PRENYL TRANSFERASES			
 (I) (II)			
(57) Abstract A family of compounds capable of inhibiting the activity of prenyl transferases. The compounds are covered by one of the two formulas (I) and (II). Each of the R groups is defined in the disclosure.			

INHIBITORS OF PRENYL TRANSFERASES

Background of the Invention

The Ras family of proteins are important in the
5 signal transduction pathway modulating cell growth. The
protein is produced in the ribosome, released into the
cytosol, and post- translationally modified. The first
step in the series of post-translational modifications is
the alkylation of Cys¹⁶⁸ with farnesyl or geranylgeranyl
10 pyrophosphate in a reaction catalyzed by prenyl
transferase enzymes such as farnesyl transferase and
geranylgeranyl transferase (Hancock, JF, et al., Cell
57:1167-1177 (1989)). Subsequently, the three C-terminal
amino acids are cleaved (Gutierrez, L., et al., EMBO J.
15 8:1093-1098 (1989)), and the terminal Cys is converted to
a methyl ester (Clark, S., et al., Proc. Nat'l Acad. Sci.
(USA) 85:4643-4647 (1988)). Some forms of Ras are also
reversibly palmitoylated on cysteine residues immediately
N-terminal to Cys¹⁶⁸ (Buss, JE, et al., Mol. Cell. Biol.
20 6:116-122 (1986)). It is believed that these
modifications increase the hydrophobicity of the C-
terminal region of Ras, causing it to localize at the
surface of the cell membrane. Localization of Ras to the
cell membrane is necessary for signal transduction
25 (Willumsen, BM, et al., Science 310:583-586 (1984)).

Oncogenic forms of Ras are observed in a
relatively large number of cancers including over 50
percent of colon cancers and over 90 percent of
pancreatic cancers (Bos, JL, Cancer Research 49:4682-4689
30 (1989)). These observations suggest that intervention in
the function of Ras mediated signal transduction may be
useful in the treatment of cancer.

Previously, it has been shown that the C-terminal
tetrapeptide of Ras is a "CAAX" motif (wherein C is
35 cysteine, A is an aliphatic amino acid, and X is any

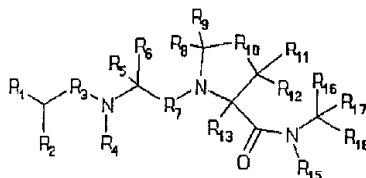
- 2 -

amino acid). Tetrapeptides having this structure have been shown to be inhibitors of prenyl transferases (Reiss, et al., Cell 62:81-88 (1990)). Poor potency of these early farnesyl transferase inhibitors has prompted
5 the search for new inhibitors with more favorable pharmacokinetic behavior (James, GL, et al., Science 260:1937-1942 (1993); Kohl, NE, et al., Proc. Nat'l Acad. Sci. USA 91:9141-9145 (1994); deSolms, SJ, et al., J. Med. Chem. 38:3967-3971 (1995); Nagasu, T, et al., Cancer
10 Research 55:5310-5314 (1995); Lerner, EC, et al., J. Biol. Chem. 270:26802-26806 (1995); Lerner, EC, et al., J. Biol. Chem. 270:26770 (1995); and James, et al., Proc. Natl. Acad. Sci. USA 93:4454 (1996)).

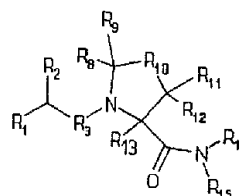
Recently, it has been shown that a prenyl
15 transferase inhibitor can block growth of Ras-dependent tumors in nude mice (Kohl, NE, et al., Proc. Nat'l Acad. Sci. USA 91:9141-9145 (1994)). In addition, it has been shown that over 70 percent of a large sampling of tumor cell lines are inhibited by prenyl transferase inhibitors
20 with selectivity over non-transformed epithelial cells (Sepp-Lorenzino, I, et al., Cancer Research, 55:5302-5309 (1995)).

Summary of the Invention

In one aspect, the invention features a compound of formula I or formula II



formula I



formula II

5 wherein

R_1 is H or $\text{NR}_{20}\text{R}_{21}$;

R_2 is $(\text{CH}_2)_m\text{SR}_{22}$, $(\text{CH}_2)_m\text{SSR}_{22}$, substituted or unsubstituted heterocycle, or substituted or unsubstituted heterocycle lower alkyl, where m is 1-6 and the substituent is lower alkyl, lower alkenyl, aryl, or aryl lower alkyl;

each of R_3 and R_7 , independently, is CH_2 or $\text{C}(\text{O})$;

each of R_4 and R_{15} , independently, is H or lower alkyl;

each of R_5 and R_{16} , independently, is H or a substituted or unsubstituted moiety selected from lower alkyl, thio lower alkyl, lower alkenyl, thio lower alkenyl, cycloalkyl, cycloalkyl lower alkyl, aryl, and aryl lower alkyl, where the substituent is lower alkyl, hydroxy, halo, $\text{C}(\text{O})\text{NR}_{23}\text{R}_{24}$, or COOH ;

each of R_6 , R_8 , R_9 , R_{11} , R_{12} , R_{13} , and R_{17} , independently, is H or a substituted or unsubstituted moiety selected from lower alkyl, lower alkenyl, thio lower alkyl, cycloalkyl, aryl, and aryl lower alkyl, where the substituent is lower alkyl, halo, hydroxy, $\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$, or COOH ;

R_{10} is S, SO, or SO_2 ;

R_{18} is COOR_{27} or $\text{C(O)NR}_{28}\text{R}_{29}$, or, together with R_{16} , forms $-\text{COOCH}_2\text{CH}_2-$.

R_{19} is a substituted (with one or more substituents; same below) or unsubstituted moiety
5 selected from lower alkyl, lower alkenyl, aryl, and aryl lower alkyl, where the substituent is lower alkyl (e.g., an alkyl group can also be deemed as a substituent too), halo, or alkoxy; and

each of R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} ,
10 and R_{29} , independently, is H or lower alkyl; provided that if R_2 is $(\text{CH}_2)_m\text{SH}$ and R_5 is thio lower alkyl, the free thio groups of R_2 and R_5 can form a disulfide bond either intramolecularly or to another molecule of formula I or II; or a pharmaceutically
15 acceptable salt thereof.

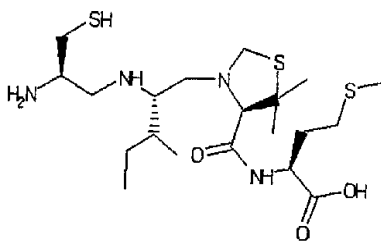
In one embodiment, the compound is of formula I where R_2 is $(\text{CH}_2)_m\text{SR}_{22}$, heterocycle, or heterocycle lower alkyl; each of R_4 and R_{15} , independently, is H; R_5 is lower alkyl; R_6 is H; each of R_8 , R_9 , R_{11} , and R_{12} ,
20 independently, is H or lower alkyl; R_{10} is S; R_{13} is H; R_{16} is lower alkyl or substituted thio lower alkyl wherein the substituent is lower alkyl; and R_{17} is H. In this embodiment, R_1 can be $\text{NR}_{20}\text{R}_{21}$ (e.g., NH_2); R_2 can be $(\text{CH}_2)_m\text{SR}_{22}$ (e.g., CH_2SH); R_3 can be CH_2 ; each of R_8 and R_9 ,
25 independently, can be H; and R_{18} can be COOR_{27} ; furthermore, R_5 can be $\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $(\text{CH}_2)_3\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, or $\text{C}(\text{CH}_3)_3$; each of R_{11} and R_{12} , independently, can be CH_3 ; R_{16} can be $(\text{CH}_2)_2\text{SCH}_3$ or $\text{CH}_2\text{CH}(\text{CH}_3)_2$; and R_{18} can be COOH or COOCH_3 . In the same embodiment, R_1 can be
30 H; R_2 can be heterocycle or heterocycle lower alkyl; R_3 can be CH_2 ; each of R_8 and R_9 , independently, can be H; and R_{18} can be COOR_{27} where R_{27} is H or lower alkyl; furthermore, R_2 can be imidazolyl or imidazolyl lower alkyl; R_5 can be $\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $\text{CH}(\text{CH}_3)_2$, or $\text{C}(\text{CH}_3)_3$; each of R_{11} and R_{12} , independently, can be CH_3 ; R_{16} can be



$(\text{CH}_2)_2\text{SCH}_3$, $(\text{CH}_2)_3\text{CH}_3$, or $\text{CH}_2\text{CH}(\text{CH}_3)_2$; and R_{18} can be COOH or COOCH_3 .

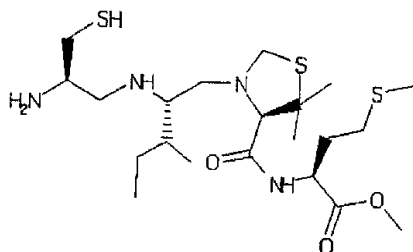
In another embodiment, the compound is of formula II where R_2 is $(\text{CH}_2)_m\text{SR}_{20}$, heterocycle, or heterocycle lower alkyl; each of R_8 , R_9 , R_{11} , and R_{12} , independently, is H or lower alkyl; R_{10} is S; R_{13} is H; and R_{15} is H. In this embodiment, R_1 can be $\text{NR}_{20}\text{R}_{21}$; R_2 can be $(\text{CH}_2)_m\text{SR}_{22}$; R_3 can be CH_2 ; each of R_8 and R_9 , independently, can be H; and R_{19} can be substituted or unsubstituted aryl lower alkyl wherein the substituent is halo or lower alkyl; furthermore, R_1 can be NH_2 ; R_2 can be CH_2SH ; each of R_{11} and R_{12} , independently, can be CH_3 ; and R_{19} is 2,3-dichlorobenzyl or 1-naphthyl-methyl. In the same embodiment, R_1 can be H; R_2 can be heterocycle, or heterocycle lower alkyl; R_3 can be CH_2 ; each of R_8 and R_9 , independently, can be H; and R_{19} can be substituted or unsubstituted aryl lower alkyl wherein the substituent is halo or lower alkyl; furthermore, R_2 can be imidazolyl or imidazolyl lower alkyl; each of R_{11} and R_{12} , independently, can be CH_3 ; and R_{19} can be 2,3-dichlorobenzyl or 1-naphthylmethyl.

Examples of the present invention include the following:

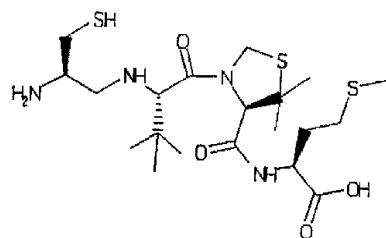


Compound 1;

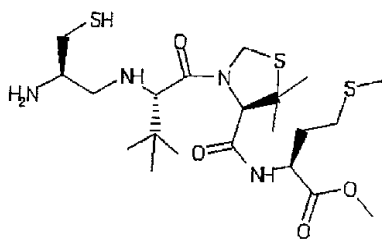
Compound 2;



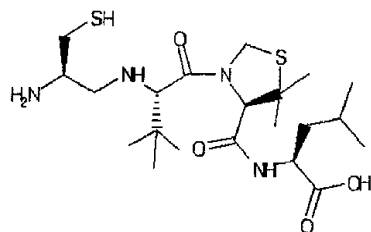
Compound 3;



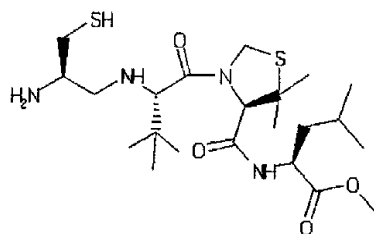
Compound 4;



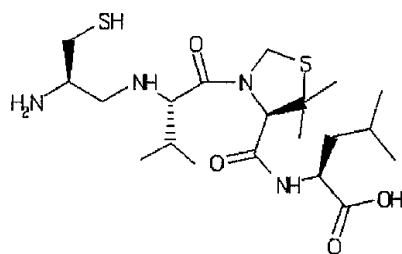
Compound 5;



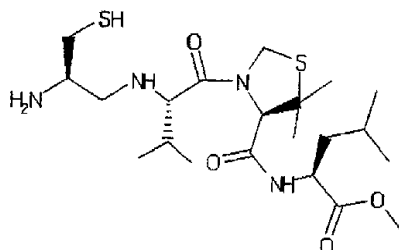
Compound 6;



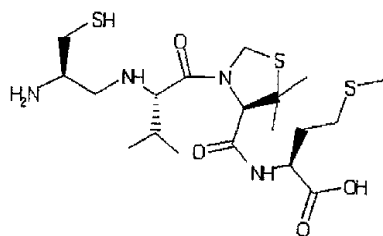
Compound 7;



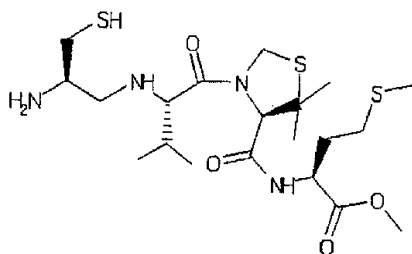
Compound 8;



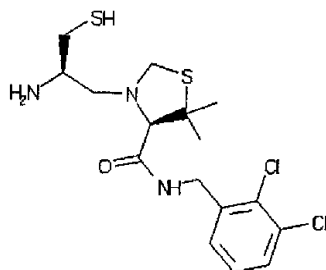
Compound 9;



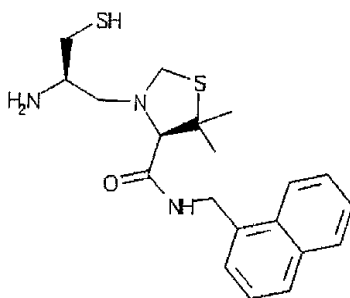
Compound 10;



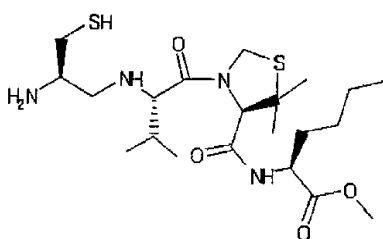
-Compound 11;



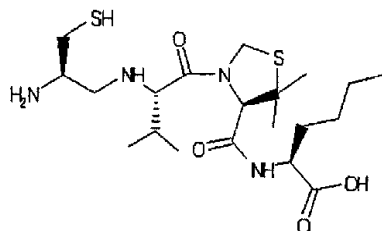
Compound 12;



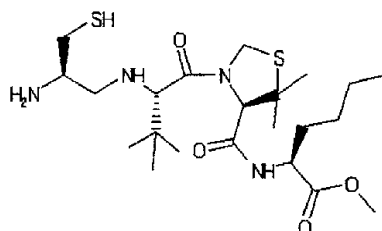
Compound 13;



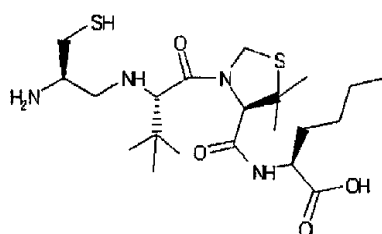
Compound 14;



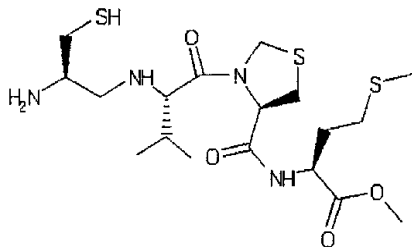
Compound 15;



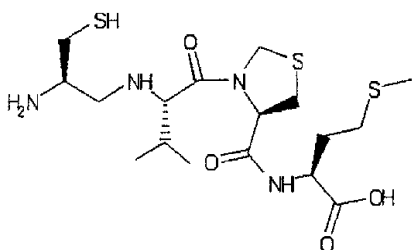
Compound 16;



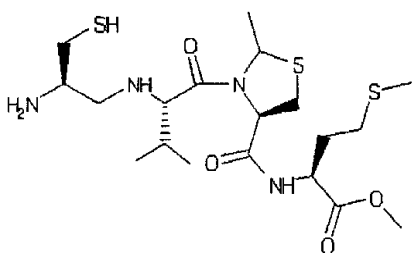
Compound 17;



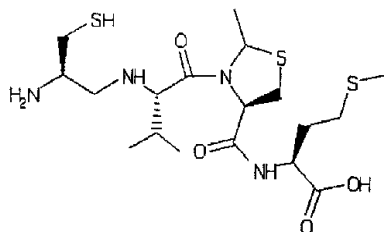
Compound 18;



Compound 19;

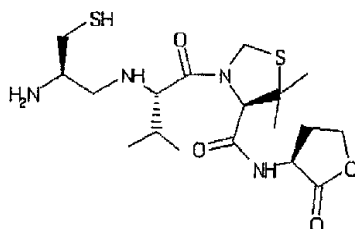


Compound 20;

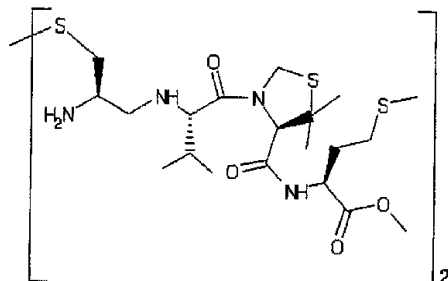


and

Compound 21.



In another aspect, the invention features a dimeric
5 compound consisting of a first moiety and a second moiety,
wherein each of the first and second moieties,
independently, is of formula I or formula II shown above
except that each R_2 of the first moiety and R_2 of the second
moiety, independently, are $-(CH_2)_mS-$ and form a disulfide
10 bond; or a pharmaceutically acceptable salt thereof. The
first and second moieties can be identical or different.
Indeed, R_2 of the first moiety and R_2 of the second moiety
can also be identical or different. An example of such a
dimeric compound is shown below:



Compound 22.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. For simplicity, where no specific configuration is depicted in the structural formulae, it is understood that all enantiometric forms and mixtures thereof are represented.

As used herein, "lower alkyl" is intended to include saturated aliphatic hydrocarbon groups having 1-6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, and the like. "Lower alkenyl" groups include those groups having 2-6 carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, butenyl, pentenyl, hexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, and the like. "Lower alkoxy" groups include those groups having 1-6 carbons. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, and the like. All alkyl, alkenyl, and alkoxy groups may be branched or straight chained, but are noncyclic. The term "cycloalkyl" means a 3-7 carbon ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "halo" means chloro, bromo, iodo, or

- 14 -

fluoro. The terms "heterocycle lower alkyl," "thio lower alkyl," "thio lower alkenyl," "aryl lower alkyl," and "hydroxy lower alkyl," are substituted, respectively, with one to three heterocycle, thio, thio, aryl, and hydroxy groups.

As used herein, "aryl" is intended to include any stable monocyclic, bicyclic, or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl, and the like.

The term heterocycle, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11 to 15-membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl,

- 15 -

thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thiazolidinyl, thienofuryl, thienothienyl, thienyl, and the like.

When a group is substituted, it may be substituted one to four times. The various substituents may be attached to carbon atoms or to heteroatoms (e.g., S, N, or O).

The compounds of this invention can be provided in the form of pharmaceutically acceptable salts. Acceptable salts include, but are not limited to acid addition salts of inorganic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulfonate, p-toluenesulfonate, pamoate, salicylate, oxalate, and stearate. Also within the scope of the present invention, where applicable, are salts formed from bases such as sodium or potassium hydroxide. For further examples of pharmaceutically acceptable salts see, "Pharmaceutical Salts," J. Pharm. Sci. 66:1 (1977).

In a still further aspect, the invention features a method of inhibiting prenyl transferases (e.g., farnesyl transferase or geranylgeranyl transferase) in a subject, e.g., a mammal such as a human, by administering to the subject a therapeutically effective amount of a compound of formula I or formula II. In particular, the present invention also covers a method of treating restenosis or tissue proliferative diseases (i.e., tumor) in a subject by administering to the subject a therapeutically effective amount of a compound or its salt. Examples of tissue proliferative disease include both those associated with benign (e.g., non-malignant) cell proliferation such as fibrosis, benign prostatic hyperplasia, atherosclerosis, and restenosis, and those associated with malignant cell proliferation, such as cancer (e.g., ras mutant tumors). Examples of treatable tumors include breast, colon, pancreas, prostate, lung, ovarian, epidermal, and

hematopoietic cancers (Sepp-Lorenzino, I, et al., Cancer Research 55:5302 (1995)).

A therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle) together form a pharmaceutical composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, or subcutaneously) to a subject in need of the compound. The pill, tablet, or capsule can be coated with a substance capable of protecting the composition from the gastric acid or intestinal enzymes in the subject's stomach for a period of time sufficient to allow the composition to pass undigested into the subject's small intestine.

The dose of a compound of the present invention for treating the above-mentioned diseases or disorders varies depending upon the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the compound as determined by the attending physician or veterinarian is referred to herein as a "therapeutically effective amount."

Also contemplated within the scope of the invention are pharmaceutical preparations of compounds of formula I and formula II, methods of preparing the compounds of formula I or formula II, and the novel chemical intermediates used in these syntheses as described herein.

Other features and advantages of the present invention will be apparent from the detailed description of the invention and from the claims.

Detailed Description of the Invention

- 17 -

It is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

The following is a description of the synthesis of Compounds 1 to 12. Other compounds of the invention can be prepared in an analogous manner by a person of ordinary skill in the art.

The compounds of this invention were prepared by using standard solution phase peptide synthesis methodologies as well as other standard manipulations such as ester hydrolysis and reductive akylation of an amine by an aldehyde, e.g., as described in Greenstein, et al., Chemistry of the Amino Acids, Vols. 1-3 (J. Wiley, New York (1961)); and M. Bodanszky, et al., The Practice of Peptide Synthesis (Springer-Verlag, 1984)). For amide formation reactions, EDC/HOBt or HBTU/DIEA/DMF was used as the coupling agent. Deprotection of the protecting groups was done by using TFA/DCM. The reducing agent used in the reductive alkylation of an amine was sodium cyanoborohydride. The final products were purified by using preparative HPLC and analyzed by ¹H NMR or mass spectroscopy.

EXAMPLE 1: N-[N'-(2(S)-(2(R)-Amino-3-mercaptopropylamine)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine (Compound 1)

- 18 -

- (a) N- α -(tert-Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxylic acid:

A solution of L-5,5-dimethylthiazolidine-4-carboxylic acid (2.5 g, 15.5 mmol) in water (10 mL), dioxane (20 mL), and 2N NaOH (7.8 mL) was stirred and cooled in an ice-water bath. Di-tert-butyl dicarbonate (3.72 g, 17.1 mmol) was added and stirring was continued at room temperature overnight. The solution was concentrated in vacuo to about 25 mL and ethyl acetate (EtOAc; 30 mL) was added. The pH of the solution was adjusted to 2 at 0°C by addition of 2N HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The two organic layers were combined, washed with water (2 times), dried over anhydrous MgSO₄, filtered, and evaporated in vacuo. The title compound, as a white solid (3.60 g; Yield: 89%), was obtained, and it was used in the next reaction without further purification. ¹H NMR (300 MHz, CDCl₃) δ 4.68 (m, 2H), 4.39 (s, 1H) 4.23 (s, 1H), 1.60-1.40 (m, 15H).

- (b) N-[(tert -Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxylic]-L-methionine methyl ester:

A solution of N-(tert-butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxylic acid (1.00 g, 3.83 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 0.734 g; 3.83 mmol), 1-hydroxybenzotriazole (HOBt; 0.517 g; 3.83 mmol), and diisopropylethylamine (DIEA; 0.495 g; 3.83 mmol) in dichloromethane (DCM; 20 mL) was stirred at 0°C for 10 minutes. To this solution was added methionine methyl ester hydrochloride (0.765 g, 3.83 mmol). The mixture was warmed to room temperature and stirred overnight. The solvent was removed in vacuo. The residue was dissolved in EtOAc, washed with 5% citric acid (2 times), 5% Na₂CO₃ (2 times), and brine (2 times), dried over anhydrous MgSO₄, and filtered. The residue obtained after concentration was further purified by column chromatography

- 19 -

on silica, eluting with hexanes/EtOAc (2:1). The title compound, as a white solid (1.09 g; Yield: 70%), was obtained. ¹H NMR (300 MHz, CHCl₃) δ 6.67 (d, 1H), 4.78-4.60 (m, 3H), 4.11 (s, 1H), 3.75 (s, 3H), , 2.55 (m, 2H),
5 2.24-2.00 (m, 5H), 1.56-1.40 (m, 15H).

(c) N-α-(tert-Butoxycarbonyl)-N-methoxy-N-methyl-L-isoleucinamide

A solution of N-α-(tert-butoxycarbonyl)-isoleucine (8.00 g, 33.3 mmol), O-benzotriazole-N,N,N',N'-tetramethyl-
10 uronium-hexafluorophosphate (HBTU; 12.63 g; 33.3 mmol), DIEA (17.21g, 133.2 mmol) in dimethylformamide (DMF, 35 mL) was stirred at room temperature for 2 minutes. To this solution was added N,O-dimethylhydroxylamine hydrochloride (3.25 g, 33.3 mmol), and the mixture was stirred at room temperature
15 overnight. The solvent was removed in vacuo, and the residue was dissolved in EtOAc and washed with 5% citric acid (2 times), 5% Na₂CO₃ (2 times) and brine (2 times), dried over anhydrous MgSO₄, and filtered. The residue obtained after concentration was further purified by column
20 chromatography on silica, eluting with EtOAc/hexanes (1:1). 8.5 g (Yield: 90%) of the title compound was obtained. ¹H NMR (300 MHz, CDCl₃) δ 5.12 (d, 1H), 4.62 (m, 1H), 3.79 (s, 3H), 3.23 (s, 3H), 1.72 (m, 1H), 1.58 (m, 1H), 1.45 (s, 9H), 1.30-1.05 (m, 1H), 1.00-0.85 (m, 6H).

25 (d) N-α-(tert-Butoxycarbonyl)-L-isoleucinal

LiAlH₄ (0.20 g, 5.25 mmol) in 20 mL of anhydrous ether was stirred at room temperature for 30 minutes. The suspension was cooled to -45°C, and a solution of N-α-(tert-butoxycarbonyl)-N-methoxy-N-methyl-L-isoleucinamide (1.10 g, 3.89 mmol) in 6 mL of tetrahydrofuran (THF) was added
30 dropwise to the suspension. The mixture was warmed to 0°C and stirred for 2 hours. The mixture was then cooled to -45°C. To this solution was slowly added a solution of KHSO₄ (1.17 g) in H₂O (10 mL). The resulting mixture was filtered
35 through Celite. The filtrate was washed with 5% citric acid (2 times) and brine (2 times), dried over anhydrous MgSO₄,

- 20 -

filtered, and concentrated to dryness. 0.70 g of the title compound, as a colorless oil, was obtained and was immediately used in the next step without further purification.

- 5 (e) N-[N'-[2(S)-(tert-Butoxycarbonylamino)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester

N-[(tert-Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxyl]-L-methionine methyl ester (1.09 g, 2.68 mmol)
10 was dissolved in a mixture of TFA (15 mL) and DCM (15 mL) and stirred at room temperature for 30 minutes. The solution was concentrated *in vacuo*. The resulting residue and N- α -(tert-butoxycarbonyl)-L-isoleucinal (0.70 g, 3.25 mmol) were dissolved in a mixture of methanol (MeOH; 15 30 mL) and acetic acid (0.6 mL). To this solution was added in portions sodium cyanoborohydride (0.204 g, 3.25 mmol) over a period of 30 minutes. MeOH was removed *in vacuo*. To the rest of the solution was added EtOAc and saturated NaHCO₃. The organic layer was separated and washed with 20 saturated NaHCO₃ (1 time), water (1 time) and brine (1 time), dried over anhydrous MgSO₄, filtered, and concentrated. The residue obtained was further purified by column chromatography on silica, eluting with EtOAc/hexanes (1:2). 1.06 g (Yield: 78%) of the title compound was 25 obtained. ¹H NMR (300 MHz, CDCl₃) δ 8.70 (d, 1H), 4.68 (m, 1H), 4.53 (s, 2H), 3.90 (m, 1H), 3.79 (s, 1H), 3.75 (s, 3H), 3.42 (s, 1H), 2.95 (dd, 1H), 2.78 (dd, 1H), 2.50-2.70 (m, 2H), 2.22 (m, 2H), 2.13 (s, 3H), 1.60-1.40 (m, 12H), 1.36 (m, 2H), 1.38 (m, 2H), 0.92 (m, 9H); mass spectroscopy (electron spray) ((MS(ES)): 505.4, Calculated molecular weight (Calc. MW) = 505.7.

- (f) N- α -(tert -Butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinal

The title compound was synthesized starting with N- 35 α -(tert-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteine by

using the same procedure described in the synthesis of N- α -(*tert*-butoxycarbonyl)-L-isoleucinal.

- (g) N-[N'-[2(S)-(2(R)-(tert-Butoxycarbonylamino)-3-triphenylmethyl-mercaptopropylamine)-3(S)-methylpentyl]-L-5, 5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester
- 5 N-[N'-[2(S)-(tert-Butoxycarbonylamino)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (1.06 g, 2.10 mmol) was dissolved in
- 10 a mixture of trifluoroacetic acid (TFA; 15 mL) and DCM (15 mL) and stirred for 30 minutes at room temperature. The solution was concentrated *in vacuo*. The residue obtained and N- α -(*tert*-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinyl (1.10 g, 2.46 mmol) were dissolved in a mixture of
- 15 MeOH (15 mL) and HOAc (0.3 mL). To this was added in portions sodium cyanoborohydride (0.158 g, 2.52 mmol) over a period of 30 minutes. The mixture was stirred at room temperature overnight. 5 mL of saturated NaHCO₃ was added, and MeOH was removed *in vacuo*. To the rest of the solution
- 20 was added EtOAc and saturated NaHCO₃. The organic layer was separated and washed with saturated NaHCO₃ (1 time) and brine (2 times), dried over anhydrous MgSO₄, and filtered. Concentration *in vacuo* gave the title compound, which was used directly in the next step without further purification.
- 25 MS(ES): 836.5, Calc. MW=836.8.

- (h) N-[N'-[2(S)-(2(R)-Amino-3-mercaptopropylamine)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine
- N-[N'-[2(S)-(2(R)-(tert-Butoxycarbonylamino)-3-triphenylmethylmercaptopropylamine)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester
- 30 (0.50 g, 0.42 mmol) was dissolved in a mixture of MeOH (16 mL) and 5 N NaOH (4 mL) at 0°C and stirred for 3 hours. The solution was neutralized to pH 7 by addition of 2N HCL.
- 35 MeOH was removed *in vacuo* and EtOAc was added. The mixture was cooled to 0°C, and the aqueous layer was acidified to pH 2 by adding 2N HCL. The organic layer was separated, and

the aqueous layer was extracted with EtOAc. The organic layers were pooled, washed with brine (1 time), dried over anhydrous MgSO_4 , and filtered. The residue obtained after concentration in vacuo was dissolved in a mixture of trifluoroacetic acid (TFA; 6 mL), DCM (6 mL), and triethylsilane (0.6 mL). The solution was stirred at room temperature for 40 minutes. The residue after concentration in vacuo was partitioned between ether and 0.1% TFA aqueous solution. The aqueous layer was separated, purified on a preparative high performance liquid chromatography (HPLC) eluting with 0.1% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ buffer, and lyophilized to give the title compound. MS(ES): 480.3, Calc. MW=480.8

EXAMPLE 2: N-[N'-[2(S)-(2(R)-Amino-3-mercaptopropylamine)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (Compound 2)

N-[N'-[2(S)-(2(R)-(tert-Butoxycarbonylamino)-3-triphenylmethylmercaptopropylamine)-3(S)-methylpentyl]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (0.60 g, 0.718 mmol; Example 1(g)) was dissolved in a mixture of TFA (10 mL), DCM (10 mL), and triethylsilane (1 mL). The reaction mixture was stirred at room temperature for 30 minutes. The solution was concentrated in vacuo. The residue was partitioned between 1% TFA aqueous solution and ether. The aqueous layer was separated, purified by HPLC, and lyophilized to give the title compound. MS(ES): 494.3, Calc. MW=494.8.

EXAMPLE 3: N-[N'-[N''-(2(R)-Amino-3-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine (Compound 3)

(a) N-[N'[(tert-Butoxycarbonyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]methionine methyl ester

N-[(tert-Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (1.63 g; 4.01 mmol; Example 1(b)) was dissolved in a mixture of TFA (5 mL) and

- 23 -

DCM (5 mL) and stirred at room temperature for 30 minutes. The solution was concentrated *in vacuo*. The residue was dissolved in toluene, and the solution was condensed *in vacuo*. This procedure was repeated three times and a white foam was obtained.

A solution of N- α -(*tert*-butoxycarbonyl)-*tert*-leucine (1.0 g, 4.01 mmol), EDC (0.769 g, 4.01 mmol), HOBT (0.650 g, 4.81 mmol), and DIEA (0.570 g, 4.41 mmol) in DCM (15 mL) was stirred at room temperature for 10 minutes. To it was added the above white foam. The mixture was stirred overnight. The solution was diluted with DCM (15 mL) and washed with 5% NaHCO₃ (2 times), 5% citric acid (2 times), and brine (2 times), dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with hexanes:EtOAc (2:1) and hexanes:EtOAc (1:1). 0.63 g of the title compound was obtained (Yield: 30%). ¹H NMR (300 MHz, CDCl₃) δ 6.48 (d, 1H), 5.25 (d, 1H), 5.12 (d, 1H), 4.95-4.62 (m, 2H), 4.43-4.30 (m, 2H), 3.77 (s, 3H), 2.58 (m, 2H), 2.21, (m, 1H), 2.11 (s, 3H), 2.04 (m, 1H), 1.55-1.33 (m, 12H), 1.12-0.94 (m, 12H).

(b) N-[N'-(N''-(2(R)-(tert-Butoxycarbonylamino)-3-triphenylmethyl-mercaptopropyl)-*tert*-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester

0.6 g (1.15 mmol) of N-[N'-(*tert*-butoxycarbonyl)-*tert*-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester was dissolved in a mixture of TFA (5 mL), DCM (5 mL) and triethylsilane (Et₃SiH) (1 mL) and stirred at room temperature for 30 minutes. The solution was concentrated *in vacuo*. The residue was dissolved in toluene, and the solution was condensed to dryness. This procedure was repeated until a white foam was obtained (4 times). This foam and 0.5 g (1.12 mmol) of N- α -(*tert*-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinal (Example 1(f)) were dissolved in 4 mL of methanol and 0.2 mL of

- 24 -

acetic acid. To this mixture was added NaBH_3CN (72 mg, 1.15 mmol), and it was stirred for 30 minutes. 0.5 g (1.12 mmol) of N- α -(tert-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinyl and 72 mg (1.15 mmol) of NaBH_3CN were added. The reaction mixture was stirred for 30 minutes. 0.5 g (1.12 mmol) of N- α -(tert-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinyl and 72 mg (1.15 mL) of NaBH_3CN were then added followed by addition of 0.1 mL of acetic acid. The solution was stirred overnight and concentrated in vacuo. The residue was dissolved in EtOAc and washed with saturated NaHCO_3 (2 times) and brine (2 times), dried over anhydrous MgSO_4 , filtered, and condensed in vacuo. The residue was purified by using column chromatography (silica), eluting with EtOAc:hexanes (1:2) and EtOAc:hexanes (1:1). 930 mg (Yield: 95%) of the title compound, as a white solid, was obtained. MS(ES): 850.5 Calc. MW = 850.8

(c) N-[N'-[N''(2(R)-Amino-3-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine

230 mg (0.27 mmol) of N-[N'-[N''-(2(R)-(tert-butoxycarbonylamino)-3-triphenylmethyl-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester was dissolved in 2 mL of methanol at 0°C. To it was added 0.4 mL of 1 N KOH solution. The white precipitate was dissolved by addition of 0.8 mL of THF. The mixture was warmed to room temperature and stirred for 1.5 hours. To the solution was added 2 N HCl at 0°C until the pH was about 2. The solution was diluted to 25 mL by addition of EtOAc and then 10 mL of brine was added. The organic layer was separated, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo to give a white solid (220 mg). The white solid was dissolved in a mixture of 5 mL of DCM and 1 mL of triethylsilane (Et_3SiH). To it was added 5 mL of TFA, and the solution was stirred for 40 minutes. The solution was concentrated in vacuo. The white solid was triturated with hexanes and then dissolved in 0.1

- 25 -

% TFA aqueous solution. It was purified on a preparative HPLC and lyophilization gave the title compound (47 mg; Yield: 36 %). ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, 1H), 5.02 (d, 1H), 4.74 (d, 1H), 4.66 (m, 1H), 4.53 (s, 1H), 4.47 (m, 1H), 3.30 (m, 2H), 2.77 (m, 2H), 2.58 (m, 1H), 2.51 (m, 4H), 2.03 (m, 4H), 1.82 (m, 1H) 1.54 (s, 2H), 1.38 (s, 3H), 1.03 - 0.88 (m, 12H); MS (ES): 494.2, Calc. MW=494.7

EXAMPLE 4: N-[N'-[N''-(2(R)-Amino-3-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (Compound 4)
660 mg (0.776 mmol) of N-[N'-[N''-(2(R)-(tert-butoxycarbonyl-amino)-3-triphenylmethyl-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine methyl ester (Example 3(b)) was dissolved in a mixture of DCM (5 mL) and Et₃SiH (1 mL). To it was added 5 mL of TFA. The mixture was stirred at room temperature for 0.5 hours. The solution was concentrated *in vacuo*. The residue was triturated with hexanes and then dissolved in 0.1 % TFA aqueous solution. It was purified by a preparative HPLC, eluting with a gradient (buffer A: 0.1 % TFA in H₂O, buffer B: 0.1 % TFA in CH₃CN). Lyophilization gave the title compound as a white solid (310 mg; Yield: 78%). MS (ES): 508.3, Calc. MW = 508.8.

EXAMPLE 5: N-[N'-[N''-(2(R)-Amino-3-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-leucine (Compound 5)

The title compound was synthesized by using an analogous procedure described in the synthesis of Example 3. MS(ES): 476.2, Calc. MW = 476.3.

EXAMPLE 6: N-[N'-[N''-(2(R)-Amino-3-mercaptopropyl)-tert-leucine]-L-5,5-dimethylthiazolidine-4-carboxyl]-leucine-methyl ester

- 26 -

The title compound was synthesized by using an analogous procedure described in the synthesis of Example 4. MS(ES): 490.3, Calc. MW = 490.7.

5 EXAMPLE 7: N-[N'-(N''-(2(R)-Amino-3-mercaptopropyl)-valine]-L-5,5-dimethylthiazolidine-4-carboxyl]-leucine (Compound 7)

The title compound was synthesized by using an analogous procedure described in the synthesis of Example 3. MS(ES): 462.4, Calc. MW = 462.7.

10 EXAMPLE 8: N-[N'-(N''-(2(R)-Amino-3-mercaptopropyl)-valine]-L-5,5-dimethylthiazolidine-4-carboxyl]-leucine-methyl ester (Compound 8)

The title compound was synthesized by using an analogous procedure described in the synthesis of Example 4. 15 MS(ES): 476.3, Calc. MW = 476.7.

EXAMPLE 9: N-[N'-(N''-(2(R)-Amino-3-mercaptopropyl)-valine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine (Compound 9)

The title compound was synthesized by using an analogous procedure described in the synthesis of Example 3. 20 MS(ES): 480.3, Calc. MW = 480.7.

EXAMPLE 10: N-[N'-(N''-(2(R)-Amino-3-mercaptopropyl)-valine]-L-5,5-dimethylthiazolidine-4-carboxyl]-methionine-methyl ester (Compound 10)

25 The title compound was synthesized by using an analogous procedure described in the synthesis of Example 4. MS(ES): 494.3, Calc. MW = 494.8.

EXAMPLE 11: [N-(2(R)-Amino-3-mercaptopropyl)-L-5,5-dimethylthiazolidine-4-carboxyl]-2,3-dichlorobenzamide (Compound 11)

30 (a) [(tert-Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxyl]-2,3-dichlorobenzamide

A solution of N- α -(tert-butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxylic acid (0.65 g, 2.50 mmol;

- 27 -

- Example 1(a)), HBTU (0.948 g, 2.50 mmol), and DIEA (1.3 g, 10 mmol) in DMF (25 mL) was stirred at room temperature for 3 minutes. To it was added 2, 3-dichlorobenzylamine (0.44 g, 2.50 mmol). The mixture was stirred overnight.
- 5 The solvent was removed in vacuo, and the residue was dissolved in EtOAc, washed with 5% NaHCO₃ (2 times), 5% citric acid (2 times), and brine (2 times), dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The title compound (0.83 g; Yield: 79%) was obtained after
- 10 chromatography (silica) with EtOAc:hexanes (1:2). ¹H NMR (300 MHz, CDCl₃) δ 7.40 (m, 2H), 7.18 (m, 1H), 6.55 (bs, 1H), 4.65 (m, 3H), 4.52 (m, 1H), 4.07 (s, 1H), 1.58 (s, 3H), 1.20, (m, 12H).
- 15 (b) [N-(2(R)-Amino-3-mercaptopropyl)-L-5,5-dimethyl-thiazolidine-4-carboxyl]-2,3-dichlorobenzamide [(tert-Butoxycarbonyl)-L-5,5-dimethylthiazolidine-4-carboxyl]-2,3-dichlorobenzamide (0.419 g, 1 mmol) was dissolved in 10 mL of 50 % TFA in DCM. The mixture was stirred at room temperature for 0.5 hours. TFA and the
- 20 solvent were removed in vacuo. The residue and N-α-(tert-butoxycarbonyl)-S-(triphenylmethyl)-L-cysteinyl (2 mmol; Example 1(f)) were dissolved in MeOH (10 mL) and HOAc (0.2 mL). To it was added in portions sodium cyanoborohydride (94 mg, 1.5 mmol). The mixture was stirred
- 25 at room temperature overnight. The solvents were removed in vacuo, and the residue was dissolved in EtOAc. The solution was washed with 5% NaHCO₃ (2 times), 5% citric acid (2 times) and brine (2 times), dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The residue was
- 30 dissolved in 15 mL of DCM and 2 mL of triisopropylsilane. To the solution was added 10 mL of TFA. The reaction mixture was stirred at room temperature for 0.5 hours. The solution was condensed in vacuo, and the resulting residue was partitioned between 0.1% TFA aqueous solution and EtOAc.
- 35 The organic layer was concentrated in vacuo. The residue was triturated with hexanes and then purified by HPLC.

- 28 -

Lyophilization gave the title compound (339 mg; Yield: 83%).
MS (ES): 407.0, Calc. MW = 407.4. ¹H NMR (300 MHz, CDCl₃)
δ 8.21 (bs, 2H), 7.61 (t, 1H), 7.41 (dd, 1H), 7.27 (dd, 1H),
7.19 (dd, 1H), 4.55 (d, 2H), 4.43 (d, 1H), 3.88, (d, 1H),
5 3.28 (s, 1H), 3.22 (m, 1H), 3.10 (m, 2H), 2.79 (m, 2H), 1.73
(bs, 1H), 1.57 (s, 3H), 1.38 (s, 3H).

EXAMPLE 12: [N-(2(R)-Amino-3-mercaptopropyl)-L-5,5-
dimethylthiazolidine-4-carboxyl]-naphthylmethyl
amide (Compound 12)

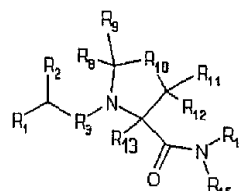
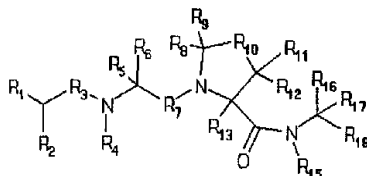
10 The title compound was synthesized by using an
analogous procedure to Example 11. MS(ES): 389.1, Calc. MW
= 389.6 ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, 1H), 7.90 (m,
1H), 7.82 (d, 1H), 7.61-7.41 (m, 5H), 5.22 (dd, 1H), 4.63
(dd, 1H), 4.39 (d, 1H), 3.78 (d, 1H), 3.24 (s, 1H), 2.97 (m,
15 2H), 2.76 (m, 1H), 2.48 (m, 2H), 1.57 (s, 3H), 1.40 (s, 3H),
1.28 (m, 1H).

Other Embodiments

It is to be understood that while the invention has
been described in conjunction with the detailed description
20 thereof, that the foregoing description is intended to
illustrate and not limit the scope of the invention, which
is defined by the scope of the appended claims. Other
aspects, advantages, and modifications are within the
claims.

What is claimed is:

1. A compound of formula I or formula II



formula I

formula II

5 wherein

R_1 is H or $NR_{20}R_{21}$;

R_2 is $(CH_2)_mSR_{22}$, $(CH_2)_mSSR_{22}$, substituted or unsubstituted heterocycle, or substituted or unsubstituted heterocycle lower alkyl, where m is 1-6 and said substituent
 10 is lower alkyl, lower alkenyl, aryl, or aryl lower alkyl;
 each of R_3 and R_7 , independently, is CH_2 or $C(O)$;
 each of R_4 and R_{15} , independently, is H or lower alkyl;

each of R_5 and R_{16} , independently, is H or a
 15 substituted or unsubstituted moiety selected from lower alkyl, thio lower alkyl, lower alkenyl, thio lower alkenyl, cycloalkyl, cycloalkyl lower alkyl, aryl, and aryl lower alkyl, where said substituent is lower alkyl, hydroxy, halo, $C(O)NR_{23}R_{24}$, or $COOH$;

20 each of R_6 , R_8 , R_9 , R_{11} , R_{12} , R_{13} , and R_{17} , independently, is H or a substituted or unsubstituted moiety selected from lower alkyl, lower alkenyl, thio lower alkyl, cycloalkyl, aryl, and aryl lower alkyl, where said substituent is lower alkyl, halo, hydroxy, $C(O)NR_{25}R_{26}$, or
 25 $COOH$;

R_{10} is S, SO, or SO_2 ;

R_{18} is $COOR_{27}$ or $C(O)NR_{28}R_{29}$, or, together with R_{16} , forms $-COOCH_2CH_2-$.

R_{19} is a substituted or unsubstituted moiety selected
5 from lower alkyl, lower alkenyl, aryl, and aryl lower alkyl, where said substituent is lower alkyl, halo, or alkoxy; and

each of R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , and R_{29} , independently, is H or lower alkyl; provided that if R_2 is $(CH_2)_mSH$ and R_5 is thio lower alkyl,
10 said free thio groups of R_2 and R_5 can form a disulfide bond either intramolecularly or to another molecule of formula I or II; or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein said compound has formula I; or a pharmaceutically acceptable salt thereof.

15 3. A compound of claim 1, wherein said compound has formula II; or a pharmaceutically acceptable salt thereof.

4. A compound of claim 2, wherein R_2 is $(CH_2)_mSR_{22}$, heterocycle, or heterocycle lower alkyl; each of R_4 and R_{15} ,
20 independently, is H; R_5 is lower alkyl; R_6 is H; each of R_8 , R_9 , R_{11} , and R_{12} , independently, is H or lower alkyl; R_{10} is S; R_{13} is H; R_{16} is lower alkyl or substituted thio lower alkyl wherein said substituent is lower alkyl; and R_{17} is H; or a pharmaceutically acceptable salt thereof.

25 5. A compound of claim 4, wherein R_1 is $NR_{20}R_{21}$ and R_2 is $(CH_2)_mSR_{22}$; or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5, wherein R_3 is CH_2 ; each of R_8 and R_9 , independently, is H; and R_{18} is $COOR_{27}$; or a pharmaceutically acceptable salt thereof.



7. A compound of claim 6, wherein R_1 is NH_2 ; R_2 is CH_2SH ; R_5 is $CH(CH_3)(CH_2CH_3)$, $CH(CH_3)_2$, or $C(CH_3)_3$; each of R_{11} and R_{12} , independently, is CH_3 ; R_{16} is $(CH_2)_2SCH_3$, $(CH_2)_3CH_3$, or $CH_2CH(CH_3)_2$; and R_{18} is $COOH$ or $COOCH_3$; or a
5 pharmaceutically acceptable salt thereof.

8. A compound of claim 4, wherein R_1 is H ; and R_2 is heterocycle or heterocycle lower alkyl; or a pharmaceutically acceptable salt thereof.

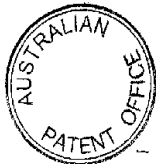
9. A compound of claim 8, wherein R_3 is CH_2 ; each of
10 R_8 and R_9 , independently, is H ; and R_{18} is $COOR_{27}$; or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9, wherein R_2 is imidazolyl or imidazolyl lower alkyl; R_5 is $CH(CH_3)(CH_2CH_3)$, $CH(CH_3)_2$, or $C(CH_3)_3$; each of R_{11} and R_{12} , independently, is CH_3 ; R_{16}
15 is $(CH_2)_2SCH_3$, $(CH_2)_3CH_3$, or $CH_2CH(CH_3)_2$; and R_{18} is $COOH$ or $COOCH_3$; or a pharmaceutically acceptable salt thereof.

11. A compound of claim 3, wherein R_2 is $(CH_2)_mSR_{22}$, heterocycle, or heterocycle lower alkyl; each of R_8 , R_9 , R_{11} , and R_{12} , independently, is H or lower alkyl; R_{10} is S ;
20 R_{13} is H ; and R_{15} is H ; or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11, wherein R_1 is $NR_{20}R_{21}$; and R_2 is $(CH_2)_mSR_{22}$; or a pharmaceutically acceptable salt thereof.

25 13. A compound of claim 12, wherein R_3 is CH_2 ; R_8 and R_9 are H ; and R_{19} is substituted or unsubstituted aryl lower alkyl where said substituent is halo or lower alkyl; or a pharmaceutically acceptable salt thereof.



14. A compound of claim 13, wherein R_1 is NH_2 ; R_2 is CH_2SH ; each of R_{11} and R_{12} , independently, is CH_3 ; and R_{19} is 2,3-dichlorobenzyl or 1-naphthylmethyl; or a pharmaceutically acceptable salt thereof.

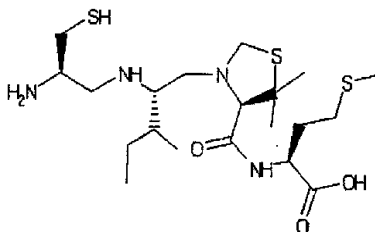
5 15. A compound of claim 11, wherein R_1 is H and R_2 is heterocycle or heterocycle lower alkyl; or a pharmaceutically acceptable salt thereof.

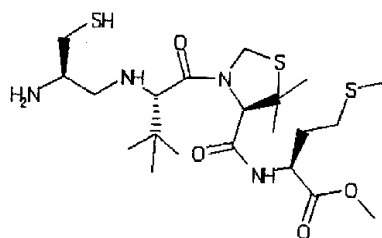
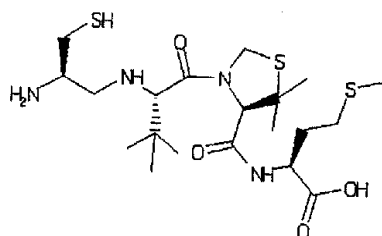
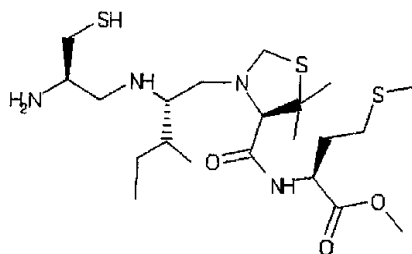
16. A compound of claim 15, wherein R_3 is CH_2 ; each of R_8 and R_9 , independently, is H; and R_{19} is substituted or
10 unsubstituted aryl lower alkyl where said substituent is halo or lower alkyl; or a pharmaceutically acceptable salt thereof.

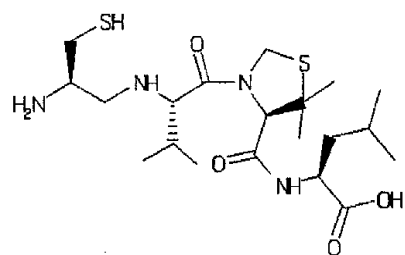
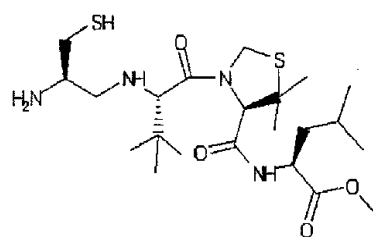
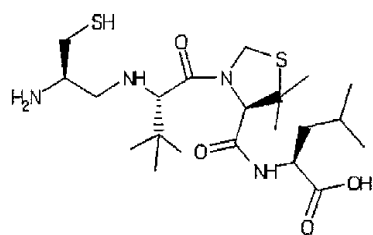
17. A compound of claim 16, wherein R_2 is imidazolyl or imidazolyl lower alkyl; each of R_{11} and R_{12} ,
15 independently, is CH_3 ; and R_{19} is 2,3-dichlorobenzyl or 1-naphthylmethyl; or a pharmaceutically acceptable salt thereof.

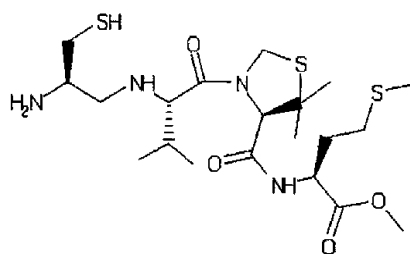
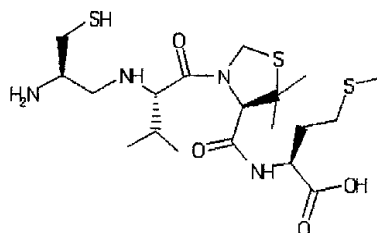
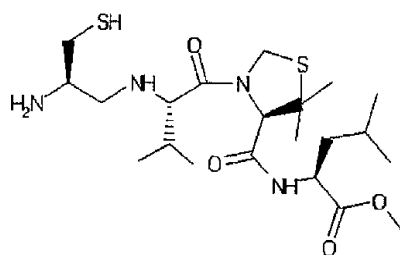
18. A compound of claim 1, said compound being of the formula:

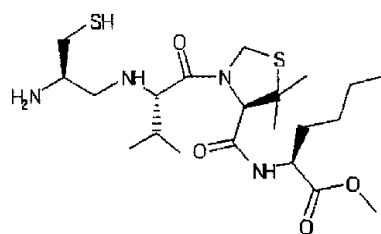
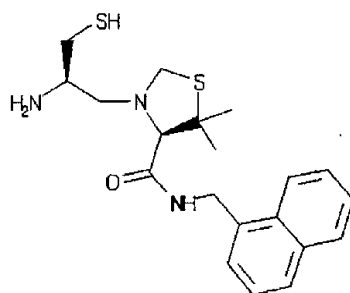
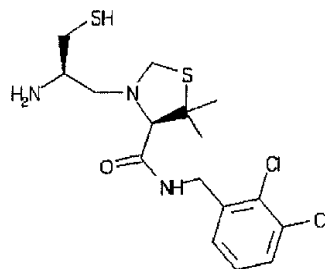
20

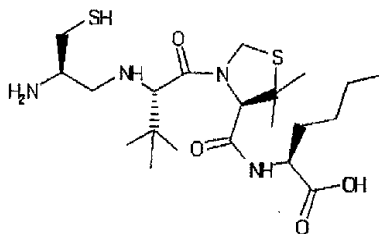
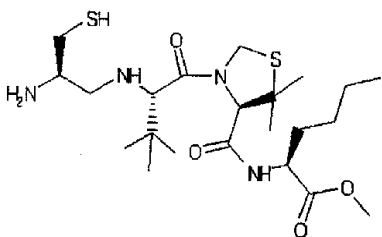
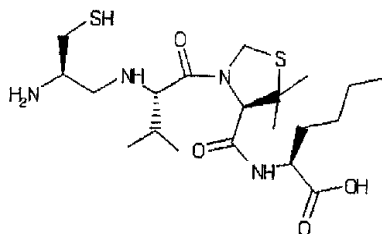












- 38 -

19. A compound consisting of a first moiety and a second moiety, wherein each of said first and second moieties, independently, is of formula I or formula II of claim 1 except that each R_2 of said first moiety and R_2 of said second moiety, independently, are $-(CH_2)_mS-$ and form a disulfide bond; or a pharmaceutically acceptable salt thereof.

20. A compound of claim 19 wherein said first and second moieties are identical; or a pharmaceutically acceptable salt thereof.

21. A method of treating tumors or restenosis in a subject in need of said treatment, which comprises administering to said subject a therapeutically effective amount of the compound or salt of claim 1.

22. A method of claim 21, wherein said compound or salt is that of claim 18.

23. A method of claim 22, wherein said compound or salt is that of claim 19.