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**PRENYL TRANSFERASE INHIBITORS****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 Cys<sup>168</sup> with farnesyl or geranylgeranyl  
10 pyrophosphate in a reaction catalyzed by prenyl  
transferase enzymes such as farnesyl tranferase 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 Cys<sup>168</sup> (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.

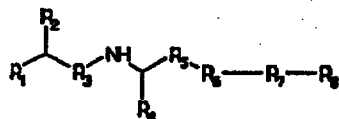
Previously, it has been shown that the C-terminal  
tetrapeptide of Ras has the "CAAX" motif (wherein C is  
35 cysteine, A is an aliphatic amino acid, and X is any

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)).

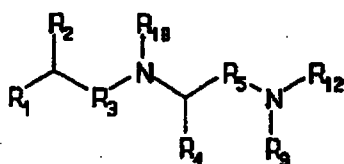
Recently, it has been shown that a prenyl  
15 transferase inhibitor can block growth of Ras-dependent tumors in nude mice (Kohl, NE, et al., Proc. Nat'l Acad. Sci. USA 91:9141-9145 (1994)). In addition, it has been shown that over 70 percent of a large sampling of tumor cell lines are inhibited by prenyl 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



5



Formula I

Formula II

wherein

- $R_1$  is  $N(R_{10})(R_{11})$ ;
- $R_2$  is thio lower alkyl;
- 10 each of  $R_3$  and  $R_5$ , independently, is  $CH_2$  or  $C(O)$ ;
- $R_4$  is substituted or unsubstituted thio lower alkyl, wherein said substituent is  $CH_2NHC(O)R_{13}$  and said substituent is attached to said thio group;
- $R_6$  is a residue of a natural or synthetic  $\alpha$ -amino
- 15 acid;
- $R_7$  is a residue of a natural or synthetic  $\alpha$ -amino acid;
- $R_8$  is OH or lower alkoxy, or, together with  $R_7$ , forms homoserinelactone;
- 20 each of  $R_9$ ,  $R_{10}$  and  $R_{11}$ , independently, is H or lower alkyl;
- $R_{12}$  is substituted or unsubstituted cycloalkyl, cycloalkyl lower alkyl, aryl, aryl lower alkyl, heterocycle, or heterocycle lower alkyl, wherein said
- 25 substituent is lower alkyl, aryl, halo, lower alkoxy, or  $C(O)-R_7-R_8$ ;

$R_{13}$  is lower alkyl, aryl, or aryl lower alkyl;  $R_{18}$  is H or, together with  $R_9$ , forms  $\text{CH}_2\text{CH}_2$ ; provided if  $R_4$  is unsubstituted thio lower alkyl, the free thio group of  $R_2$  and the free thio group of  $R_4$  may  
5 form a disulfide bond; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound is of formula I where  $R_6$  is  $-\text{N}(\text{R}_{14})\text{CH}(\text{R}_{15})\text{C}(\text{O})-$  where  $R_{14}$  is H or lower alkyl, and  $R_{15}$  is substituted or unsubstituted lower  
10 alkyl, aryl, aryl lower alkyl, heterocycle, or heterocycle lower alkyl where said substituent is lower alkyl, halo, or lower alkoxy, or where  $R_{15}$ , together with  $\text{NR}_{14}\text{C}$  attached thereto, form heterocycle; and  $R_7$  is  $-\text{N}(\text{R}_{16})\text{CH}(\text{R}_{17})\text{C}(\text{O})-$  where  $R_{16}$  is H or lower alkyl, and  $R_{17}$   
15 is  $(\text{CH}_2)_m\text{S}(\text{O})_n\text{CH}_3$  or substituted or unsubstituted lower alkyl, thio lower alkyl, where said substituent is  $\text{C}(\text{O})\text{N}(\text{R}_{10})(\text{R}_{11})$ ,  $m$  is 1-6,  $n$  is 0-2, and  $R_8$  is OH or lower alkoxy. In this embodiment,  $R_2$  can be  $\text{CH}_2\text{SH}$ ;  $R_4$  can be  $\text{C}(\text{CH}_3)_2\text{SH}$  or  $\text{CH}_2\text{SH}$  wherein the free thio group of  $R_2$  and  
20 the free thio group of  $R_4$  form a disulfide bond;  $R_{15}$ , together with  $\text{NR}_{14}\text{C}$  attached thereto, can form heterocycle;  $R_{16}$  can be H; and  $R_{17}$  can be  $(\text{CH}_2)_2\text{S}(\text{O})_n\text{CH}_3$ ; furthermore,  $R_1$  can be  $\text{NH}_2$ ;  $R_3$  can be  $\text{CH}_2$ ;  $R_5$  can be CO; and  $R_8$  can be OH or  $\text{OCH}_3$ . In the same embodiment,  $R_2$  can  
25 be  $(\text{CH}_2)\text{SH}$ ;  $R_4$  can be  $\text{C}(\text{CH}_2)_2\text{SCH}_2\text{NHCOCH}_3$  or  $\text{CH}_2\text{SCH}_2\text{NHCOCH}_3$ ;  $R_{15}$ , together with  $\text{NR}_{14}\text{C}$  attached thereto, can form heterocycle;  $R_{16}$  can be H, and  $R_{17}$  can be  $(\text{CH}_2)_2\text{S}(\text{O})_n\text{CH}_3$ ; furthermore,  $R_1$  is  $\text{NH}_2$ ;  $R_3$  is  $\text{CH}_2$ ;  $R_5$  is  $\text{C}(\text{O})$ ; and  $R_8$  is OH or  $\text{OCH}_3$ .

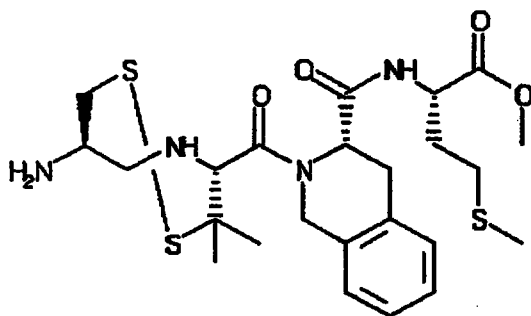
30 In another embodiment, the compound is of formula II, wherein  $R_2$  is  $\text{CH}_2\text{SH}$ ;  $R_4$  is  $\text{C}(\text{CH}_3)_2\text{SH}$  or  $\text{CH}_2\text{SH}$  wherein the free thio group of  $R_2$  and the free thio group of  $R_4$  form a disulfide bond;  $R_{12}$  is substituted or unsubstituted aryl or aryl lower alkyl, and  $R_{18}$  is H. In this  
35 embodiment,  $R_1$  can be  $\text{NH}_2$ ;  $R_3$  can be  $\text{CH}_2$ ;  $R_5$  can be  $\text{C}(\text{O})$ ;  $R_9$  can be H; and  $R_{12}$  can be substituted or unsubstituted

phenyl or benzyl, wherein said substituent is lower alkyl or halo.

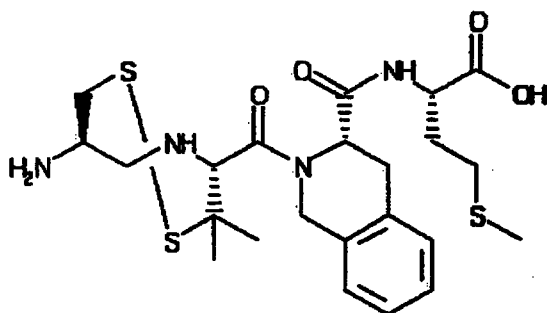
In a still further embodiment,  $R_2$  is  $(CH_2)SH$ ;  $R_4$  is  $C(CH_2)_2SCH_2NHC(=O)CH_3$  or  $CH_2SCH_2NHC(=O)CH_3$ ; and  $R_{12}$  is substituted or unsubstituted aryl or aryl lower alkyl. In this embodiment,  $R_1$  can be  $NH_2$ ;  $R_3$  can be  $CH_2$ ;  $R_5$  can be  $CO$ ;  $R_9$  can be  $H$ ; and  $R_{12}$  can be substituted or unsubstituted phenyl or benzyl, wherein said substituent is lower alkyl or halo.

10 Examples of the present invention include the following:

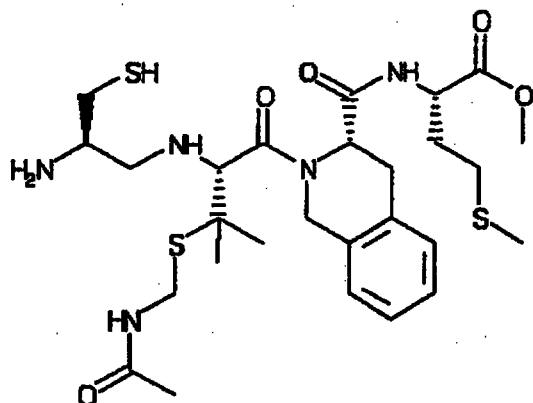
Compound 1;



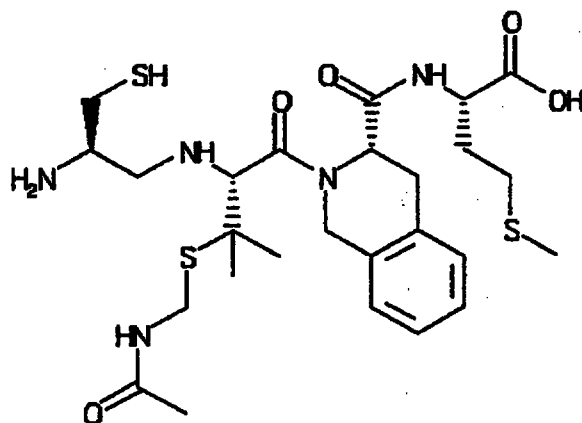
Compound 2;



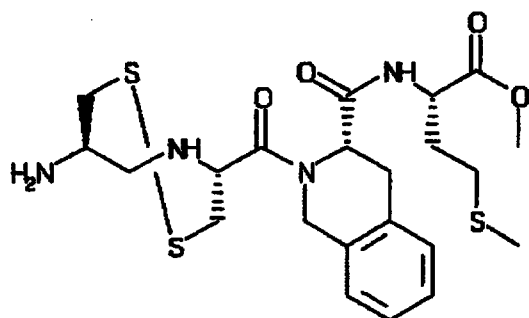
Compound 3;



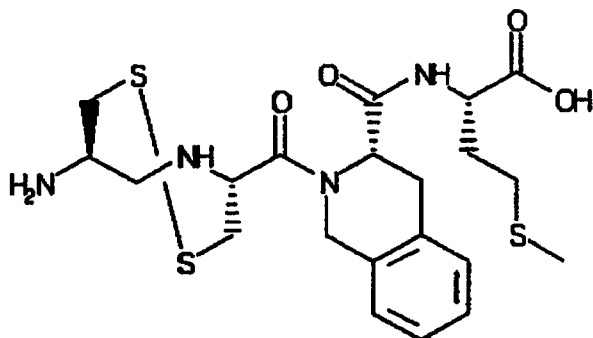
Compound 4;



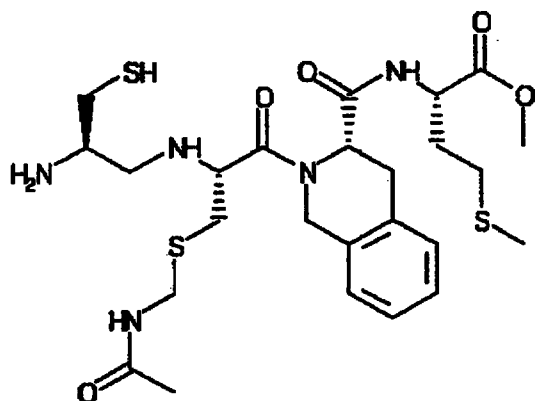
Compound 5;



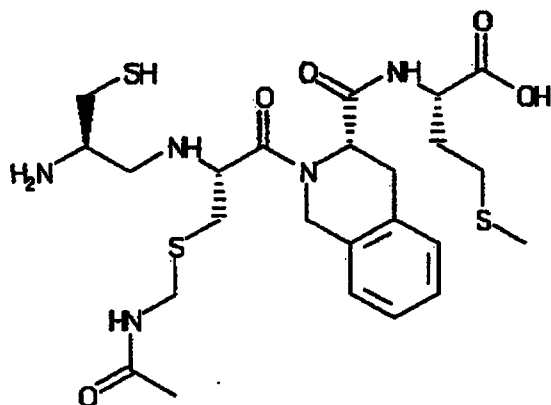
Compound 6;



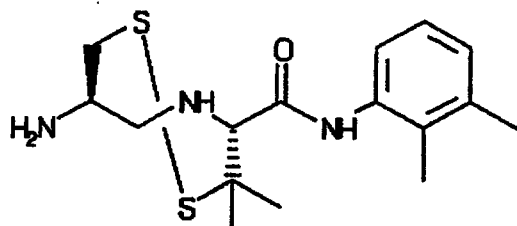
Compound 7;



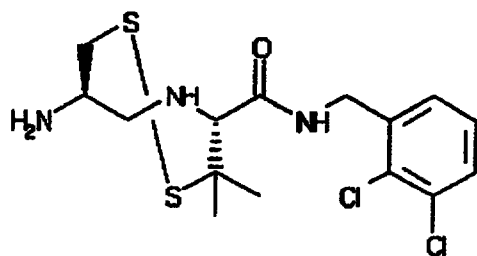
Compound 8;



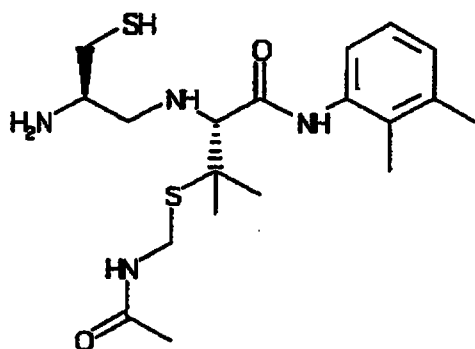
Compound 9;



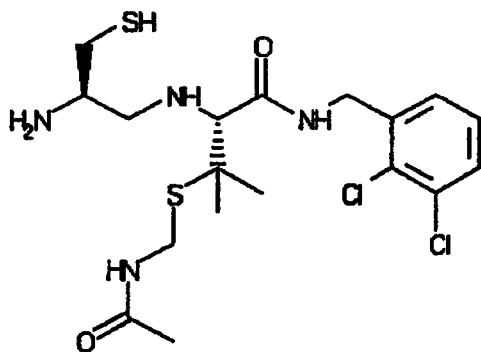
Compound 10;



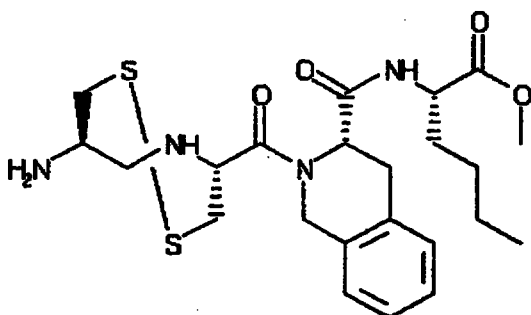
Compound 11;



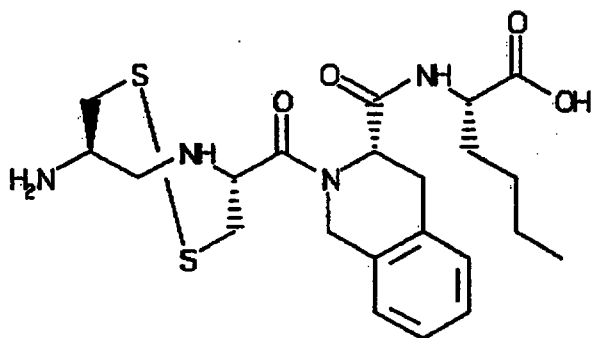
Compound 12;



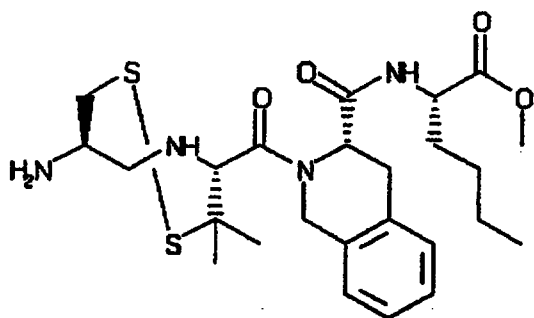
Compound 13;



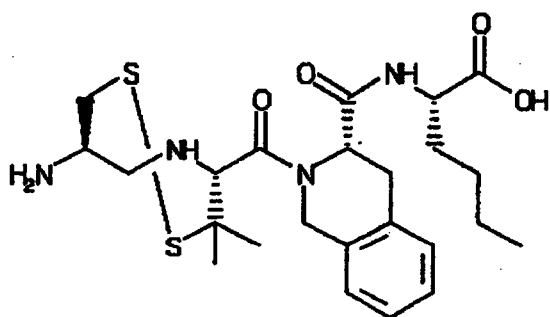
Compound 14;



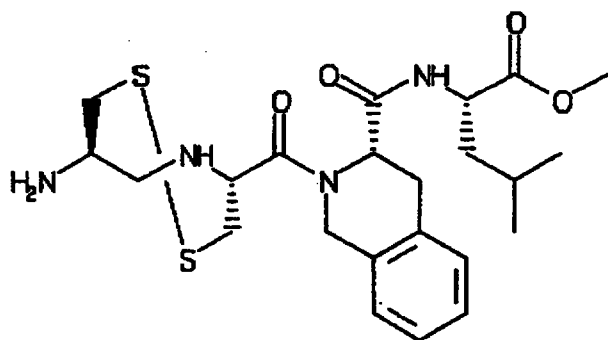
Compound 15;



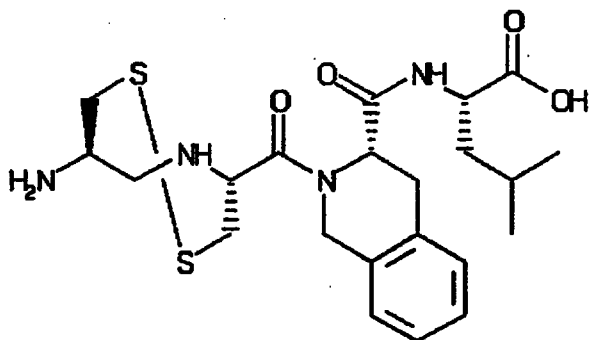
Compound 16;



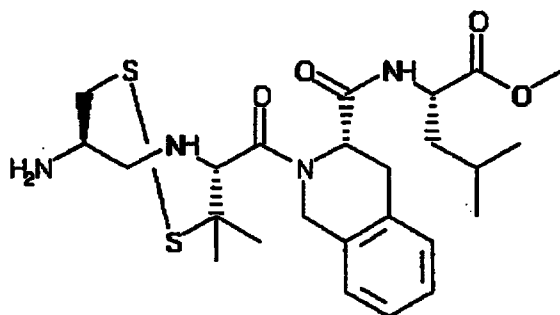
Compound 17;



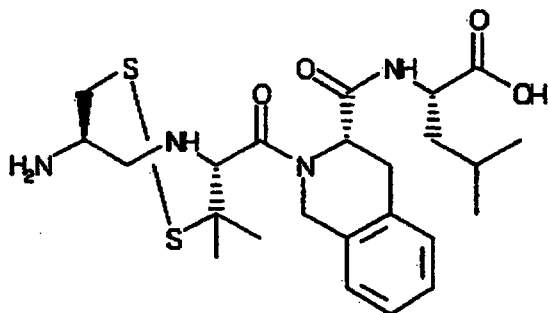
Compound 18;



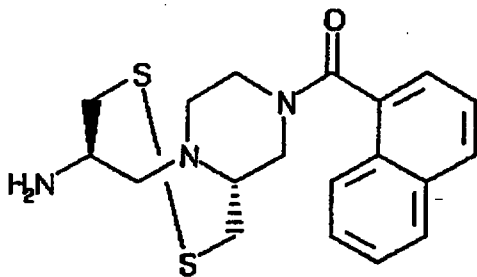
Compound 19;



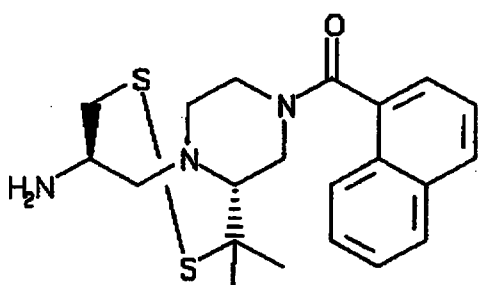
Compound 20;



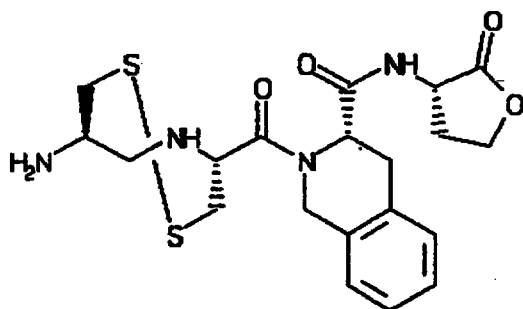
Compound 21;



Compound 22;

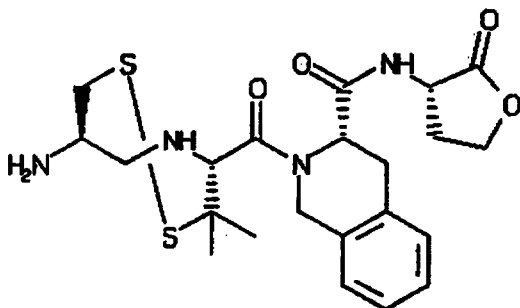


Compound 23;



and

Compound 24.



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, sec-butyl, t-butyl, 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 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 fluoro. The terms "heterocycle lower alkyl," "thio lower alkyl," "cycloalkyl lower alkyl", and "aryl lower alkyl," are substituted, respectively, with one to three heterocycle, thio, cycloalkyl, and aryl 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  
5 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  
10 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  
15 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,  
20 benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl,  
25 imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl,  
30 piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thiazolidinyl, thienofuryl, thienothienyl, thienyl, and the like.

35 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).

As used herein, the term "residue of an  $\alpha$ -amino acid" stands for an  $\alpha$ -amino acid residue which is either  
5 a natural  $\alpha$ -amino acid which is found in nature (e.g., cysteinyl, methionyl, phenylalaninyl, leucinyl, etc.) or a synthetic  $\alpha$ -amino acid which is not found in nature (e.g., neurleucyl or the residue of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid or  
10 penicillamine, etc.).

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,  
15 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.  
20 For further examples of pharmaceutically acceptable salts see, "Pharmaceutical Salts," J. Pharm. Sci. 66:1 (1977).

In another aspect, the invention features a method of inhibiting prenyl transferases (e.g., farnesyl transferase or geranylgeranyl transferase) in a subject,  
25 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  
30 by administering to the subject a therapeutically effective amount of a compound or its salt. Examples of a tissue proliferative disease include both those associated with benign (e.g., non-malignant) cell proliferation such as fibrosis, benign prostatic  
35 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  
5 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)  
10 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  
15 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  
20 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  
25 physician or veterinarian is referred to herein as a  
"therapeutically effective amount."

Also contemplated within the scope of the  
invention are a method of preparing the compounds of  
formula I or formula II and the novel chemical  
30 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

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  
5 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  
10 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  
15 compounds 1, 4, and 9. Other compounds of the invention can be prepared in an analogous manner by a person of ordinary skill in the art.

The compounds of the invention were prepared using standard solution phase methodologies, e.g., as described  
20 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)). The condensation reactions were carried out in an inert organic solvent, e.g., dimethylformide,  
25 dichloromethane, tetrahydrofuran, benzene or acetonitrile, using a suitable mild condensing agent, e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide-HCl (EDC, 0-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), and optionally a catalyst,  
30 e.g., 1-hydroxybenzotriazole (HOBt). The reaction temperature was maintained below room temperature (-15°C to room temperature) in order to minimize side reactions. Cyclic disulfide formation was carried out under high dilute condition using iodine in various solvents (e.g.,  
35 methanol, tetrahydrofuran (THF), acetic acid, water, etc.). B. Kamber, et al., Helv. Chim. Acta, 63(96):899

(1980). The intermediate and final products were isolated and purified by standard methods, e.g., column chromatography or HPLC. Compounds where  $R_8$ , together with  $R_9$ , forms  $\text{CH}_2\text{CH}_2$  can be made according to the methods of Williams, et al., J. Med. Chem. 39(7):1346 (1996), e.g., by starting with protected cysteine.

Example I: N-[2-(R)-amino-3-mercaptopropyl]-L-penicillaminy-1,2,3,4-tetrahydro-3(s)-isoquinoline carbonyl methionine methylester cyclic disulfide (Compound 1)

a) N-t-butoxycarbonyl-S-trityl-L-cysteiny-N,O-dimethylamide

To an ice-cooled solution of N-t-butoxycarbonyl-L-cysteine (8.0 g) and N,O-dimethylhydroxylamine hydrochloride (7.1 g) in 80 ml dimethylformide was added 4.2 ml diethylcyanophosphonate and 14.7 ml diisopropylethylamine, and after stirring at 0°C for 1 hr, the reaction mixture was allowed to room temperature overnight. Volatile substances were removed in vacuo to dryness, and the residue was partitioned between ethylacetate and water. Ethylacetate layer was washed with aqueous  $\text{NaHCO}_3$ , water, and dried ( $\text{MgSO}_4$ ). Solvent was evaporated in vacuo to dryness, and the residue was chromatographed on silica gel (165 g) using  $\text{CHCl}_3$  as an eluant. Appropriate fractions were pooled, and solvent was removed in vacuo to dryness. White foam 8.08 g TLC (silica gel:  $\text{CHCl}_3$ /acetone = 9:1  $R_f$  = 0.58).

b) 2(R)-t-Butoxycarbonylamino-3-triphenylmethylmercapto-propanal

To an ice-cooled solution of N-t-Butoxycarbonyl s-trityl-L-cysteiny-N,O-dimethylamide (0.85 g) in 20 ml tetrahydrofuran (THF) was added dropwise 3 ml 1.0 M  $\text{LiAlH}_4$  in THF under nitrogen atmosphere. After the mixture was stirred for 30 min. at 0°C, 1M  $\text{KHSO}_4$  was slowly added, and the resulting emulsion was filtered through celite pad and further washed with ethylacetate. After drying over anhydrous  $\text{MgSO}_4$ , the solvent was removed in vacuo to

dryness resulting in 0.7 g of the above-titled compound  
TLC (silica gel;  $\text{CHCl}_3/\text{acetone} = 4:1$ ;  $R_f = 0.88$ ).

c) N-t-butoxycarbonyl-S-acetamidomethylpenicillaminy-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methylester

To an ice-cooled solution of N-t-butoxycarbonyl-L-1,2,3,4-tetrahydro-3(S)-isoquinoline (2.77 g) and L-methionine methylester hydrochloride (2.0 g), 1-hydroxybenzotriazole (HOBT) (1.37 g) and O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (3.87 g) in 30 ml dimethylformide was added 4.9 ml diisopropylethylamine (DIEA). After stirring at 0°C for 30 min, the reaction mixture was allowed to room temperature overnight. Volatile substances were evaporated in vacuo to dryness, and the residue was partitioned between EtOAc and water. EtOAc layer was washed with aqueous  $\text{NaHCO}_3$ , water, and dried ( $\text{MgSO}_4$ ). Solvent was evaporated in vacuo to dryness. It was treated with 50% trifluoroacetic acid in chloroform (40 ml) containing 4.8 ml triethylsilane for 1 hour, and volatile substances were removed in vacuo to dryness. Trace of trifluoroacetic acid (TFA) was further evaporated with toluene. To the above L-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl methionine methylester TFA salt (2.2 g) in dichloromethane (20 ml) cooled to 0°C was added 1.2 ml DIEA followed by a solution of HOBT (0.7 g), N-t-butoxycarbonyl-S-acetamidomethyl penicillin (1.6 g) in DMF (3 ml), and EDC (1.2 g). The mixture was stirred at 0°C for 30 min and then allowed to room temperature overnight. Volatile substances were removed in vacuo to dryness. The residue was partitioned between EtOAc and water. Ethylacetate layer was washed with aqueous  $\text{NaHCO}_3$ , water, and then dried ( $\text{MgSO}_4$ ). Solvent was evaporated in vacuo to dryness to yield 3.3 g orange solid.

d) L-[S-acetamidomethylpenicillaminy-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl methionine methylester and its TFA salt

N-t-butoxycarbonyl-S-acetamidomethyl-penicillaminy-1,2,3,4-tetrahydro-3[S]-isoquinolinecarbonyl methionine methylester (3.3 g) was treated with 50% TFA in  $\text{CH}_2\text{Cl}_2$  (20 ml) containing 1 ml triethylsilane for 30 min. Volatile substances were removed in vacuo to dryness. Trace of TFA was removed by co-evaporation with toluene several times. The TFA salt was dissolved in  $\text{CHCl}_3$  (30 ml), treated with excess triethylamine, washed with water, dried ( $\text{MgSO}_4$ ), and solvent was evaporated in vacuo to give free base.

e) N-[2(R)-(t-butoxycarbonyl)amino-3-triphenylmethylmercapto-propyl]-L-[S-acetamidomethyl-penicillaminy-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl methionine methylester

To a solution of 2(R)-t-butoxycarbonylamino-3-triphenylmethyl-mercapto-propanal (0.7 g) and L-[S-acetamidomethylpenicillaminy-1,2,3,4-tetrahydro-3(s)-isoquinolinecarbonyl methionine methylester (0.43 g) in  $\text{CH}_2\text{Cl}_2$  (20 ml) containing 1% acetic acid was added triacetoxysodiumborohydride  $\text{Na}(\text{OAc})_3\text{BH}$  (360 mg) in one portion. After stirring for 2 hours, the mixture was washed with water, 5% aqueous  $\text{NaHCO}_3$ , water, and then dried ( $\text{MgSO}_4$ ). The solvent was evaporated in vacuo to dryness, and the residue was chromatographed on silica gel (50 g) using  $\text{CHCl}_3$ /acetone (19:1 to 9:1) as eluants. Appropriate fractions were pooled and solvents were removed in vacuo to dryness resulting in a white foam (390 mg) of the above title compound. TLC (silica gel;  $\text{CHCl}_3$ /acetone = 4:1;  $R_f$  = 0.4).

f) N-[2(R)-(t-butoxycarbonyl)amino-3-mercaptopropyl]-L-penicillaminy-1,2,3,4-tetrahydro-3(S)-isoquinoline carbonyl methionine methylester cyclic disulfide

To a solution of N-[2(R)-(t-butoxycarbonyl)amino-3-triphenylmethylmercaptopropyl]-L-[S-acetamidomethyl-penicillaminy-1,2,3,4-tetrahydro-3(S)-isoquinoline carbonyl methionine methylester (500 mg) in 50 ml 90% aqueous MeOH was added dropwise a solution of iodine (250 mg) in methanol (MeOH) (10 ml). After stirring for

1 hour, most of methanol was removed in vacuo to a small volume, diluted with water, and extracted with ethylacetate. The ethylacetate extract was washed with water, aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , water, and then dried ( $\text{MgSO}_4$ ).

- 5 The solvent was evaporated in vacuo to dryness resulting in 400 mg of the above title compound.

g) N-[2-(R)-amino-3-mercaptopropyl]-L-penicillaminyll-1,2,3,4-tetrahydro-3(S)-isoquinoline carbonyl methionine methylester cyclic disulfide

- 10 Crude N-[2(R)-(t-butoxycarbonyl)amino-3-mercaptopropyl]-L-penicillaminyll-1,2,3,4-tetrahydro-3(S)-isoquinoline carbonyl methionine methylester cyclic disulfide (400 mg) was treated with 90% trifluoroacetic acid (TFA) in water TFA/ $\text{H}_2\text{O}$  (9:1) (10 ml) for 30 min.
- 15 Volatile substances were removed in vacuo to dryness, and a trace of TFA was evaporated with toluene several times and triturated with hexane, decanted, and then dried. Crude product was subjected to preparative high performance liquid chromatography (HPLC) using  $\text{C}_{18}$  column
- 20 and 0.1% TFA and  $\text{CH}_3\text{CN}$  as mobile phase. Appropriate fractions were pooled, and solvents were removed giving the above title compound as a white solid (78 mg). M/e = 541.1.

- Example 2: N-[2-(R)-amino-3-mercaptopropyl]-L-[s-acetamidomethyl-penicillaminyll-1,2,3,4-tetrahydro-3(S)-isoquinoline carbonyl methionine (Compound 4)
- 25

- To a solution of N-[2(R)-(t-butoxycarbonyl)-amino-3-triphenylmethylmercaptopropyl]-L-[s-
- 30 acetamidomethyl penicillaminyll-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl methionine methylester (Example I e)) (500 mg) in 10 MeOH (50 ml) was added 2 ml 2 N-NaOH. After 30 min., most of MeOH was removed in vacuo to a small volume, diluted with water, acidified with 5%
- 35 aqueous citric acid, and extracted with ethylacetate. The ethylacetate extract was then dried ( $\text{MgSO}_4$ ). Solvent was evaporated in vacuo to dryness. The residue was treated with 50% TFA in  $\text{CH}_2\text{Cl}_2$  containing triethylsilane

(Et<sub>3</sub>SiH) (0.5 ml) for 40 min. Volatile substances were removed in dryness, and a trace of TFA was evaporated with toluene and then dried. Crude product was purified by prep. HPLC giving the above titled compound (100 mg) as a white solid. M/e = 600.2

Example 3: N-[2-(R)-amino-3-mercaptopropyl]-L-penicillaminy]-2,3-dimethylanilide cyclic disulfide (Compound 9)

a) [N-t-Butoxycarbonyl-S-acetamidomethyl]penicillaminy]-2,3-dimethylanilide

To an ice-cooled solution of N-[t-butoxycarbonyl]-S-acetamidomethyl penicillamine (Bachem California, Torrance, CA) (0.64 g), 2,3-dimethylaniline (0.25 g), hydroxybenzotriazole (0.41 g) in dimethylformide (DMF)/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 20 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (0.57 g). The mixture was stirred at 0-5°C for 30 min. and then the temperature was slowly allowed to room temperature overnight. After evaporation of the solvents, the residue was partitioned between ethyl acetate (EtOAc) and water. EtOAc extract was washed with aqueous NaHCO<sub>3</sub>, water, and then dried (MgSO<sub>4</sub>). The solvent was evaporated in vacuo to dryness. The residue was chromatographed on silica gel (40 g) using CHCl<sub>3</sub>/acetone = 19:1 as eluants, appropriate fractions were pooled, and solvents were removed in vacuo to dryness giving 350 mg of the above titled compound. TLC (silica gel: CHCl<sub>3</sub>/acetone = 4:1, R<sub>f</sub> = 0.77).

b) L-[S-acetamidomethylpenicillaminy]-2,3-dimethylanilide TFA salt

[N-t-butoxycarbonyl-S-acetamidomethyl]-penicillaminy]-2,3-dimethylanilide was treated with 50% TFA in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) for 30 min. Volatile substances were removed in vacuo to dryness. Trace of TFA was removed by co-evaporation with toluene several times. The TFA salt was dissolved in CHCl<sub>3</sub> (30 ml), treated with excess triethylamine, washed with water, dried (MgSO<sub>4</sub>), and solvent was evaporated in vacuo to give free base.

- c) N-[2(R)-(t-butoxycarbonyl)amino-3-triphenylmethylmercapto propyl]-L-[S-acetamidomethylpenicillaminy]-2,3-dimethylamilide  
To a stirred solution of 2(R)-t-

5 butoxycarbonylamino-3-triphenylmethylmercaptopropanal (0.5 g; Example 1b) and L-[S-acetamidomethylpenicillaminy]-2,3-dimethylamilide TFA salt (0.3 g) in MeOH containing 1% acetic acid (HOAc) (10 ml) was added portionwise NaCNBH<sub>3</sub> (100 mg). The  
10 mixture was stirred at room temperature overnight. Most of the solvent was evaporated in vacuo to a small volume, which was partitioned between EtOAc and water. EtOAc layer was further washed with aqueous NaHCO<sub>3</sub>, water, and then dried (MgSO<sub>4</sub>). After evaporation of solvent, the  
15 residue was chromatographed on silica gel (30 g) using CHCl<sub>3</sub>-acetone (19:1 to 9:1) as eluants. Appropriate fractions were pooled, and solvents were evaporated in vacuo to dryness giving 360 mg of the above titled compound. TLC (silica gel: CHCl<sub>3</sub>/acetone = 9:1, R<sub>f</sub> =  
20 0.13.

- d) N-[2-(R)-amino-3-mercaptopropyl]-L-penicillaminy]-2,3-dimethylamilide cyclic disulfide

To a stirred solution of N-[2(R)-(t-  
25 butoxycarbonyl) amino-3-triphenylmethylmercaptopropyl]-L-[S-acetamidomethyl penicillaminy]-2,3-dimethylamilide (350 mg) in 50 ml 90% MeOH in water was added a solution of iodine (250 mg) in MeOH (5 ml). After 1 hour, most of the solvent was evaporated in vacuo to a small volume,  
30 diluted with water, extracted with EtOAc. EtOAc layer was washed with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, water, then dried (MgSO<sub>4</sub>). Solvent was removed in vacuo to dryness (220 mg), treated with 90% aqueous TFA (ml) for 30 min, and volatile substances were removed in vacuo to dryness.  
35 Crude product was purified by preparative HPLC giving 62 mg of the above titled compound as a white solid. M/e = 340.2.

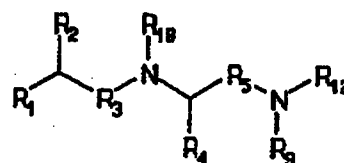
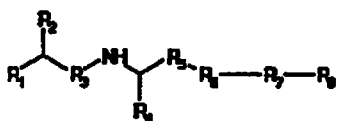
Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is  
5 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  $N(R_{10})(R_{11})$ ;

$R_2$  is thio lower alkyl;

each of  $R_3$  and  $R_5$ , independently, is  $CH_2$  or  $C(O)$ ;

$R_4$  is substituted or unsubstituted thio lower  
10 alkyl, wherein the substituent is  $CH_2NHC(O)R_{13}$  and  
attached to the thio group;

$R_6$  is a residue of a natural or synthetic  $\alpha$ -amino  
acid;

$R_7$  is a residue of a natural or synthetic  $\alpha$ -amino  
15 acid;

$R_8$  is OH or lower alkoxy, or, together with  $R_7$ ,  
forms homoserinelactone;

each of  $R_9$ ,  $R_{10}$  and  $R_{11}$ , independently, is H or  
lower alkyl;

20  $R_{12}$  is a substituted or unsubstituted moiety  
selected from cycloalkyl, cycloalkyl lower alkyl, aryl,  
aryl lower alkyl, heterocycle, and heterocycle lower  
alkyl, wherein the substituent is lower alkyl, aryl,  
halo, lower alkoxy, or  $C(O)-R_7-R_8$ ;

25  $R_{13}$  is lower alkyl, aryl, or aryl lower alkyl;

$R_{18}$  is H or, together with  $R_9$ , forms  $-CH_2CH_2-$ ;  
provided that if  $R_4$  is unsubstituted thio lower alkyl,  
the free thio groups of  $R_2$  and  $R_4$  can form a disulfide  
bond;

30 or a pharmaceutically acceptable salt thereof.



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

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

4. A compound of claim 2, wherein

$R_6$  is  $-N(R_{14})CH(R_{15})C(O)-$  where  $R_{14}$  is H or lower alkyl, and  $R_{15}$  is a substituted or unsubstituted moiety selected from lower alkyl, aryl, aryl lower alkyl, heterocycle, and heterocycle lower alkyl, in which said substituent is lower alkyl, halo, or lower alkoxy, or  $R_{15}$ , together with  $N(R_{14})C$  attached thereto, form a heterocycle;

$R_7$  is  $-N(R_{16})CH(R_{17})C(O)-$  where  $R_{16}$  is H or lower alkyl; and  $R_{17}$  is  $(CH_2)_mS(O)_nCH_3$  where  $m$  is 1-6 and  $n$  is 0-2, or is a substituted or unsubstituted moiety selected from lower alkyl and thio lower alkyl, where said substituent is  $C(O)N(R_{10})(R_{11})$ ; and

$R_8$  is OH or lower alkoxy; or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4, wherein

$R_2$  is  $CH_2SH$ ; and

$R_4$  is  $C(CH_3)_2SH$  or  $CH_2SH$ ;

in which the free thio groups of  $R_2$  and  $R_4$  form a disulfide bond; or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5, wherein  $R_{15}$ , together with  $N(R_{14})C$  attached hereto, form a heterocycle;  $R_{16}$  is H; and  $R_{17}$  is  $(CH_2)_2S(O)_nCH_3$ ; or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6, wherein

$R_1$  is  $\text{NH}_2$ ;  
 $R_3$  is  $\text{CH}_2$ ;  
 $R_5$  is  $\text{C}(\text{O})$ ; and  
 $R_8$  is  $\text{OH}$  or  $\text{OCH}_3$ ;



5 or a pharmaceutically acceptable salt thereof.

8. A compound of claim 4, wherein  
 $R_2$  is  $\text{CH}_2\text{SH}$ ; and  
 $R_4$  is  $\text{C}(\text{CH}_3)_2\text{SCH}_2\text{NHC}(\text{O})\text{CH}_3$  or  $\text{CH}_2\text{SCH}_2\text{NHC}(\text{O})\text{CH}_3$ ;  
or a pharmaceutically acceptable salt thereof.

10 9. A compound of claim 8, wherein  $R_{15}$ , together with  $\text{N}(\text{R}_{14})\text{C}$  attached thereto, form a heterocycle;  $R_{16}$  is  $\text{H}$ ; and  $R_{17}$  is  $(\text{CH}_2)_2\text{S}(\text{O})_n\text{CH}_3$ ; or a pharmaceutically acceptable salt thereof.

15 10. A compound of claim 9, wherein  
 $R_1$  is  $\text{NH}_2$ ;  
 $R_3$  is  $\text{CH}_2$ ;  
 $R_5$  is  $\text{C}(\text{O})$ ; and  
 $R_8$  is  $\text{OH}$  or  $\text{OCH}_3$ ;  
or a pharmaceutically acceptable salt thereof.

20 11. A compound of claim 3, wherein  
 $R_2$  is  $\text{CH}_2\text{SH}$ ; and  
 $R_4$  is  $\text{C}(\text{CH}_3)_2\text{SH}$  or  $\text{CH}_2\text{SH}$ ;  
in which the free thio groups of  $R_2$  and  $R_4$  form a  
disulfide bond; or a pharmaceutically acceptable salt  
25 thereof.

12. A compound of claim 11, wherein  $R_{12}$  is substituted or unsubstituted aryl, or substituted or unsubstituted aryl lower alkyl, and  $R_{18}$  is  $\text{H}$ ; or a pharmaceutically acceptable salt thereof.

30 13. A compound of claim 12, wherein  
 $R_1$  is  $\text{NH}_2$ ;



$R_3$  is  $\text{CH}_2$ ;

$R_5$  is  $\text{C}(\text{O})$ ;

$R_9$  is H; and

$R_{12}$  is substituted or unsubstituted phenyl or  
5 benzyl, where said substituent is lower alkyl or halo;  
or a pharmaceutically acceptable salt thereof.

14. A compound of claim 3, wherein

$R_2$  is  $(\text{CH}_2)\text{SH}$ ; and

$R_4$  is  $\text{C}(\text{CH}_3)_2\text{SCH}_2\text{NHC}(\text{O})\text{CH}_3$  or  $\text{CH}_2\text{SCH}_2\text{NHC}(\text{O})\text{CH}_3$ ;  
10 or a pharmaceutically acceptable salt thereof.

15. A compound of claim 14, wherein  $R_{12}$  is  
substituted or unsubstituted aryl or aryl lower alkyl; or  
a pharmaceutically acceptable salt thereof.

16. A compound of claim 15, wherein

15  $R_1$  is  $\text{NH}_2$ ;

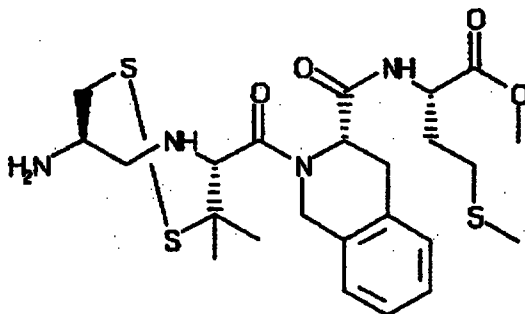
$R_3$  is  $\text{CH}_2$ ;

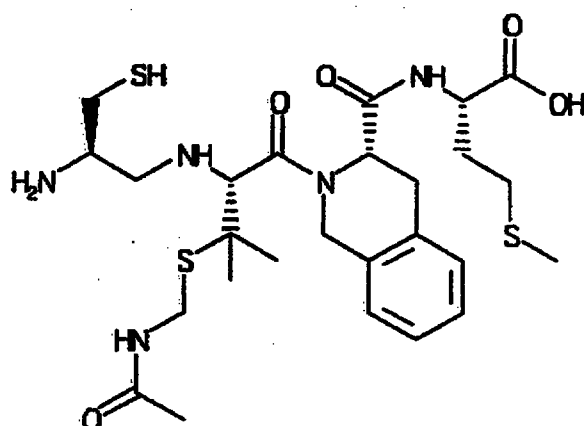
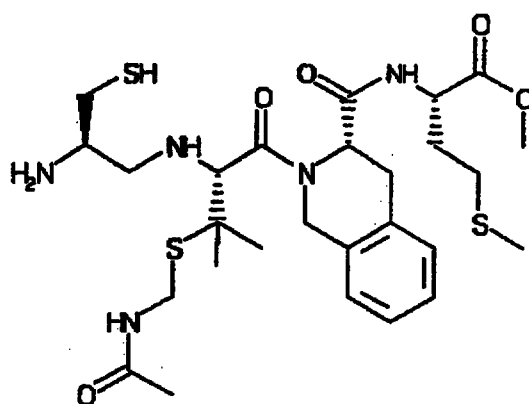
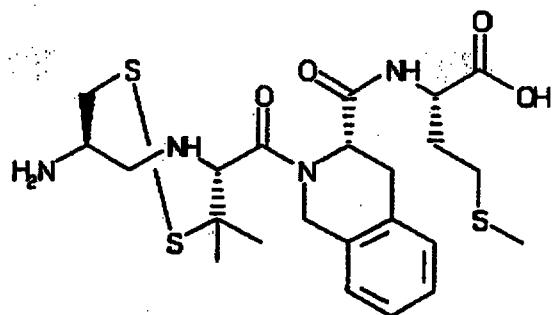
$R_5$  is  $\text{C}(\text{O})$ ;

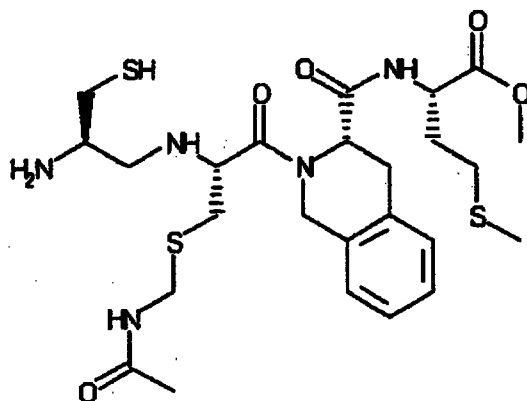
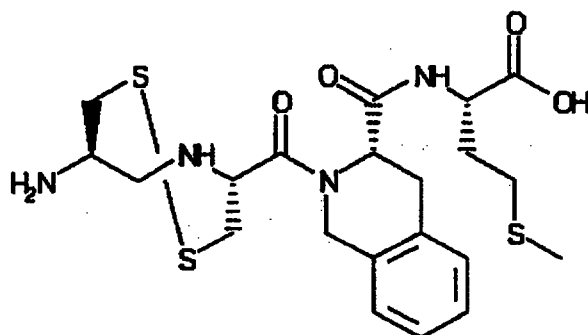
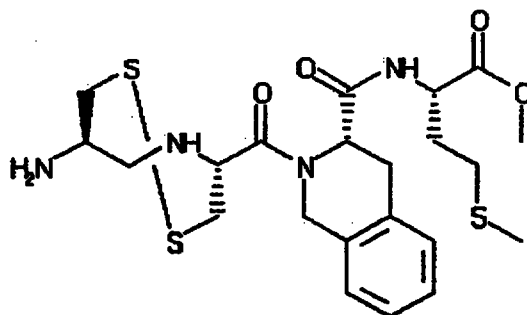
$R_9$  is H; and

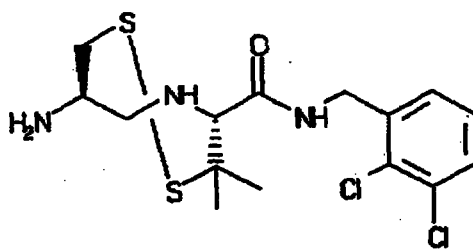
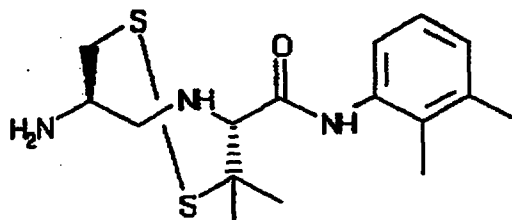
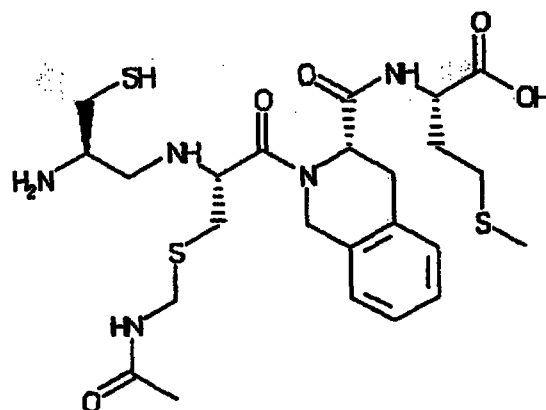
$R_{12}$  is substituted or unsubstituted phenyl or  
20 benzyl, where said substituent is lower alkyl or halo;  
or a pharmaceutically acceptable salt thereof.

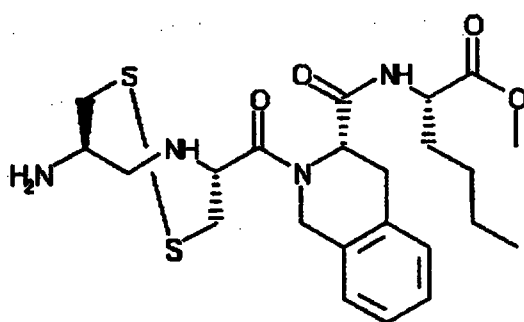
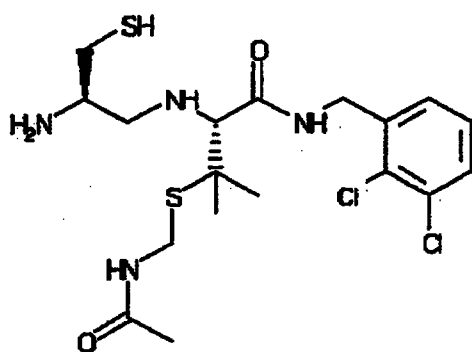
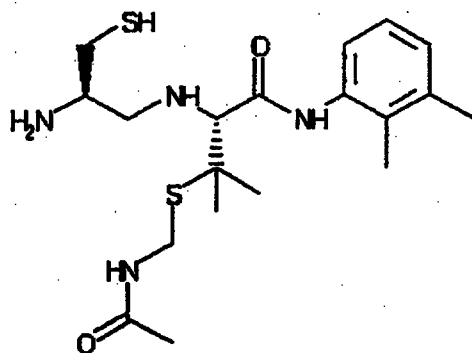
17. A compound of claim 1, said compound of the  
formula

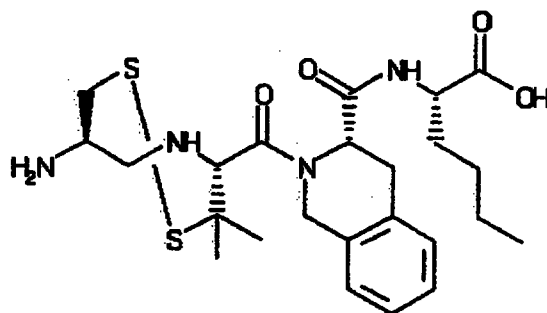
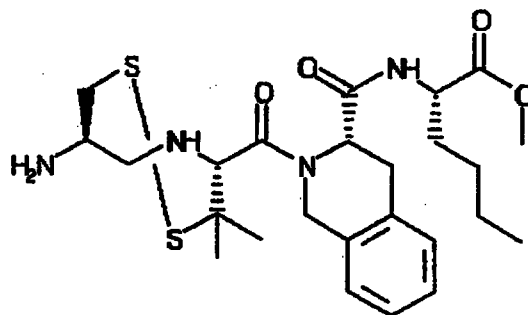
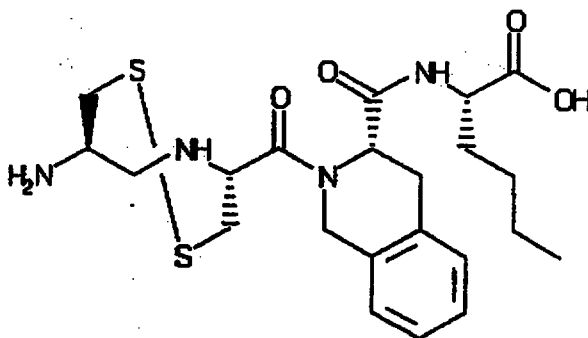


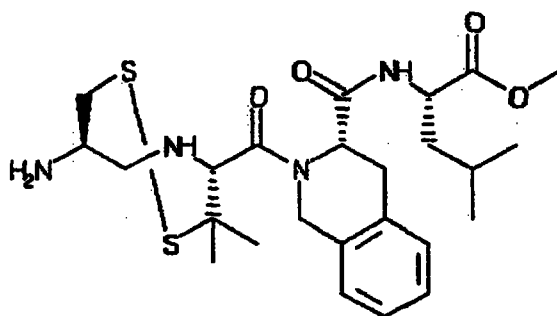
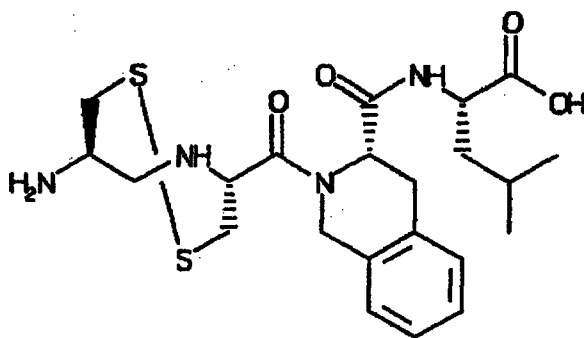
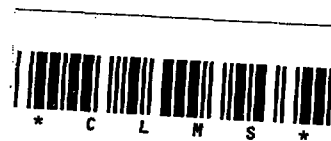
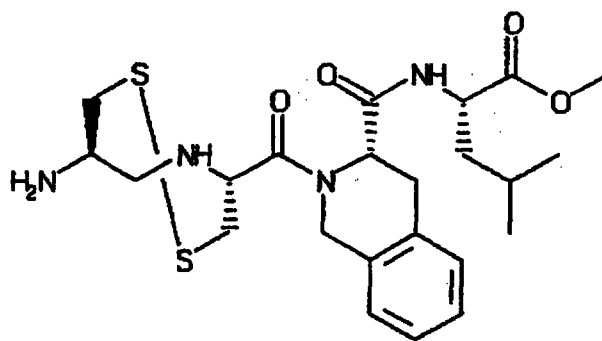


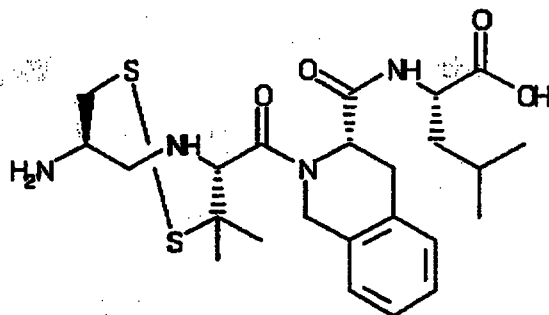








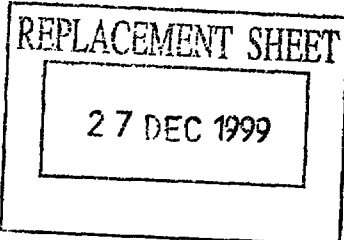




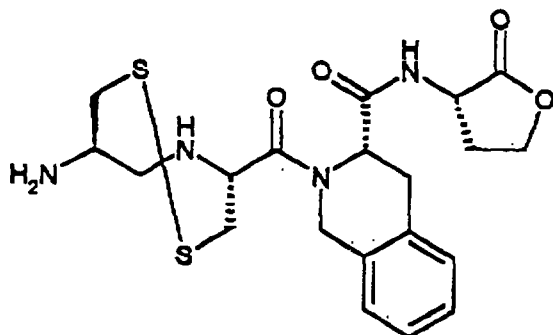
18. A method of treating tumors or restenosis in a subject in need of said treatment, which comprises administering to said subject a therapeutically effective amount of the compound or salt of claim 1.

19. A method of claim 18, wherein said compound or salt is that of claim 17.

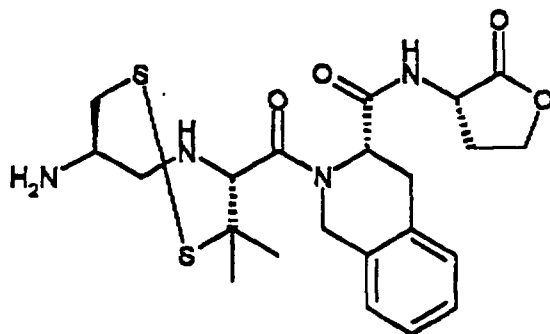
20. A pharmaceutical composition comprising a compound of claim 1.



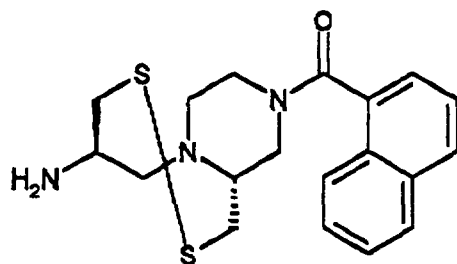
21. A compound of the formula



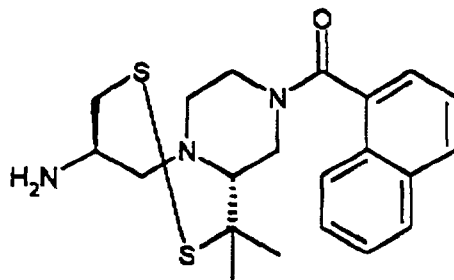
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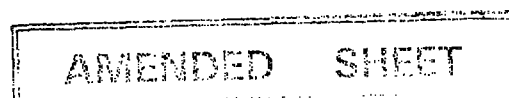


; or



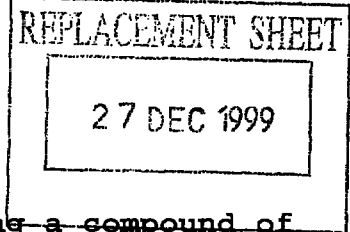
;

or a pharmaceutically acceptable salt thereof.

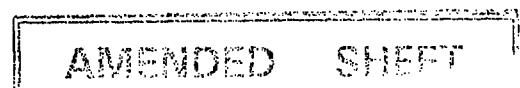




- 37 -



22. A pharmaceutical composition comprising ~~a compound of~~  
claim 21 and a pharmaceutically acceptable carrier.





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|------------------------------------------------------------------------------------|----|-------------------------------------------------------|-------------------------------------------------------------------|
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(71) Applicant (for all designated States except US): BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Millford, MA 01757-3650 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): KIM, Sun, H. [US/US]; 423 Deedham Avenue, Needham, MA 02192 (US).

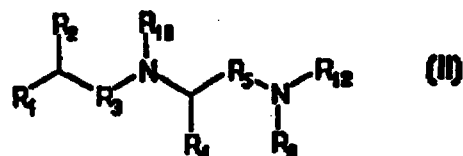
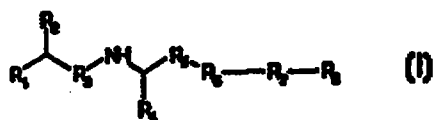
(74) Agent: TSAO, Y., Rocky; Fish &amp; Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).

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(54) Title: PRENYL TRANSFERASE INHIBITORS



(57) Abstract

A family of compounds capable of inhibiting the activity of prenyl transferases. The compounds are covered by either of two formulas (I, II). Each of the R groups is defined in the disclosure.