

- 1 -

FARNESYL TRANSFERASE INHIBITORS**Background of the Invention**

Ras is a 21,000 molecular weight protein important in the signal transduction pathway for normal 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 pyrophosphate in a reaction catalyzed by the enzyme farnesyl transferase (Hancock, JF, et al., Cell 57:1167-1177 (1989)). Subsequently, the three C-terminal amino acids are cleaved (Gutierrez, I, et al., EMBO J. 8:1093-1098 (1989)), and the terminal Cys¹⁶⁸ is methyl esterified (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. 6:116-122 (1986)). 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 normal function (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, over 30 percent of lung cancers, and over 90 percent of pancreatic cancers (Bos, JL, Cancer Research 49:4682-4689 (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 cysteine, A is an aliphatic amino acid, and X is any amino acid). Tetrapeptides having this structure have

- 2 -

- been shown to be inhibitors of farnesyl transferase (Reiss, et al., Cell 62:81-88 (1990)). Poor potency of these early farnesyl transferase inhibitors has prompted the search for new inhibitors with more favorable
- 5 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 Research 55:5310-5314 (1995); Lerner, EC, et al., J.
- 10 Biol. Chem. 270:26802-26806 (1995)).

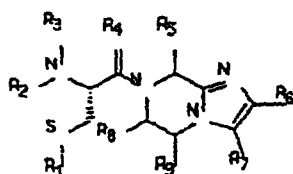
Recently, it has been shown that a farnesyl transferase inhibitor will block growth of Ras-dependent tumors in nude mice (Kohl, NE, et al., Proc. Nat'l Acad. Sci. (USA) 91:9141-9145 (1994)). In addition, it has

15 been shown that over 70 percent of a large sampling of tumor cell lines are inhibited by farnesyl transferase inhibitors with selectivity over non-transformed epithelial cells (Sepp-Lorenzino, I, et al., Cancer Research, 55:5302-5309 (1995)).

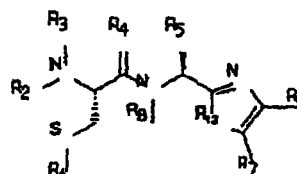
20

Summary of the Invention

In one aspect, the invention features a compound having the formula (I) or formula (II):



I



II

- 3 -

wherein:

R_1 is H, lower alkyl, cycloalkylthio, or lower alkylthio, or, together with R_2 , form $-\text{CH}_2-$, $-\text{CO}-$, or $-\text{C}(\text{CH}_3)_2-$;

5 each of R_2 and R_3 , independently, is H, lower alkyl, and cycloalkyl;

R_4 is H_2 or O;

R_5 is H, or substituted or unsubstituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is lower alkyl, $-\text{O}-R_{10}$, $-\text{S}(\text{O})_m R_{10}$ (where m is 0, 1, or 2), $-\text{N}(\text{R}_{10})(\text{R}_{11})$, $-\text{N}-\text{C}(\text{O})-\text{R}_{10}$, $-\text{NH}-(\text{SO}_2)-\text{R}_{10}$; $-\text{CO}_2-\text{R}_{10}$, $-\text{C}(\text{O})-$ 15 $\text{N}(\text{R}_{10})(\text{R}_{11})$, or $-(\text{SO}_2)-\text{N}(\text{R}_{10})(\text{R}_{11})$;

each of R_6 and R_7 , independently, is H, $-\text{C}(\text{O})-\text{NHCHR}_{13}\text{CO}_2\text{R}_{14}$, or substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, 20 heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is OH, lower alkyl, lower alkoxy, aryloxy, aryl lower alkoxy, $-\text{N}(\text{R}_{10})(\text{R}_{11})$, $-\text{COOH}$, $-\text{CON}(\text{R}_{10})(\text{R}_{11})$, or halo, or R_6 and R_7 , together, form aryl or heterocyclyl;

each of R_8 and R_9 , independently, is H, or 25 substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is OH, lower alkyl, lower alkoxy, $-\text{N}(\text{R}_{10})(\text{R}_{11})$, COOH , $-\text{C}(\text{O})\text{N}-$ 30 $(\text{R}_{10})(\text{R}_{11})$, or halo, or R_8 and R_9 , together, form aryl or heterocyclyl;

each of R_{10} and R_{11} , independently, is H, lower alkyl, aryl, aryl lower alkyl, cycloalkyl, cycloalkyl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl;

35 R_{12} is NR_9 , S, or O;

- 4 -

R_{13} is substituted or unsubstituted lower alkyl wherein the substituent is lower alkyl, $-OR_{10}$, $-S(O)_mR_{10}$ (wherein m is 0, 1, or 2) or $-N(R_{10})(R_{11})$; and

R_{14} is H or lower alkyl; or

5 a pharmaceutically acceptable salt thereof.

Examples of the present invention include the following:

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 1);

10 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 2);

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-
15 pyrazine (Compound 3);

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 4);

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-
20 pyrazine (Compound 5);

7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-ethyl)-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 6);

25 7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 7);

2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl)-5-phenyl-imidazole (Compound 8);

2-(((2-amino-1-oxo-3-mercapto-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine (Compound
30 9);

7-(2-amino-1-oxo-3-thio-propyl)-2-(2-methoxyphenyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazine (Compound 11);

- 5 -

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-ethoxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 13);

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 14);

2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl-5-(2-methoxyphenyl)-imidazole (Compound 15);

7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 17);

7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 18);

S-(dimethylethyl)-s'-[2-amino-3-oxo-3(8-butyl-2-(2-methoxyphenyl))-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl)propyl]disulfide (Compound 21);

7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 22);

7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 24);

7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 25);

7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 26);

7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 27);

- 6 -

7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro[1,2a]pyrazine (Compound 29);

2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydro-7-((thiazolidin-4-yl)carbonyl)-imidazo[1,2a]pyrazine (Compound 31);

7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 32);

10 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo-[1,2a]pyrazine (Compound 34);

7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 15 36);

7-(2-amino-1-oxo-3-thiopropyl)-2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 37);

7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 20 42);

7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 44);

25 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 46);

7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 30 47);

7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine (Compound 49);

- 7 -

- 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine (Compound 51);
- [S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-propyl]-S'-cyclohexyl]disulfide (Compound 52);
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl) methyl-2-(2-methoxyphenyl)-5,6,7,8-
10 terahydroimidazo[1,2a] pyrazine (cis isomer) (Compound 53);
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(4-piperidinylmethyl)-5,6,7,8-
terahydroimidazo[1,2a] pyrazine (Compound 54);
- 15 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-piperidinylmethyl)-5,6,7,8-
terahydroimidazo[1,2a] pyrazine (Compound 55);
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(3-piperidinylmethyl)-5,6,7,8-
20 terahydroimidazo[1,2a] pyrazine (Compound 56);
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(1-naphthyl)-5,6,7,8-
tetrahydroimidazo[1,2a] pyrazine (Compound 57);
- [S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-propyl]-S'-ethyl]disulfide (Compound 58);
- 25 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-methylthio)-ethyl-5,6,7,8-
tetrahydroimidazo[1,2a] pyrazine (Compound 59);
- 30 7-(2-amino-1-oxo-3-thiopropyl)-8-(3-indolinylmethyl)-2-(2-methoxyphenyl)-8-5,6,7,8-
tetrahydroimidazo[1,2a] pyrazine (Compound 60); and
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylimidazol-3-yl) methyl-2-(2-methoxyphenyl)-8-
35 5,6,7,8-tetrahydroimidazo [1,2a] pyrazine (Compound 61).

- 8 -

8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-7-(2-oxo-thiazolidin-4-carbonyl)-5,6,7,8-

tetrahydroimidazo[1,2a]pyrazine (Compounds 62); and

7-(2-amino-1-oxo-3-thiopropyl)-2-(2-

5 methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-

tetrahydroimidazo[1,2a]pyrazine (Compound 63).

In another aspect, the invention features a dimeric compound made of two identical or different compounds (monomers) as described above, or a

10 pharmaceutically acceptable salt thereof. The monomers are linked to each other to form the dimer via a disulfide bond. More specifically, R₁ in the first monomer and R₁ in the second monomer, in combination, form a disulfide bond.

15 Examples of dimers of the invention include:

bis-1,1'-[2-amino-3-(8-butyl-2-(2-methoxyphenyl))-5,6,7,8-tetrahydro-imidazo[1,2a]piperazine-7-yl)-3-oxo]propyl disulfide (Compound 10);

bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-8-(2-
20 methylpropyl))-5,6,7,8-tetrahydro-imidazo[1,2a]piperazine-7-yl)-3-oxo]propyl disulfide (Compound 12);

bis-1,1'-[2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methylamino)-pentyl)-5-(2-methoxyphenyl)imidazole] disulfide (Compound 16);

25 bis-1,1'-7-(2-amino-1-oxo-3-thiopropyl)-(2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl) disulfide (Compound 19).

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(
30 (methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 20);

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 23).

- 9 -

- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 28).
- 5 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 30);
- bis-1,1'-[2-amino-3-(8-butyl-2-cyclohexyl-5,6,7,8-tetrahydro-imidazo-[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide (Compound 33);
- 10 bis-1,1'-[2-amino-3-(3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo[1,2a]-pyrazin-7-yl)-3-oxo-propyl]disulfide (Compound 35);
- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-15 2,3-diphenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide (Compound 38);
- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide (Compound 39);
- 20 bis-1,1'-[2-amino-3-(2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide (Compound 40);
- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-25 (cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 41);
- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazine] disulfide (Compound 43);
- 30 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide (Compound 45);
- bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-35 (cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-

- 10 -

tetrahydroimidazo[1,2a] pyrazine] disulfide (Compound 48); and

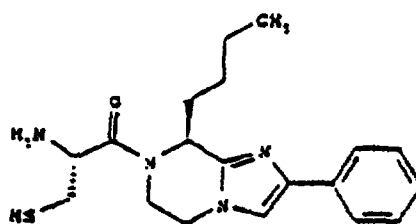
 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-
5 tetrahydroimidazo[1,2a] pyrazine] disulfide (Compound 50);

 bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-3-oxopropyl]-disulfide (Compound 64).

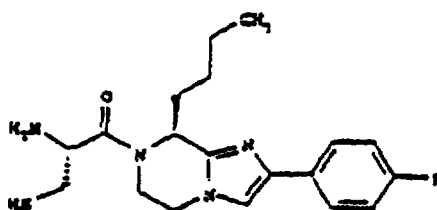
10 The structures of these compounds are listed in Table I below.

TABLE I

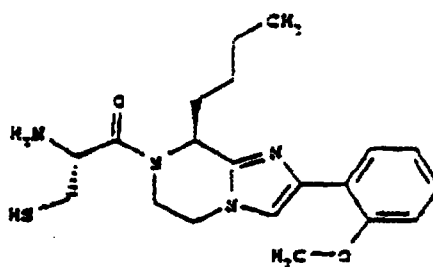
COMPOUND 1



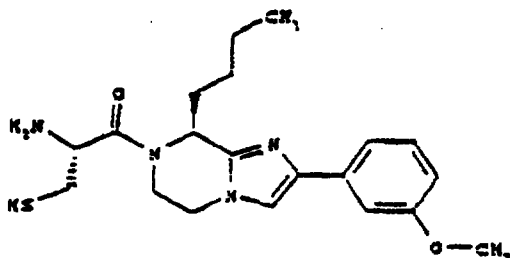
COMPOUND 2



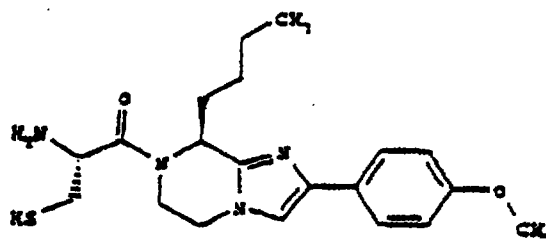
COMPOUND 3



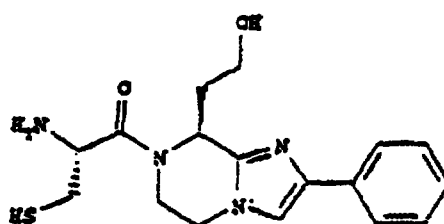
COMPOUND 4



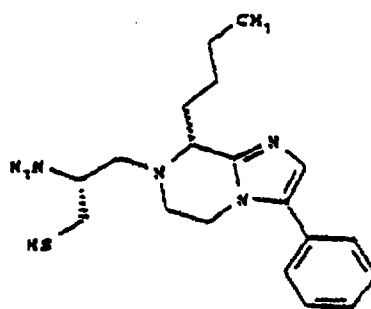
COMPOUND 5



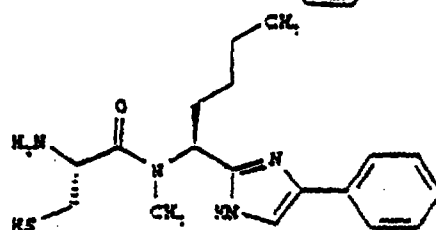
COMPOUND 6



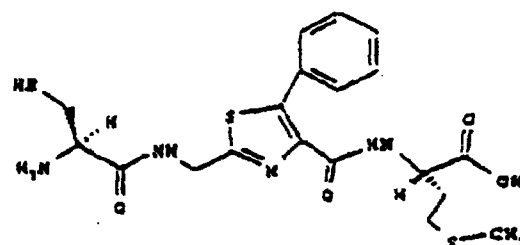
COMPOUND 7



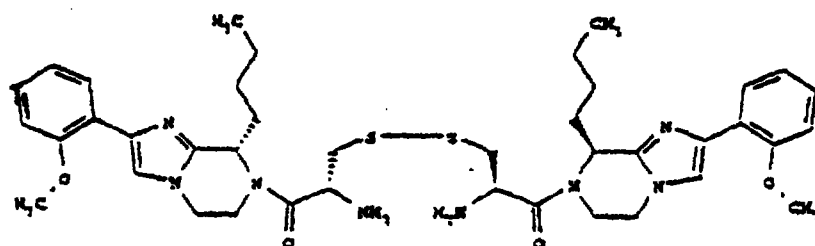
COMPOUND 8



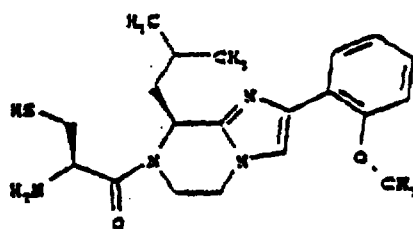
COMPOUND 9



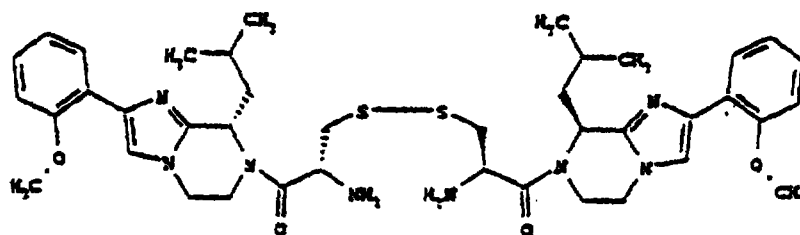
COMPOUND 10



COMPOUND 11

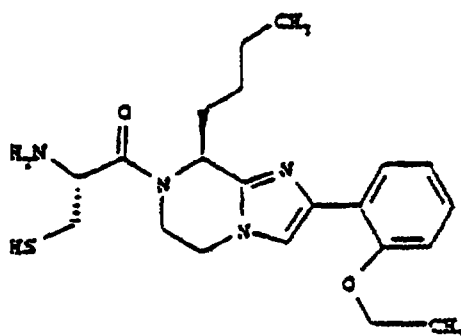


COMPOUND 12

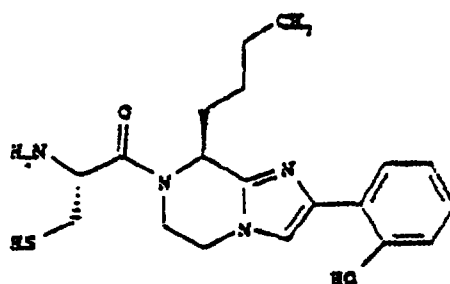


- 13 -

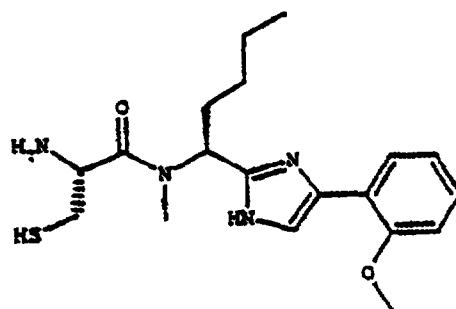
COMPOUND 13



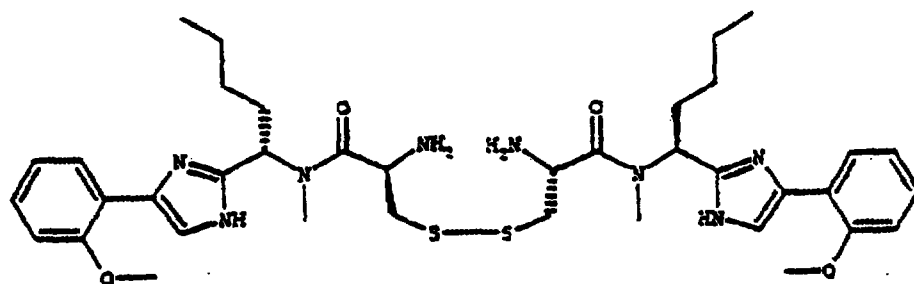
COMPOUND 14



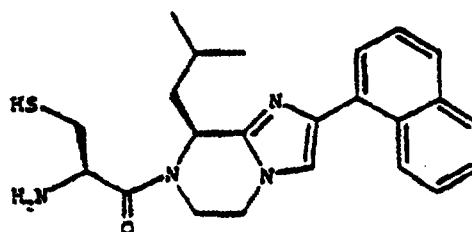
COMPOUND 15



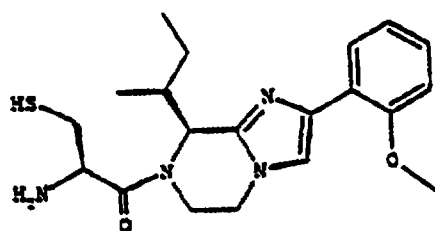
COMPOUND 16



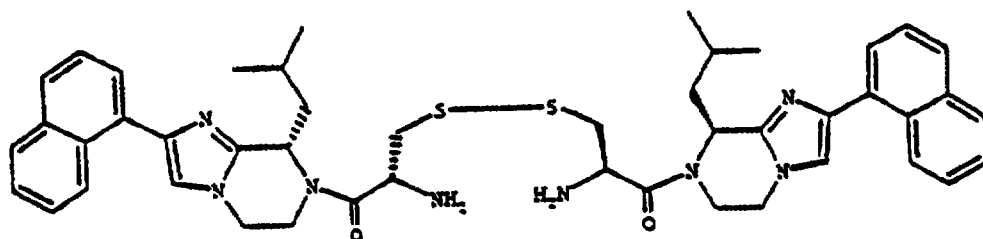
COMPOUND 17



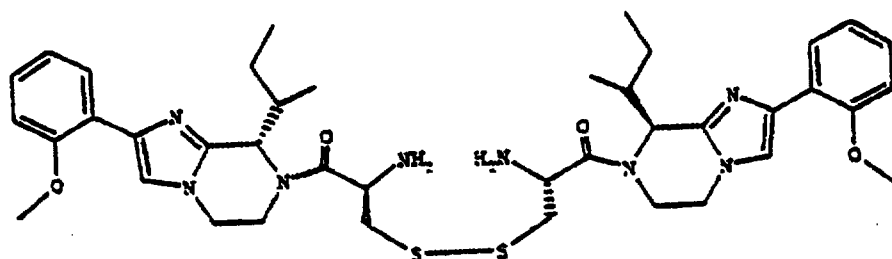
COMPOUND 18



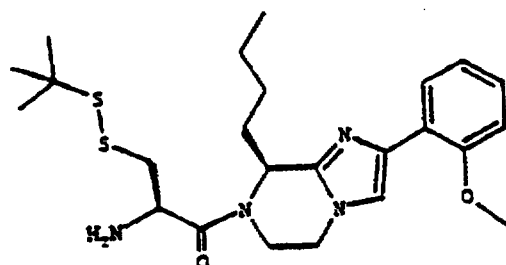
COMPOUND 19



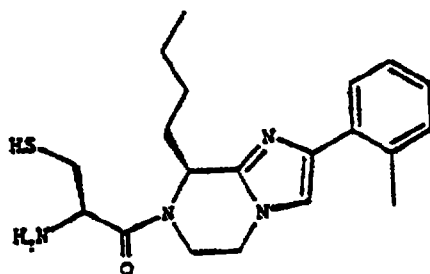
COMPOUND 20



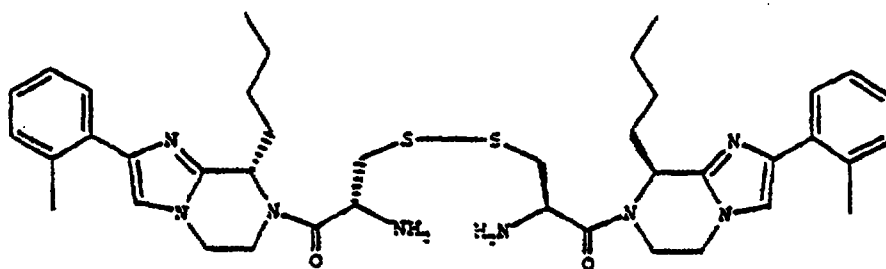
COMPOUND 21



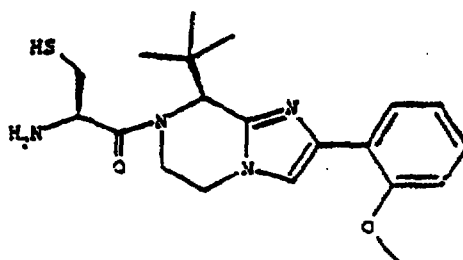
COMPOUND 22



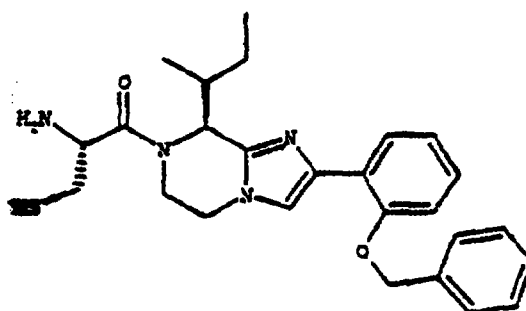
COMPOUND 23



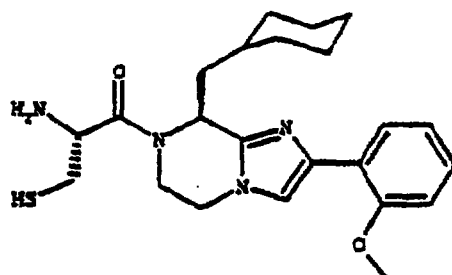
COMPOUND 24



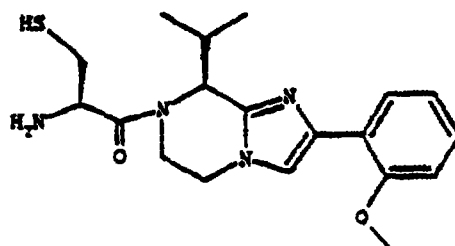
COMPOUND 25



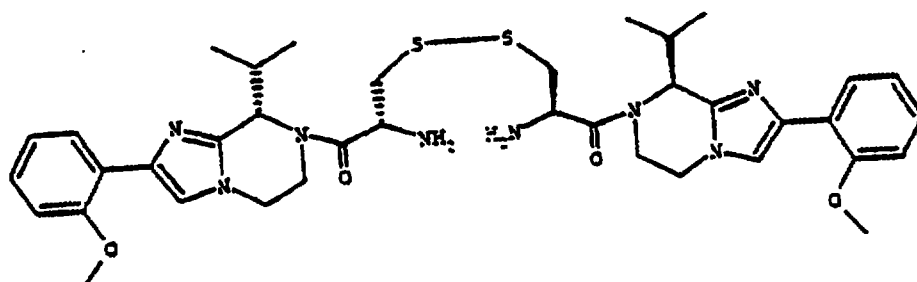
COMPOUND 26



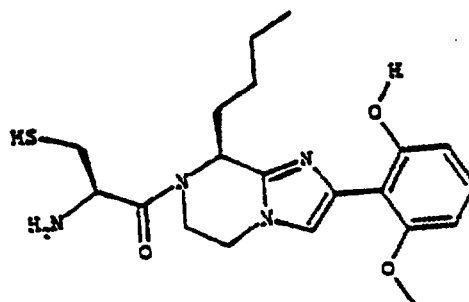
COMPOUND 27



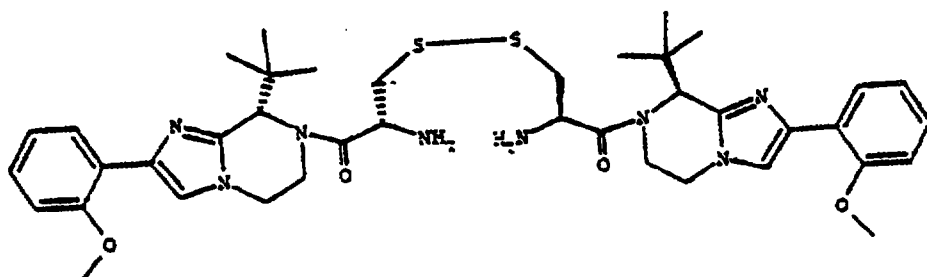
COMPOUND 29



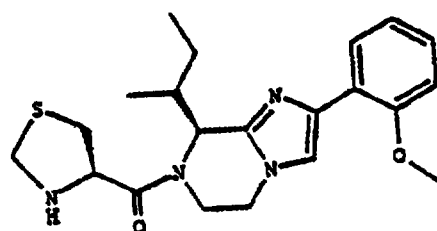
COMPOUND 29



COMPOUND 30

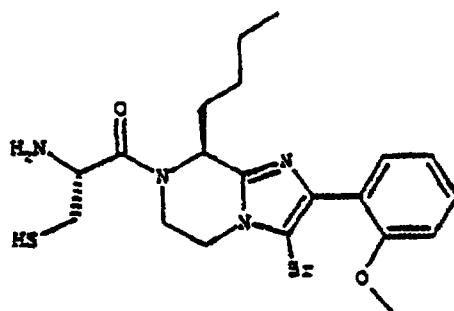


COMPOUND 31

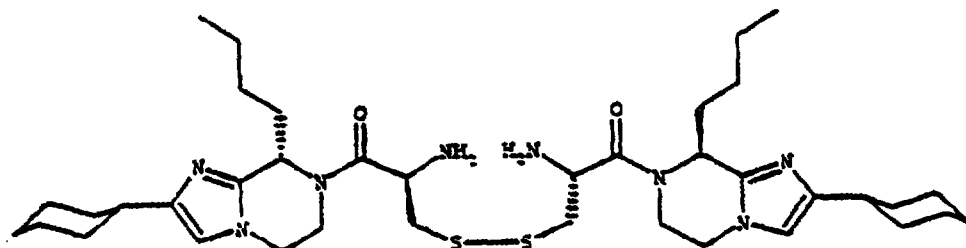


- 17 -

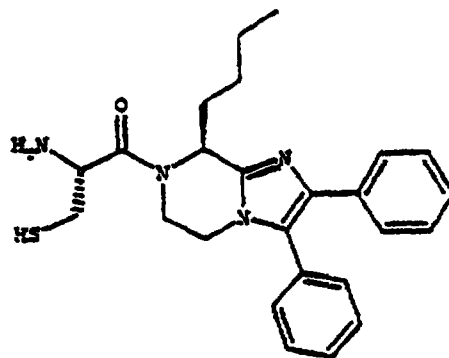
COMPOUND 32



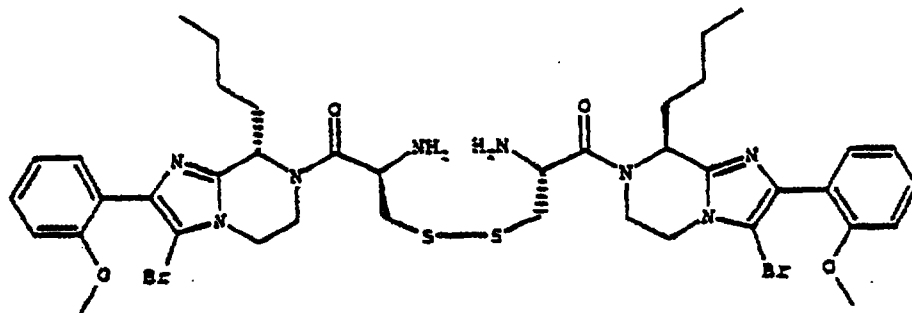
COMPOUND 33



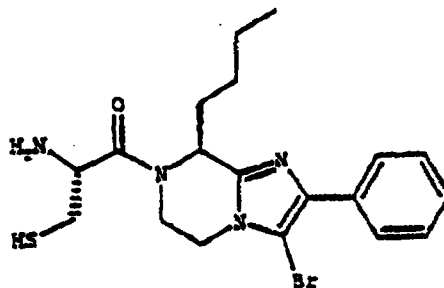
COMPOUND 34



COMPOUND 35



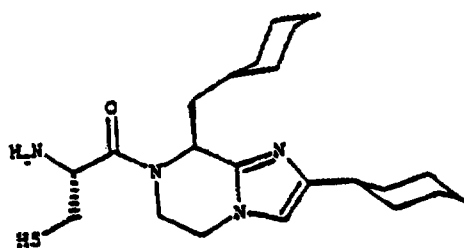
COMPOUND 36



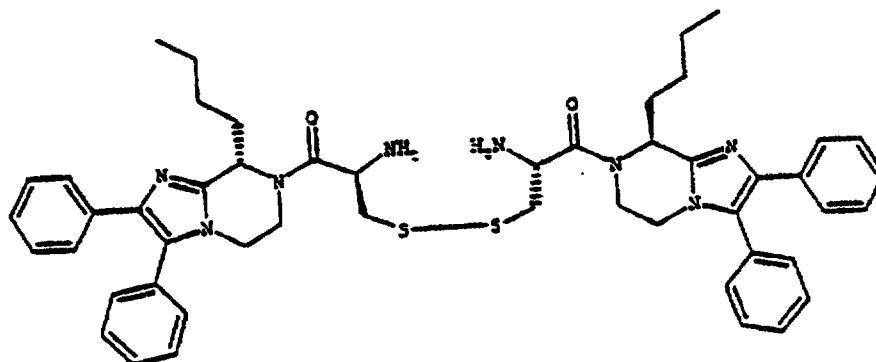
WO 97/30053

- 18 -

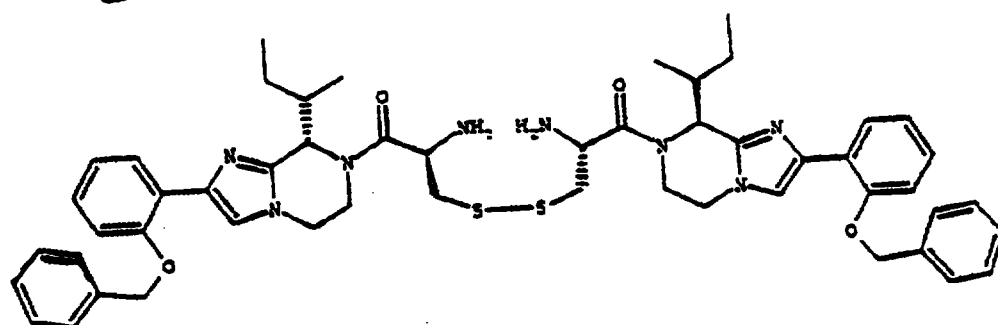
COMPOUND 37



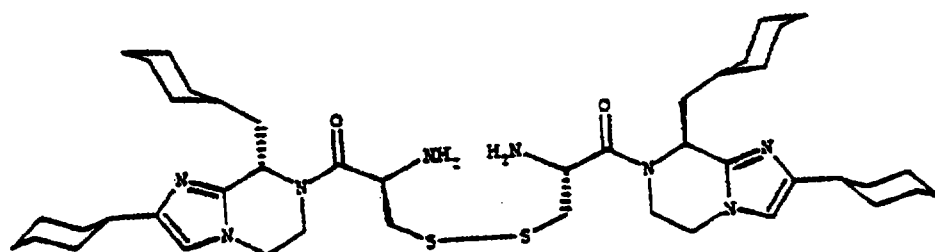
COMPOUND 38



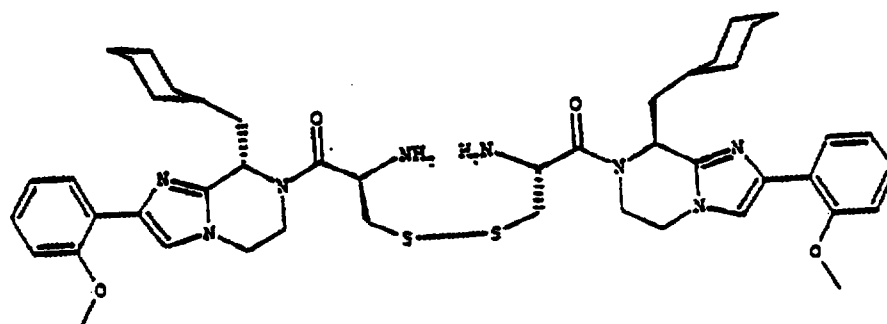
COMPOUND 39



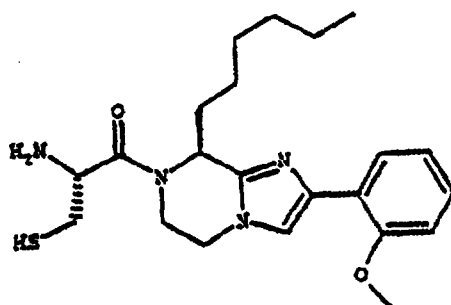
COMPOUND 40



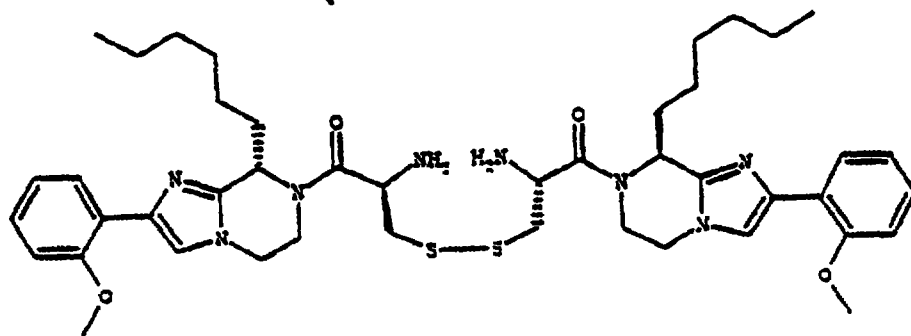
COMPOUND 41



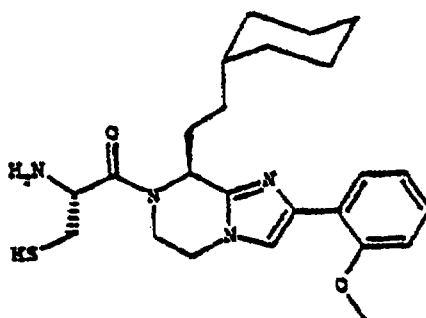
COMPOUND 42



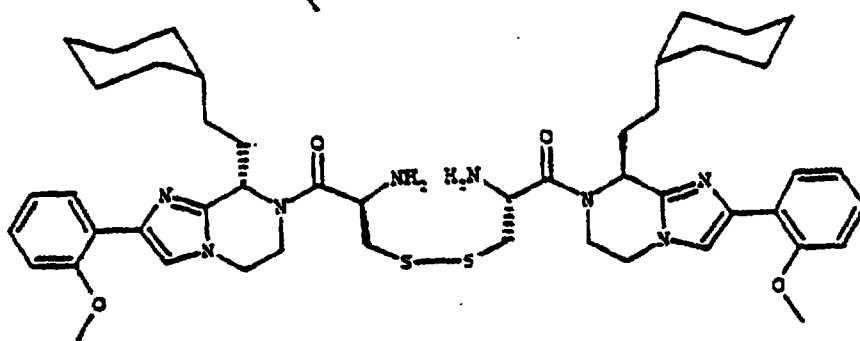
COMPOUND 43



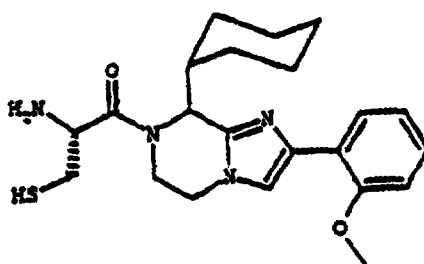
COMPOUND 44



COMPOUND 45

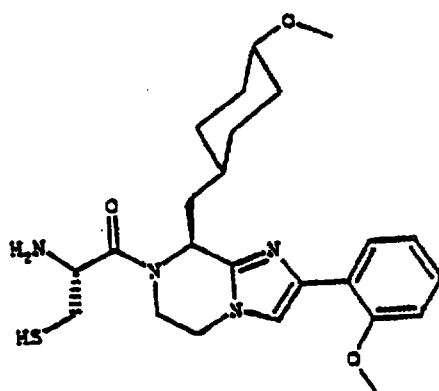


COMPOUND 46

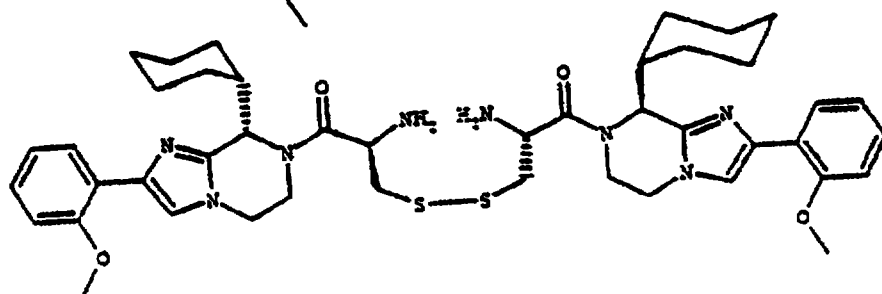


- 20 -

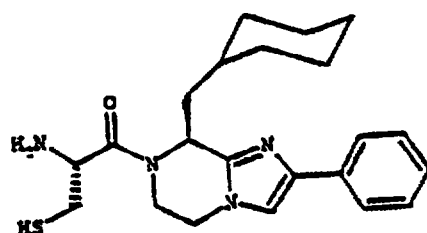
COMPOUND 47



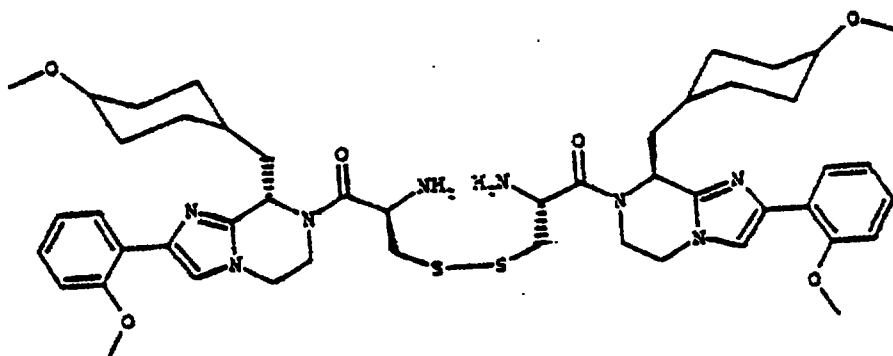
COMPOUND 48



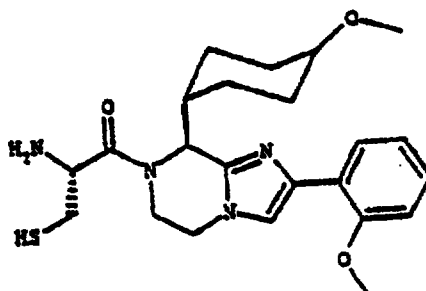
COMPOUND 49



COMPOUND 50

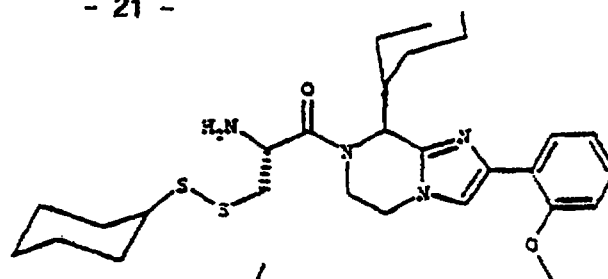


COMPOUND 51

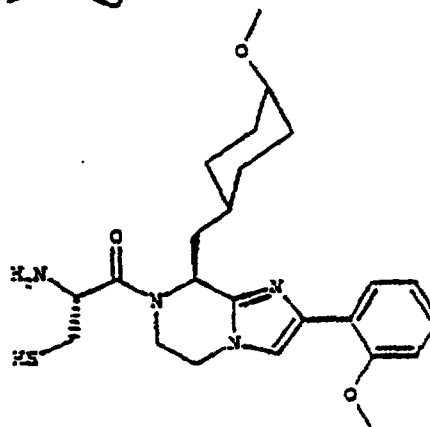


- 21 -

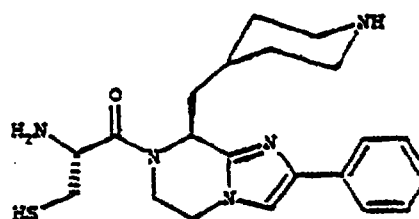
COMPOUND 52



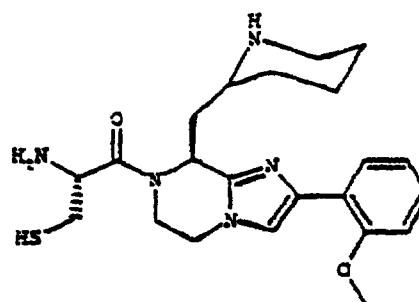
COMPOUND 53



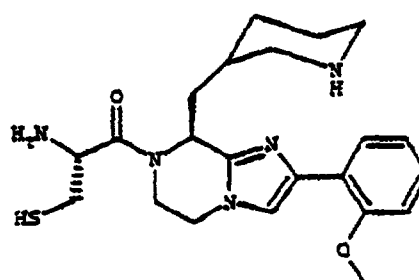
COMPOUND 54



COMPOUND 55

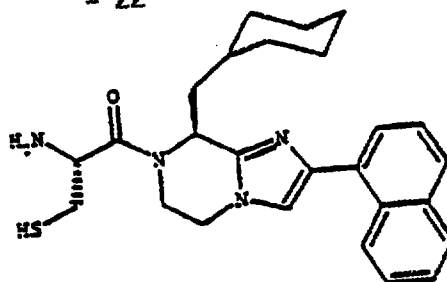


COMPOUND 56

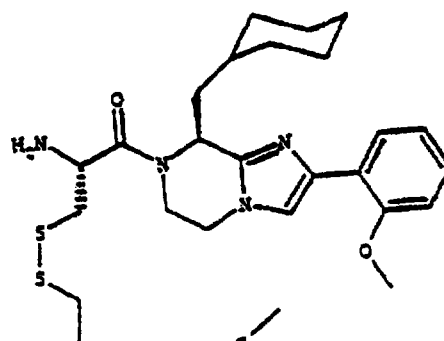


- 22 -

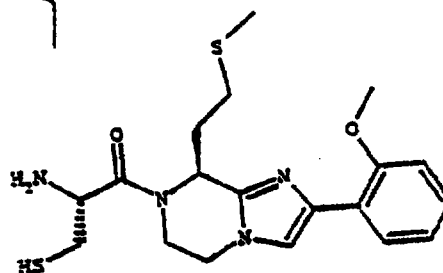
COMPOUND 57



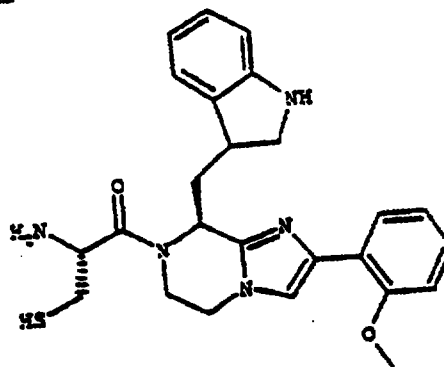
COMPOUND 58



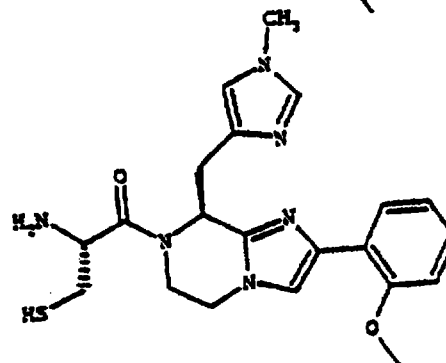
COMPOUND 59



COMPOUND 60

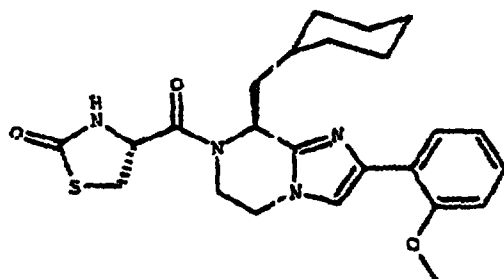


COMPOUND 61

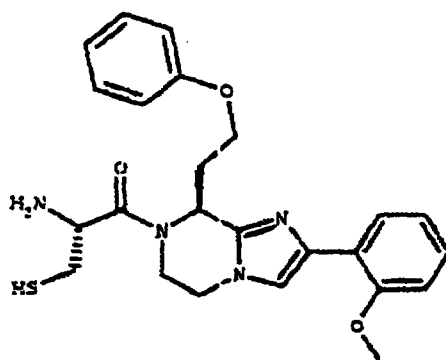


- 23 -

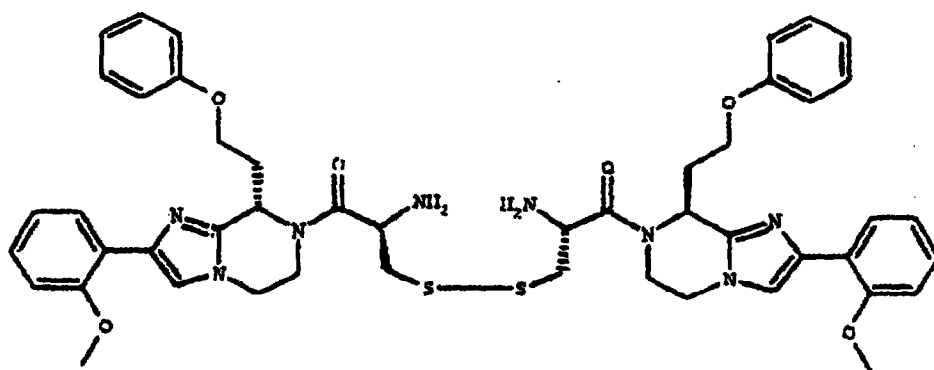
COMPOUND 62



COMPOUND 63



COMPOUND 64



- 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
5 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
10 include both branched and straight-chain saturated aliphatic hydrocarbon groups having 1-6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, sec-butyl, and the like. "Lower alkenyl" groups include those
15 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. "Alkynyl groups" include those groups having
20 2-6 carbon atoms and having one or several triple bonds. Examples of alkynyl groups include ethynyl, propynyl, 1-butyne, 2-butyne, 3-butyne, s-butyne, and the like. All alkyl, alkenyl, and alkynyl groups are noncyclic.

As used herein, "cycloalkyl" is intended to
25 include non-aromatic cyclic hydrocarbon groups having 3-10 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. "Cycloalkenyl" is intended to include non-aromatic hydrocarbon cyclic groups having 3-10 carbon
30 atoms and having one or several double bonds. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl, and the like.

As used herein, "aryl" is intended to include any
35 stable monocyclic, bicyclic, or tricyclic carbon ring(s)

- 25 -

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.

- 5 The term heterocyclyl, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from
- 10 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
- 15 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,
- 20 ~~chromanyl~~, ~~cinnol~~inyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolyl, indolyl, indolyl, isochromanyl, isoindolyl, isoquinolyl,
- 25 isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalyl, tetrahydrofuryl, tetrahydroisoquinolyl,
- 30 tetrahydro-quinolyl, thiamorpholyl, thiamorpholyl sulfoxide, thiazolyl, thiazolyl, thienofuryl, thienothienyl, thienyl, and the like.

The term halo is meant to include fluoro, chloro, bromo, and iodo.

- 26 -

The term "substituted" is meant to include the recited chemical group (e.g., lower alkyl, heterocycle, aryl, cycloalkyl, etc.) substituted with one to four of the recited substituents (e.g., halo, OH, lower alkyl, etc.). The substituent may be attached to any atom in the chemical group.

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 hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or organic 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 another aspect, the invention features a method of inhibiting farnesyl transferase in a patient, e.g., a mammal such as a human, by administering to a patient 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 patient by administering to a patient 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., tumors expressing farnesyl transferase).

- 27 -

Examples of treatable tumors are breast, colon, pancreas, prostate, lung, ovarian, epidermal, and hematopoietic cancers (Sepp-Lorenzino, I, et al., Cancer Research 55:5302 (1995)).

5 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 therapeutic composition
10 (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
15 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
20 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
25 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 is a method of preparing the compound of
30 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
35 of the invention and from the claims.

- 28 -

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 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.

Synthesis

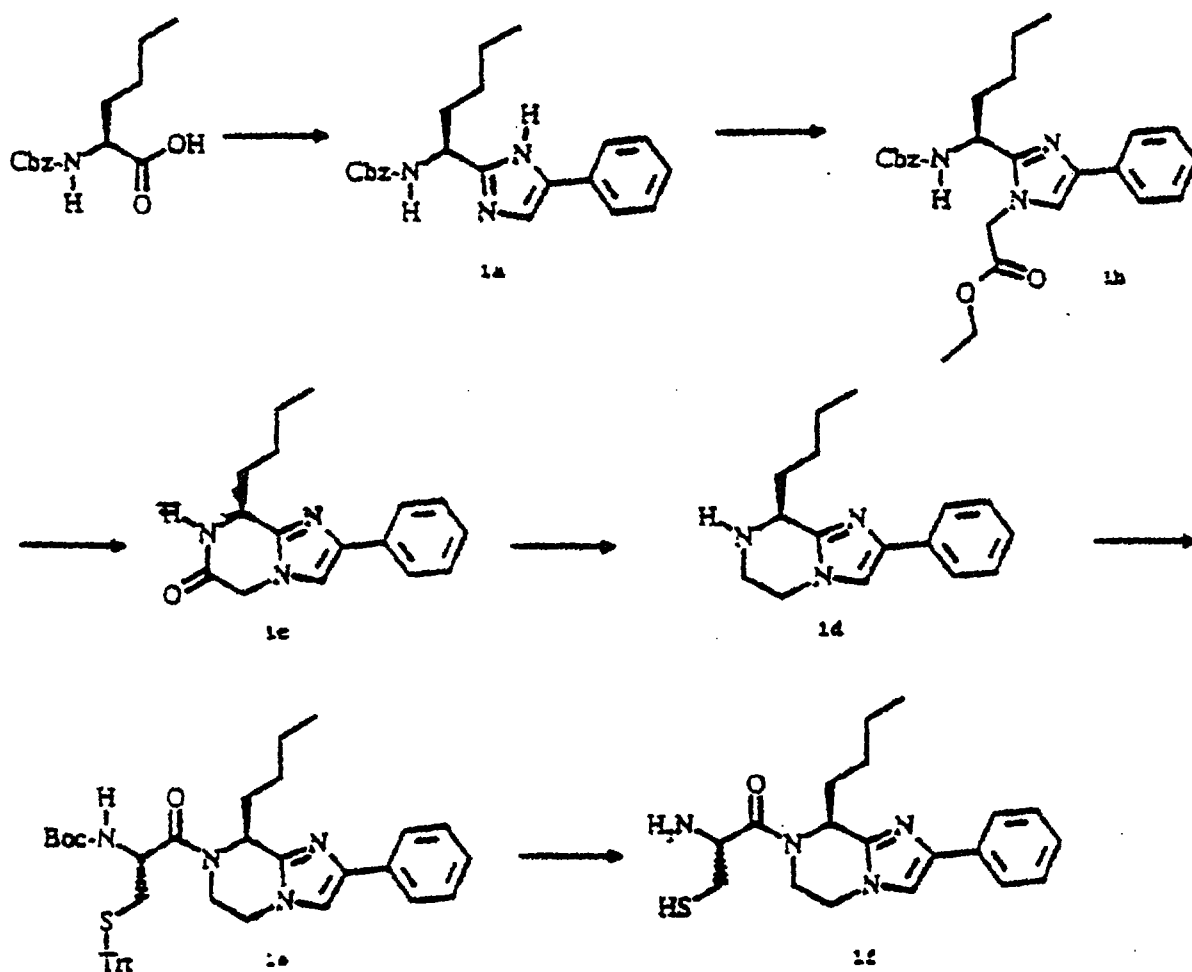
15 The following is a description of the synthesis of compounds 1 to 31. Other compounds of the invention can be prepared in an analogous manner by a person of ordinary skill in the art. As used herein, the term Cbz means carbobenzyloxy; DMF means dimethylformamide; EtOAc
20 means ethyl acetate, NH₄OAc means ammonium acetate; LAH means lithium aluminum hydride; THF means tetrahydrofuran; BOC means t-Butoxycarbonyl; Trt means trityl; Tfa means trifluoroacetic acid; Et₂O means ethyl ether; NMR means nuclear magnetic resonance; mass spec.
25 means mass spectroscopy; DMSO-d₆ means methyl sulfoxide; DCC means dicyclohexyl carbodiimide; NMM means 4-methyl morpholine; iPr₃SiH means triisopropylsilane, HPLC means high performance liquid chromatography; DIC means diisopropylcarbodiimide; MeOH means methanol; KOtBu means
30 potassium tert-butoxide; HOSU means N-hydroxysuccinimide; and iBuOCOCl means isobutyl chloroformate.

Example 1: 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 1)

- 29 -

Compound 1 was synthesized according to synthetic scheme 1 as shown below:

SCHEME 1



- 30 -

a. 2-[1-(S)-(((Phenylmethoxy)carbonyl)amino)-
penty]-4-phenyl-imidazole

Cbz-(L)-Norleucine (10.0 g, 37.7 mmole) and Cs_2CO_3 (6.14 g, 18.9 mmole) were combined in 1:1/DMF:H₂O (75 ml), and the mixture was swirled until a homogeneous mixture was obtained. Solvents were removed in vacuo. The residue was dissolved in DMF (50 ml), and the solvents were removed in vacuo again to remove any residual H₂O. The residue was dissolved in DMF (50 ml), and 2-bromoacetophenone (7.5 g, 37.7 mmole) in DMF (25 ml) was added to the solution. The solution was stirred for 15 min. at room temperature and then concentrated in vacuo. The resulting keto-ester was dissolved in EtOAc (75 ml), CsBr was filtered off, and the solution was concentrated in vacuo. NH₄OAc (50.0 g, 0.65 mole) and xylenes (150 ml) were added to the solution, and the solution was heated at reflux for 1.5 hr. The solution was then cooled, and the solvents were removed in vacuo. The residue was dissolved in EtOAc (75 ml) and washed two times with saturated NaHCO₃ solution (50 ml). The EtOAc layer was then dried over MgSO₄, filtered, and hexanes were added to turbidity. The resulting crystalline product was filtered off, and the product was dried to yield 10.04 g (73%) of product. m.r.= 136-138C, Mass spec. (MH⁺364.3). NMR (300MHz, CD₃CO₂D) 7.7 (3H, m), 7.4 (3H, m), 7.3 (5H, m), 5.1 (3H, m), 2.1 (2H, m (obscured by solvent)), 1.4 (4H, M), 0.9 (3H, t).

b. Ethyl, 2-[1-(S)-
(((Phenylmethoxy)carbonyl)amino)- penty]-
4-phenyl-1-imidazoleacetate

Ethyl bromoacetate (2.64 ml, 24 mmole), K₂CO₃ (1.93 g, 14.0 mmole), and intermediate 1a (4.36 g, 12.0 mmole) were mixed in DMF (25 ml), and the mixture was heated at 60°C for 4 hr. The mixture was then concentrated in vacuo and the residue was dissolved in

- 31 -

EtOAc (50 ml). The solution was washed with both a saturated NaHCO_3 solution (25 ml) and a saturated NaCl solution (25 ml). The solution was then dried over MgSO_4 , filtered, and the solvents were removed in vacuo.

- 5 The residue was further purified by flash chromatography on silica gel using 80:20 / hexanes:EtOAc as an eluant. Pure product fractions were combined and concentrated in vacuo to yield an oil which was crystallized. as 3.09 g (57%) of product. m.r. = 85-87°C, mass spec. 450.2
- 10 (MH+), 472.2 (MNa+). NMR (300MHz, $\text{CD}_3\text{CO}_2\text{D}$) 7.7 (2H, d), 7.5 (1H, s), 7.2-7.45 (8H, m), 5.25 (2H, dd), 5.1 (2H, dd), 5.1 (1H, m), 2.15 (2H, m), 1.4 (7H, m), 0.9 (3H, t).

c. (S)-8-Butyl-6-oxo-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine

- 15 Intermediate 1c (2.89 g, 6.44 mmole) was dissolved in 50 ml acetic acid containing 290 mg of 10% Pd on carbon. The mixture was hydrogenated for 8 hrs at room temperature. The catalyst was removed by filtration through celite. Lactamization was accomplished by
- 20 heating at 70°C for 3 hrs. The product was concentrated under reduced pressure, and the residue was distributed between EtOAc and a saturated NaHCO_3 solution. The EtOAc layer was dried over MgSO_4 and filtered. The product was crystallized from EtOAc/hexanes to yield 1.37 g (79%) of
- 25 product. m.r.=208-211°C, mass spec. 270.2 (MH+), 292.2 (MNa+). NMR (300MHz, $\text{CD}_3\text{CO}_2\text{D}$) 7.75 (2H, d), 7.5 (1H, s), 7.3-7.45 (3H, m), 5.25 (1H, m), 4.95 (2H, s), 2.1 (2H, m (obscured by solvent peak)), 1.4 (4H, m), 0.9 (3H, t).

- 30 d. (S)-8-Butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine

A solution of intermediate 1c (1.25 g, 4.65 mmole) in 20 ml THF was added dropwise to a stirred solution of 1M LAH in THF (16 ml). The mixture was heated to reflux for 1 hr. and then stirred at room temperature overnight.

- 32 -

The mixture was then quenched by the slow addition of a mixture of 3 g celite and 2 ml of a saturated K_2CO_3 solution. The mixture was stirred for 1 hr., and filtered solids were extracted three times with 25 ml EtOAc. Solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using ethyl acetate:acetic acid:pyridine:water/900:54:16:30 as an eluant. The product fractions were concentrated to oil and then taken up in ethyl acetate. The solution was washed with 25 ml of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was dried on a vacuum pump to yield 190 mg (16%) of product. Mass spec. 256.2 (MH+), 278.2 (MNa+).

- 15 e. 7-[2-(((1,1-dimethylethoxy)carbonyl)amino)-1-oxo-3-((triphenylmethyl)thio)propyl]-8-Butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine

Dicyclohexylcarbodiimide (155 mg, 0.75 mmole) and Boc-Cys(Trt)-OH (Advanced Chemtech) were dissolved in 8 ml of THF and stirred for 5 min. The resulting dicyclohexylurea was filtered off, and the filtrate was added to intermediate 1d. The resulting mixture was stirred at room temperature for 6 hrs, concentrated to a gum, and purified by flash chromatography on silica gel using 7:3/hexanes:EtOAc as an eluant. Product fractions were combined and concentrated to a glass yielding 500 mg (95%) of product. Mass spec. 701.5 (MH+), 723.5 (MNa+). NMR (300MHz, CD_3CO_2D), 7.7 (2H, d), 7.5 (1H, s), 7.2-7.45 (18H, m), 6.05 (1H, d), 4.6 (1H, t) 4.2 (2H, t), 3.95 (1H, t), 3.8 (1H, m), 2.6 (2H, m), 2.0 (2H, m (obscured by solvent)), 1.4 (9H, s), 1.2-1.4 (4H, m), 0.9 (3H, t)

- 35 f. 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 1)

- 33 -

Intermediate 1e (322 mg, 0.46 mmole) was stirred with 10 ml of Reagent B (Tfa:phenol:(iPr₃SiH):H₂O/8.8:0.5:0.2:0.5) under nitrogen for 15 min. The solvents were removed under reduced pressure, and the residue was taken up in 25 ml H₂O and washed two times with 25 ml Et₂O. The aqueous layer was purified by reverse phase column chromatography to provide 9 mg (5%) of compound 1 as a white lyophilized powder. Mass spec: 359.1 (MH⁺).

10 Example 2: 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 2)

Compound 2 was prepared by in a manner analogous to Example 1 except that 2-bromo-4'-fluoro-acetophenone was used in place of 2-bromoacetophenone in step a. Mass spec. 377.2 MH⁺. NMR (300MHz, CD₃CO₂D), (approximately 2 to 1 mixture of conformers observed) 7.8-8.0 (2H, m), 7.6-7.8 (1H, s), 7.1-7.3 (12H, m), 5.8-6.3 (1H, m), 3.5-5.3 (5H, t), 3.0-3.4 (2H, m), 2.1-2.6 (2H, m), 1.3-1.7 (4H, m), 0.8-1.0 (3H, m).

20 Example 3: 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 3)

Compound 3 was prepared in a manner analogous to Example 1 except that 2-bromo-2'-methoxy-acetophenone was used in place of 2-bromoacetophenone in step a. Mass spec. 389.3 MH⁺. NMR (300MHz, DMSO-d₆), 8.2-8.8 (3H, s), 7.7-8.0 (2H, m), 7.2-7.4 (1H, m), 6.8-7.2 (2H, m), 5.4-5.8 (1H, t), 4.5-4.8 (1H, t), 3.7-4.5 (4H, m), 3.9 (3H, s), 2.7-3.1 (2H, m), 1.8-2.1 (2H, m) 1.3-1.6 (4H, m), 0.8-1.0 (3H, t).

30 Example 4: 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 4)

- 34 -

Compound 4 was prepared in a manner analogous to Example 1 except that 2-bromo-3'-methoxy-acetophenone was used in place of 2-bromoacetophenone in step a. Mass spec. 389.3 MH+. NMR (300MHz, DMSO-d6),),

5 (approximately 4 to 1 mixture of conformers observed)
8.2-8.7 (3H, s), 7.7-8.0 (1H, s), 7.2-7.5 (3H, m), 6.8-7.0 (2H, d), 5.4-5.8 (1H, t), 4.5-4.8 (1H, t), 3.7-4.5 (4H, m), 3.8 (3H, s), 2.7-3.1 (2H, m), 1.8-2.1 (2H, m) 1.2-1.6 (4H, m), 0.8-1.0 (3H, t).

10 Example 5: 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 5)

Compound 5 was prepared in a manner analogous to Example 1 except that 2-bromo-4'-methoxy-acetophenone was
15 used in place of 2-bromoacetophenone in step a. Mass spec. 389.2 MH+. NMR (300MHz, DMSO-d6),),

(approximately 6 to 1 mixture of conformers observed)
8.2-8.8 (3H, s), 7.7-8.0 (1H, s), 7.5-7.8 (2H, d), 6.9-7.2 (2H, d), 5.4-5.8 (1H, t), 4.5-4.8 (1H, t), 3.7-4.5
20 (4H, m), 3.8 (3H, s), 2.7-3.2 (2H, m), 1.8-2.1 (2H, m) 1.2-1.6 (4H, m), 0.8-1.0 (3H, t).

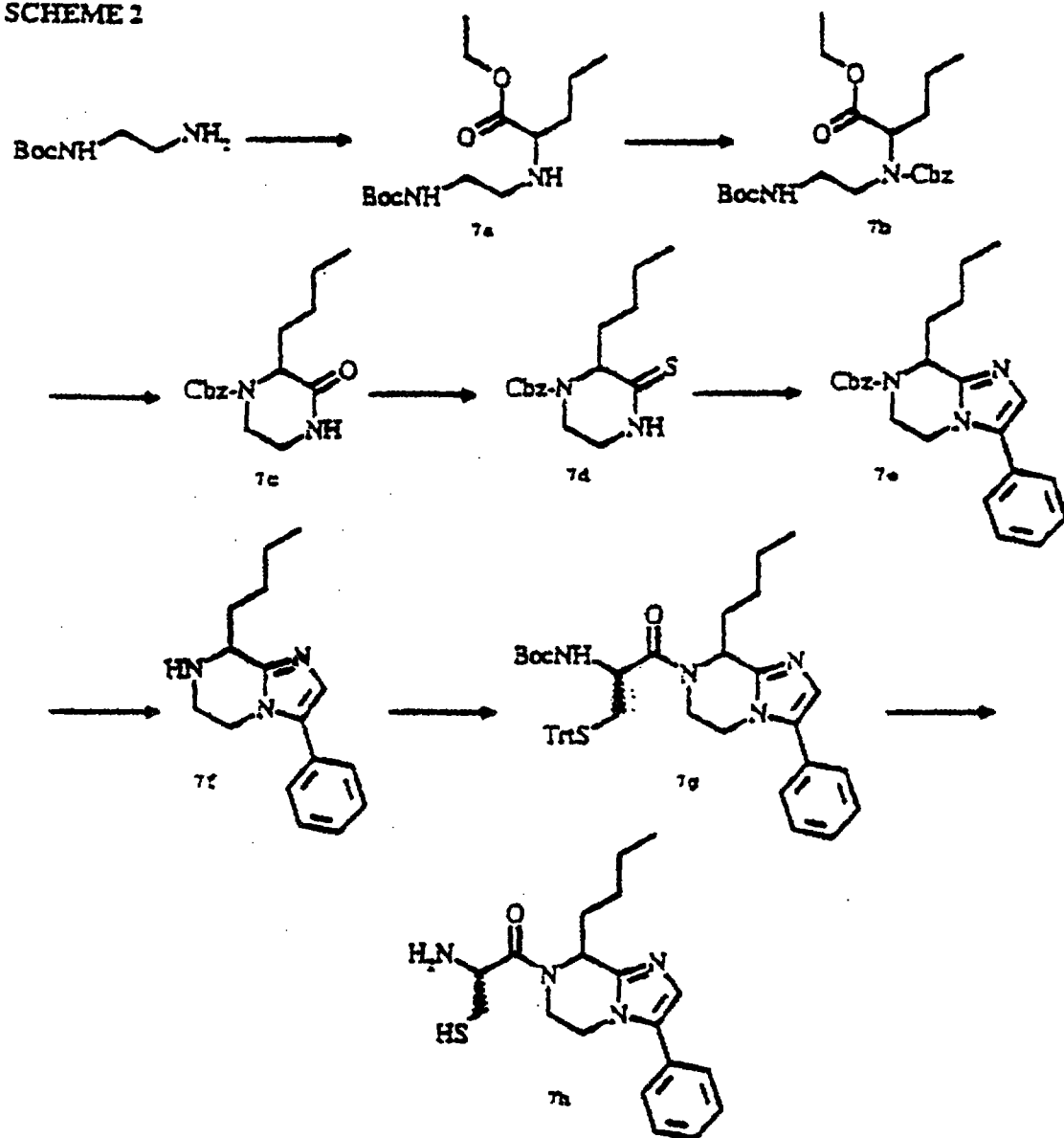
Example 6: 7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-ethyl)-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 6)

25 Compound 6 was prepared in a manner analogous to Example 1 except that 2-bromo-4'-methoxy-acetophenone in place of 2-bromoacetophenone in step a. Mass spec. 347.1 MH+.

30 Example 7: 7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 7)

Compound 7 was synthesized according to synthetic Scheme 2 as set forth below:

SCHEME 2



- 36 -

a. Ethyl, 2-((2-(((1,1-dimethylethoxy-)carbonyl-)amino-)ethyl-)amino-)-hexanoate

Boc-NHCH₂CH₂NH₂ was prepared as described by A.P. Krapcho and C.S. Kuell, Syn. Comm. 20(16):2559-2564 (1990). Boc-NHCH₂CH₂NH₂ (5.00 g, 31.25 mmole), ethyl 2-bromohexanoate (5.71 ml, 31.25 mmole), and K₂CO₃ (4.31 g, 31.25 mmole) were combined in 75ml DMF and stirred at 40°C for 1.5 hr. Solvents were removed under reduced pressure, and the residue was then distributed between Et₂O and H₂O. The ether layer was dried over MgSO₄ and filtered, and the solvents were removed under reduced pressure to yield 7.48 g (79%) of an oil. Mass spec. 303.0 MH⁺, NMR (CDCl₃), 4.9-5.1 (1H, S br), 4.1-4.4 (2H, M), 3.0-3.6 (2H, M), 2.5-3.0 (2H, M), 1.9-2.2 (1H, S br), 1.3-1.8 (2H, M), 1.5 (9H, S), 1.2-1.5 (7H, M), 0.8-1.0 (3H t).

b. Ethyl, 2-(N-(2-(((1,1-dimethylethoxy-)carbonyl-)amino-)ethyl-))-N-[(phenylmethoxy)carbonyl-]amino- hexanoate

Intermediate 7a (7.40 g, 24.5 mmole) was dissolved in 40 ml THF, and 10 ml H₂O was then added. The mixture was cooled to 5°C, and Cbz-Cl was added in four portions to the mixture. The pH of the mixture was maintained between 8-9 by addition of 2.5N NaOH. When the reaction was completed, the solvents were removed under vacuum, and the residue was taken up in EtOAc and washed with 5% citric acid solution. The solvents were removed under reduced pressure. The residue was dissolved in hexanes, filtered to remove a crystalline impurity, and dried to yield 7.34g (69%) of an oil. Mass spec. 337.2 (M-Boc)H⁺, 459.3 M Na⁺. NMR (CDCl₃), 7.2-7.6 (5H, M), 5.1-5.4 (3H, M), 3.9-4.4 (3H, M), 3.5-3.8 (1H, M), 3.1-3.5 (3H, M), 1.6-2.2 (2H, M), 1.4-1.5 (9H, S), 1.1-1.5 (7H, M), 0.8-1.0 (3H t).

- 37 -

c. 3-Butyl-2-oxo-4-((phenylmethoxy)-carbonyl)-piperazine

Intermediate 7b (7.10 g, 16.3 mmole) was dissolved in 25 ml of 9:1/Tfa:H₂O and stirred for 15 min. under
5 nitrogen. Solvents were removed under reduced pressure, and the residue was taken up in EtOAc. The solution was washed with a saturated NaHCO₃ solution, dried over MgSO₄, filtered, and solvents were removed under reduced
10 pressure. 10 ml acetic acid and 10ml pyridine was added to the residue, and it was refluxed for 1 hour under nitrogen. Solvents were removed under reduced pressure, and the residue was dissolved in EtOAc and washed two times with 5% citric acid. The solution was dried over MgSO₄, filtered, and solvents were removed under reduced
15 pressure. The product was crystallized from a solution of EtOAc/hexanes to yield 2.40g (51%) of a white powder. m.r. = 107-108°C. Mass spec. 291.2 MH⁺, 313.2 M Na⁺. NMR (CDCl₃), 7.3-7.5 (5H, S), 7.0-7.2 (1H, S br), 5.1-5.3 (2H, Q), 4.5-4.8 (1H, S br), 4.1-4.4 (1H, S br), 3.4-3.6
20 (1H, T), 3.1-3.4 (2H, D), 1.7-2.1 (2H, M), 1.2-1.5 (4H, M), 0.8-1.0 (3H S br).

d. 3-Butyl-4-((phenylmethoxy)-carbonyl)-2-thio-piperazine

Intermediate 7c (2.85 g, 9.83 mmole) and Lawsson's
25 reagent (2.02 g, 5.00 mmole) were dissolved in 20 ml THF and heated at reflux under nitrogen for 1.5 hours. The solution was cooled, and solvents were removed under reduced pressure. The residue was dissolved in 50 ml Et₂O and washed three times with 25 ml of 1N NaOH. The
30 solution was dried over MgSO₄, filtered, and solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using 65:35/hexanes:EtOAc as an eluant. The product fractions were concentrated to yield 2.19 g (73%) of an oil which
35 crystallized. m.r. = 94-96°C. Mass spec. 307.2 MH⁺,

- 38 -

329.2 M Na+. NMR (CDCl₃), 8.5-8.8 (1H, S), 7.3-7.5 (5H, S br), 4.9-5.4 (3H, M), 4.0-4.5 (1H, M), 1.1-3.6 (3H, M), 3.4-3.6 (1H, T), 2.2-2.4 (2H, S br), 1.7-2.0 (2H, M), 1.2-1.6 (4H, S br), 0.7-1.0 (3H S br).

5 e. 8-Butyl-3-phenyl-7-((phenylmethoxy)-carbonyl)-
5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine

Intermediate 7d (1.07 g, 3.5 mmole) was dissolved in 10 ml THF. Iodomethane (2.18 ml, 35.0 mmole) was added and stirred at room temperature for 8 hours. Solvents
10 were removed under reduced pressure. The residue was dissolved in 10 ml THF, and 4-methylmorpholine (771 ul, 7.0 mmole) and 2-aminoacetophenone hydrochloride (686 mg, 4.00 mmole) were added to the solution. The solution was stirred overnight at room temperature and then refluxed
15 for 2 hours. 15 ml acetic acid was added, and 15 ml solvent was distilled off. The solution was then refluxed for 1 hour and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using 70:30/hexanes:EtOAc as an eluant. The product
20 fractions were concentrated to yield 0.97g (71%) of an oil. Mass spec. 390.3 MH+, 412.2 M Na+. NMR (CD₃CO₂D), (approximately 1:1 mixture of conformers) 7.2-7.6 (11H, M), 5.6-5.8 (1H, M), 5.0-5.4 (2H, M), 4.4-4.8 (1H, M), 4.1-4.4 (1H, M), 3.9-4.1 (1H, M), 3.3-3.6 (1H, S br),
25 1.8-2.2 (obscured by solvent) (2H, M), 1.7-2.0 (2H, M), 1.1-1.6 (4H, S br), 0.7-0.9 (3H S br).

f. 8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine

Intermediate 7e (1.08 g, 2.78 mmole) was dissolved
30 in 4 ml of THF. 10 ml of 4N HCl was added, and the mixture was heated at reflux under nitrogen for 4 hours. Solvents were removed under reduced pressure to yield a

- 39 -

solid product which was washed with ether and dried to 740 mg. Mass spec. 256 MH⁺.

- 5 g. 8-butyl-7-(2-((1,1-dimethylethoxy)-carbonyl-
)amino-1-oxo-3-(triphenylmethyl-thio)-propyl)-3-
phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-
pyrazine

Boc-Cys(Trt)-OH (2.32 g, 5.00 mmole; Advanced
Chemtech) was dissolved in 20 ml of THF. DCC (515 mg,
2.50 mmole) was added to this solution. The solution was
10 allowed to stand for 15 min., and the DCC was filtered
off. The filtrate was added to a solution of
intermediate 7f (700 mg, 2.4 mmole) and NMM (655 ul, 4.80
mmole) in 20 ml of THF. The solution was stirred for two
hours at room temperature, and solvents were removed
15 under reduced pressure. The resulting product was
purified by silica gel chromatography using
70:30/hexanes:EtOAc as an eluant. The product fractions
were combined and concentrated to a foam, which was dried
to yield 1.47 g (87.5%) of product. Mass spec. 701.4
20 MH⁺, NMR (CD₃CO₂D), 7.1-7.7 (21H, M), 6.0-6.2 (1H, M),
6.5-6.7 (1H, T), 3.4-4.4 (4H, M), 2.4-2.8 (2H, M), 1.8-
2.4 (2H, M) (partially obscured by solvent signal), 1.4
(9H, S), 1.1-1.4 (4H, M), 0.7-1.0 (3H, M)).

- 25 h. 7-butyl-6-(2-((dimethylethoxy)-carbonyl-)amino-
3-(triphenylmethyl-thio)propyl)-3-phenyl-
4,5,6,7-tetrahydro-imidazo-[1,2a]piperazine

Intermediate 7g (350 mg, 0.50 mmole) was dissolved
in THf (3 ml) and 1M BH₃/THf (7 ml, 7.0 mmole) was added.
The reaction was heated at reflux for 2 hr under N₂. The
30 solution was cooled to room temperature, and the excess
reagent was destroyed by careful addition of a solution
of MeOH (8 ml) and acetic acid (2 ml). The crude product
was

- 40 -

concentrated under reduced pressure and redissolved in 3:1/acetic acid:H₂) for 1 hr. After removing solvents under reduced pressure, the residue was purified by flash chromatography on silica gel using 1% HOAc/ETOAc as
5 eluant. The product fractions were combined, concentrated, and dried to 100 mg (29%). MH+ 687.5.

i. 7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 7)

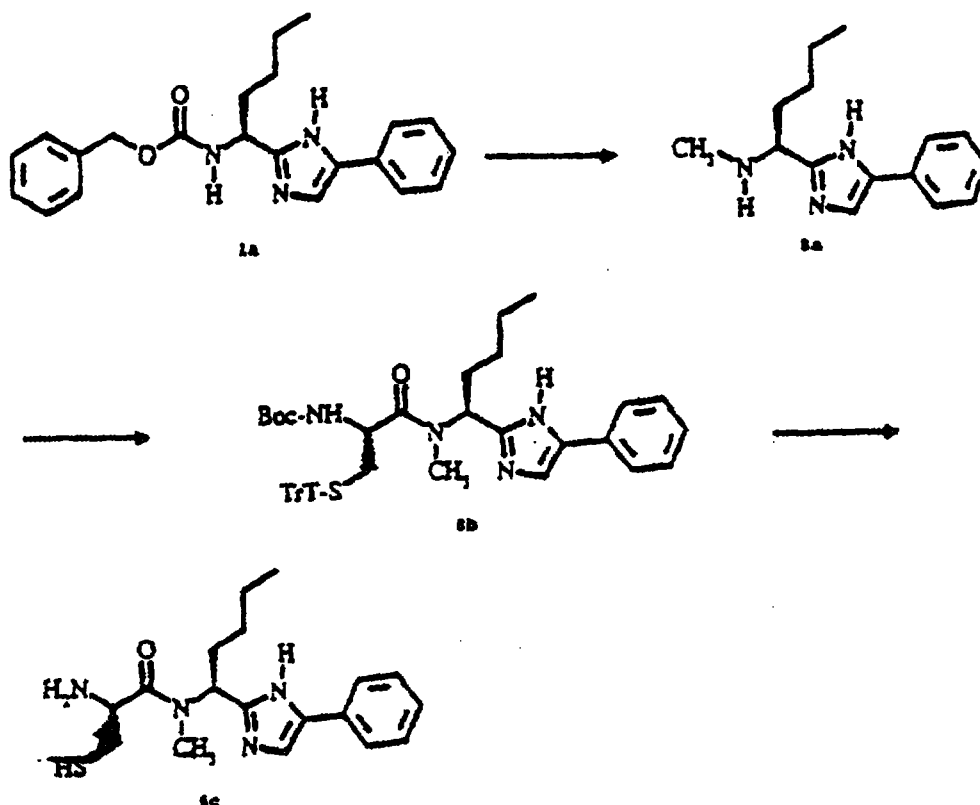
10 Intermediate 7h (100 mg, 0.146 mmole) was treated under nitrogen with a mixture of Tfa:H₂O:iPr₃SiH/93:5:2 (10 ml) for 15 min. Solvents were removed under reduced pressure, and the resulting solids were triturated eight times with 4 ml of H₂O and then filtered off. The
15 filtrate was purified by prep HPLC to yield 45 mg (74%) of lyophilized compound 7 which appeared as a 1:1 mixture of isomers on analytical HPLC. Mass spec. 345.2 MH+, NMP (CD₃CO₂D), 7.4-7.7 (6H, M), 6.0-6.4 (1H, M), 3.8-5.3 (5H, M), 3.0-3.4 (2H, M), 2.0-2.4 (2H, M), 1.2-1.7 (4H, M),
20 0.9-1.0 (3H, M).

Example 8: 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl)-5-phenyl-imidazole (Compound 8)

Compound 8 was synthesized according to Scheme 3 as
25 set forth below:

- 41 -

SCHEME 3



a. 5-(1-(Methylamino)-pentyl)-2-phenyl-imidazole

Intermediate 1a (1.50 g, 4.10 mmole) and LAH (50% in oil; Alfa Products, Danvers, MA) (1.25 g, 16.4 mmole) were combined in toluene (10 ml) and THF (5 ml) under nitrogen, and the mixture was heated to 55°C for 4 hrs. The mixture was poured into EtOAc (100 ml), and moist celite was added to the mixture. Solids were filtered off, and the filtrate was dried over Na₂SO₄ and concentrated. The crude product was used without further purification.

- 42 -

- b. 5-((N-(2-(((1,1-dimethylethoxy-)carbonyl)-amino)-1-oxo-3-(triphenylmethyl-thio)-propyl)-N-methyl-amino)-pentyl)-2-phenyl-imidazole

Boc-Cys(Trt)-OH (3.8 g, 8.2 mmole) and DIC (643 ul, 4.1 mmole) were combined in CH₂Cl₂ (50 ml) and stirred for 0.5 hours at room temperature. Intermediate 8a (1.00 g, 4.1 mmole) was added and stirred at room temperature for 1 hour. Solids were filtered off and diluted to 100 ml with CH₂Cl₂. The solution was washed with saturated NaHCO₃ (3 x 50 ml) and saturated NaCl (1 x 50 ml), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (120 g) using first CH₂Cl₂, and then 1% MeOH/CH₂Cl₂ as eluants. Product fractions were combined and concentrated to yield 1.36 g (46%) of product.

- c. 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl)-5-phenyl-imidazole (Compound 8)

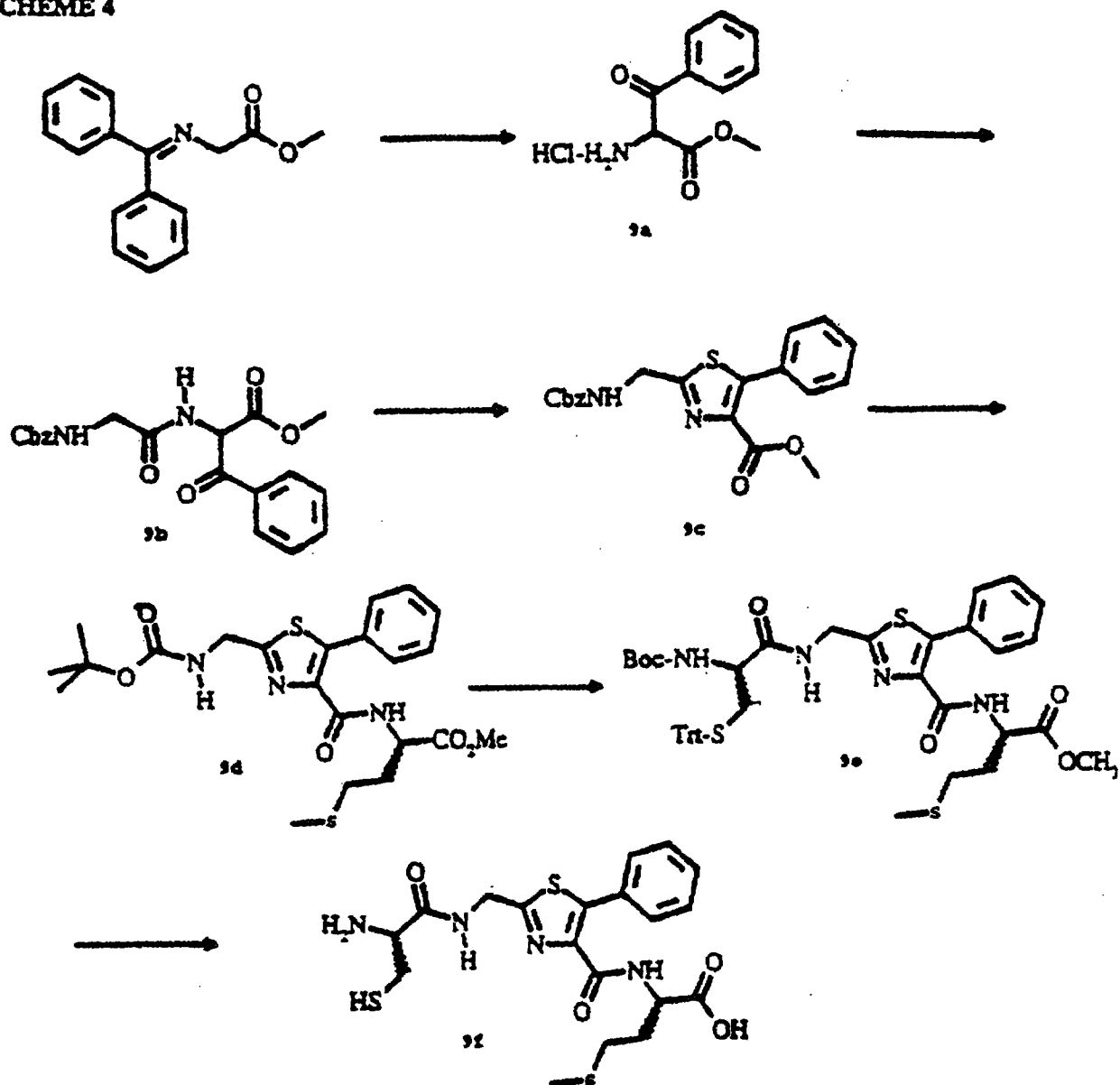
Intermediate 8b was dissolved in 10 ml of Reagent B under nitrogen, and the solution was stirred for 0.5 hours. Solids were filtered off, and solvents were removed under a stream of nitrogen. The residue was triturated with ethyl ether and purified by reverse phase HPLC to yield compound 8 as a white solid after lyophilization (74.1mg, 49%). Mass spec: 347.2 MH+.

- 25 Example 9: 2-(((2-amino-1-oxo-3-mercapto-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine (Compound 9)

- 43 -

Compound 9 was synthesized according to Scheme 4 as set forth below.

SCHEME 4



- 44 -

a. Methyl, 2-amino-3-oxo-3-phenylpropionate

Schiff base (10.0 g, 39.5 mmole) was prepared as described in (O'Donnel, et al., J. Org. Chem. 47:2663
5 (1982). Schiff base was dissolved in THF (60 ml) and added dropwise to a stirred mixture of KOtBu (4.43g, 39.5 mmole) in THF (30 ml) which was cooled to -70°C under nitrogen. The solution was stirred for 10 min. at -70°C, and the anion was transferred to a stirred solution of
10 benzoyl chloride (4.59 ml, 39.5 mmole) in THF (50 ml) which had also been cooled to -70°C under nitrogen. The solution was stirred for 45 min. at -70°C and then quenched by the addition of 4N HCl (30 ml). THF was removed under reduced pressure, and the aqueous layer was
15 washed twice with 50 ml of ethyl ether. The solution was concentrated to a solid, and the product was dissolved in MeOH (30 ml), and the KCl was filtered. The product was crystallized by the addition of ether to the point of turbidity. The product was filtered off and dried to
20 yield 2.89 g (32%) of product. Mass spec. 194.1 (MH+)

b. Methyl, 2-(((1,1-dimethylethoxy-)carbonyl-)glycyl)-amino-3-oxo-3-phenylpropionate

Boc-Gly-OH (3.15 g, 18.0 mmole) and NMM (1.98 ml, 18.0 mmole) were combined in THF (50 ml) and the solution
25 was cooled to -20°C. iBuCOCl (2.34 ml, 18.0 mmole) was added to the solution, and the mixture was stirred for 5 min. at -20°C. Intermediate 9a (4.13 g, 18.0 mmole) and NMM (1.98 ml, 18.0 mmole) was added to the solution which was stirred vigorously while returning to room
30 temperature. The solution was concentrated under reduced pressure, and the residue was dissolved in EtOAc (50 ml) and washed once with H₂O, once with 5% citric acid solution, and once with saturated NaCl solution. The solution was dried over MgSO₄, filtered, and concentrated
35 under reduced pressure. Further purification was

- 45 -

accomplished by flash chromatography on silica gel using 1:1/hexanes:EtOAc as an eluant. Product fractions were combined and concentrated to yield 3.28g (52%) of product. Mass spec. 373.2 MNa+

5 c. Methyl, 2-(((1,1-dimethylethoxy-)carbonyl-)-amino)-methyl-5-phenyl-thiazole-4-carboxylate

Intermediate 9b (3.10 g, 8.86 mmole) and Lawesson's reagent (3.6 g, 8.9 mmole; Aldrich Chem. Co., St. Louis, MO) were combined in THF (30 ml) and heated to reflux for
10 1 hour. Solvents were removed under a stream of nitrogen, and the residue was purified by flash chromatography on silica gel using 1:1/hexanes:EtOAc as an eluant. Product fractions were combined and concentrated under reduced pressure to yield 2.21 g (72%)
15 of product. Mass spec. 349.0 MH+, 371.2 MNa+.

d. 2-(((1,1-dimethylethoxy-)carbonyl-)-amino)-methyl-5-phenyl-thiazole-4-carbonyl-methionine methyl ester

Intermediate 9c was dissolved in methanol (5 ml),
20 and an aqueous solution of NaOH (344 mg, 8.61 mmole) in minimum of H₂O was added to the solution. The solution was stirred at 40°C for 1 hour, and the solvents were removed under reduced pressure. The residue was distributed between EtOAc (20 ml) and 5% citric acid (20
25 ml). The EtOAc layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (10 ml), and HOSu (330 mg, 2.87 mmole), HCl-Met-OMe (573 mg, 2.87 mmole), NMM (316 mg, 2.87 mmole) and DCC (591 mg, 2.87 mmole) were added to the
30 solution. The mixture was stirred at room temperature overnight, filtered, and concentrated under reduced pressure. The residue was taken up in EtOAc (25 ml), and washed once in 5% citric acid solution and twice in a saturated NaHCO₃ solution. The solution was dried over

- 46 -

MgSO₄, filtered, and concentrated under reduced pressure to yield 590 mg (43%) of product. Mass spec. 502.2 MNa⁺, 480.4 MH⁺

- 5 e. 2-(((2-(((1,1-dimethylethoxy)-carbonyl)-amino)-1-oxo-3-(triphenylmethyl-thio)-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine methyl ester

Intermediate 9d (590 mg, 1.23 mmole) was treated with Reagent B (10 ml) for 15 min at room temperature
10 under nitrogen. Solvents were removed under reduced pressure. The residue was triturated twice with 25 ml Et₂O and decanted. The residue was then dissolved in THF (10 ml) and added to the mixed anhydride generated from Boc-Cys(Trt)-OH (570 mg, 1.23 mmole), NMM (135 ul, 1.23
15 mmole) and iBuOCOC1 (160 ul, 1.23 mmole) at -20°C under nitrogen over 5 min. NMM (135 ul, 1.23 mmole) was added to the mixture which was then allowed to warm to room temperature. Solvents were removed under reduced
pressure. The residue was taken up in EtOAc (25 ml) and
20 washed with 25 ml of H₂O and 25 ml of 5% citric acid solution. The solution was dried over MgSO₄ and concentrated to yield 1.01g (100%) of a white foam.

- 25 f. 2-(((2-amino-1-oxo-3-mercapto-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine (Compound 9)

Intermediate 9e (250 mg, 0.30 mmole) was dissolved in MeOH (2 ml). NaOH (40 mg), dissolved in a minimum of H₂O, was added to the solution. The solution was stirred overnight at room temperature. Solvents were removed
30 under reduced pressure and the residue was dissolved in reagent B (10 ml). The solution was stirred for 15 min. at room temperature under nitrogen and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC. Product fractions were combined and

- 47 -

lyophilized to yield 32 mg (20%) of compound 9 as a white solid. Mass spec 469 MH⁺.

Example 10: bis-1,1'-[2-amino-3-(8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-
5 imidazo[1,2a]pyrazine-6-yl)-3-oxo]propyl
disulfide (Compound 10)

Intermediate 3e (300 mg, 0.41 mmole) was dissolved in methanol, and H₂O (0.3 ml) was added. A solution of iodine (104 mg, 0.41 mmol) in methanol (3 ml) was added,
10 and the mixture was stirred for 2 hours. The solvents were removed under reduced pressure, and the residue was triturated with hexanes (2 x 5 ml). The residue was then dissolved in ETOAc (5 ml) and washed with 5% Na₂S₂O₃ solution (10 ml). The organic layer was dried over
15 Na₂SO₄, filtered, and concentrated to a glass.

The glass was treated with 93:5:2/Tfa:H₂O:iPr₃SiH for 15 minutes under N₂. The solvents were removed under reduced pressure, and the residue was purified by RP HPLC and lyophilized. Yield = 48 mg (25%). Mas spec. 775.4
20 MH⁺, 388.5 M^{2H++}, NMR (DMSO-d₆), (approx. 5:1 mixture of conformers) 8.5-9.0 (3H,S), 8.0-8.2 (1H,d), 7.5-7.7 (1H,S), 7.1-7.3 (1H,t), 7.0-7.1 (1H,d), 6.9-7.1 (1H, t), 5.2-5.6 (1H,t), 4.8-5.0 (1H,t), 3.6-4.7 (1H,M), 3.8-4.0 (3H,S), 3.2-3.5 (2H,M), 1.8-2.2 (2H,M), 1.2-1.7 (4H, M),
25 0.8-1.0 (3H, t).

- 48 -

Example 11: 7-(2-amino-1-oxo-3-thio-propyl)-2-(2-methoxyphenyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine (Compound 11)

5 Compound 11 was prepared in a manner analogous to Example 3 except Boc-L-Leucine was used in place of Cbz-(L)-Norleucine in step a and the Boc group was cleaved with a 9:1/Tfa:H₂O mixture instead of by catalytic hydrogenation in step c. Mass spec. 389.1 MH⁺. NMR (300
10 MHz, DMSO-d₆) 8.6-8.8 (3H, s), 8.1-8.2 (1H, d), 7.9-8.1 (1H, s), 7.3-7.5 (1H, t), 7.1-7.3 (1H, d), 7.0-7.1 (1H, t), 5.9-6.1 (1H, d), 4.7-4.8 (1H, s), 4.5-4.7 (1H, d), 4.3-4.4 (1H, d), 4.1-4.3 (1H, t), 3.9-4.0 (3H, s), 3.8-4.0 (1H, t), 3.3-3.5 (1H, t), 2.8-3.1 (2H, m), 1.9-2.2
15 (2H, m), 1.7-1.8 (1H, m), 1.0-1.2 (3H, t), 0.8-1.0 (3H, t).

Example 12: bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo[1,2a] piperazine-7-yl)-3-oxo]propyl
20 disulfide (Compound 12)

Compound 12 was prepared in a manner analogous to Example 10 except intermediate 11e was used in place of intermediate 3e. Mass. spec 388.5 M₂H⁺⁺, 775.4 MH⁺. NMR (300 MHz, DMSO-d₆) 8.7-9.2 (3H, s), 8.1-8.2 (1H, d), 7.9-
25 8.1 (1H, s), 7.3-7.5 (1H, t), 7.1-7.3 (1H, d), 7.0-7.2 (1H, t), 5.9-6.1 (1H, d), 4.8-5.0 (1H, s), 4.5-4.7 (1H, d), 4.3-4.5 (1H, d), 4.1-4.4 (1H, t), 3.8-4.1 (1H, m), 3.8-4.0 (3H, s), 3.2-3.5 (2H, m), 1.8-2.2 (2H, m), 1.7-1.9 (1H, m), 1.0-1.2 (3H, d), 0.8-1.0 (3H, d).

- 49 -

Example 13: 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-ethoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine (Compound 13).

- a. Intermediate 3c (2.54 g, 8.50 mMole) was dissolved in THF (15 ml) and a 1M solution of borane in THF (34.0 ml, 34.0 mMole) was added dropwise over 10 minutes at room temperature. The mixture was refluxed for 2 hours and allowed to stand at room temperature overnight. A solution of 4 N HCl (25 ml) was added dropwise and the resulting mixture was heated at reflux for a hour. The mixture was concentrated to H₂O, made basic by careful addition of solid NaHCO₃, and extracted with EtOAc (2 x 25 ml). The EtOAc layers were dried over Na₂SO₄, filtered, and concentrated to an oil. A solution of 5% HCl (25 ml) was added, and the mixture was concentrated to a solid. The solid was recrystallized from methanol and ethyl ether to yield 2.72 g (89.5%) of the dihydrochloride salt. Mass spec. 286.2. M.R. = 242-247°C.
- b. Intermediate 13a (850 mg, 2.37 mMole) was distributed between CH₂Cl₂ and saturated NaHCO₃ solution, the CH₂Cl₂ layer was dried over Na₂SO₄, and filtered. A 1M solution of BBr₃ in CH₂Cl₂ was added and the resulting mixture was heated at reflux for 1 hour. The reaction was cooled and poured onto saturated NaHCO₃ solution (25 ml). The CH₂Cl₂ layer was dried over Na₂SO₄ and filtered. Di-(tert) -butyldicarbonate (523 mg, 2.40 mMole) was added and the mixture was stirred at room temperature over the weekend. Solvents were evaporated, and the resulting oil was purified by column chromatography on silica gel using 70 : 30 / hexanes : Ethyl acetate as eluant. Yield = 700 mg (80%) of a clear oil. Mass spec. 372.2 (MH⁺). NMR

- 50 -

c. Protected intermediate (13b) (600 mg, 1.62 mMole) was dissolved in THF (10 ml) and added dropwise to a solution of NaH (60% in oil, 120 mg, 3.0 mMole) in THF (10 ml) at room temperature under N₂. The reaction was stirred 15 minutes and ethyl iodide (400 ul, 5.00 mMole) was added. The mixture was stirred overnight at room temperature then concentrated under reduced pressure. Saturated NaHCO₃ solution (10 ml) was added, and the product was extracted with ethyl ether (2 x 20 ml). The ether was evaporated, and the residue was purified by column chromatography on silica gel using 3:1 / hexanes : ethyl acetate as eluant. Yield = 410mg (64%) of the ether. Mass spec. 400.3 (MH⁺). M.R. = 103-109°C.

d. Intermediate (13c) was treated with 90% TFA/H₂O (2 ml) for 0.5 hours and concentrated to remove the BOC group. Coupling with Boc-(L)-Cys(Trt)-OH and deprotection were accomplished in a manner analogous to example 1e and 1f, respectively, to yield compound 13. Mass spec. 403.2 (MH⁺). NMR (300MHz, DMSO-d₆) 8.4-8.7 (3H, broad s), 7.9-8.0 (1H, s), 7.75-7.9 (1H, d), 7.15-7.3 (1H, t), 7.0-7.1 (1H, d), 6.85-7.0 (1H, t), 5.7-5.85 (1H, m), 4.65-4.8 (1H, broad s), 4.45-4.6 (1H, d), 4.3-4.4 (1H, d,d), 4.1-4.25 (1H, m), 3.75-3.95 (1H, m), 3.1-3.3 (1H, m), 2.8-3.1 (2H, m), 1.9-2.15 (2H, m), 1.2-1.5 (4H, m), 0.8-1.0 (3H, t).

Example 14: 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazine (Compound 14).

a. Intermediate 13a (179 mg, 0.50 mMole) was distributed between CH₂Cl₂ and saturated NaHCO₃ solution, the CH₂Cl₂ layer was dried over Na₂SO₄, and filtered. A 1M solution of BBr₃ in CH₂Cl₂ was added, and the resulting mixture was heated at reflux for 1 hour. The reaction

- 51 -

was cooled and poured onto saturated NaHCO_3 solution (25 ml). The CH_2Cl_2 layer was dried over Na_2SO_4 , filtered, and stripped to yield crude de-methylated product as a gum. This material was used without further purification.

b. Coupling of (14a) with Boc-(L)-Cys(Trt)-OH and deprotection were accomplished in a manner analogous to example 1e and 1f, respectively, to yield compound 14. Mass spec. 403.2 (MH⁺). NMR (300MHz, DMSO-d₆) 8.55-8.8 (3H, broad s), 8.1-8.2 (1H, d), 7.85-7.95 (1H, s), 7.35-7.45 (1H, t), 7.15-7.25 (1H, d), 7.0-7.15 (1H, t), 5.85-6.0 (1H, d,d), 4.65-4.8 (1H, broad s), 4.55-4.7 (1H, d,d), 4.15-4.3 (2H, q), 4.1-4.2 (1H, m), 3.8-3.95 (1H, m), 3.3-3.5 (1H, t), 2.15-2.3 (1H, m), 1.95-2.15 (1H, m), 1.4-1.5 (3H, t), 1.2-1.5 (4H, m), 0.8-1.0 (3H, t).

Example 15: 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-Methyl)-amino-pentyl-5-(2-methoxyphenyl)-imidazole (Compound 15)

Compound 15 was prepared in a manner analogous to example 8 except 2-Bromo-2'-methoxyacetophenone was used in place of 2-Bromoacetophenone in step 1a. Mass Spec. 377.1 MH⁺. NMR (300MHz, CD₃CO₂D) 7.8-7.9 (1H, s), 7.65-7.75 (1H, d,d), 7.4-7.55 (1H, m), 7.14-7.2 (1H, d), 7.05-7.14 (1H, t), 5.6-5.8 (1H, t), 4.8-4.9 (1H, t), 3.9-4.0 (3H, s), 3.25-3.35 (3H, s), 3.05-3.25 (2H, m), 2.2-2.4 (2H, m), 1.2-1.6 (4H, m), 0.8-1.0 (3H, t).

- 52 -

Example 16: bis-1,1'-[2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methylamino)-pentyl]-5-(2-methoxyphenyl) imidazole] disulfide (Compound 16)

5 Compound 16 was prepared in a manner analogous to example 10 except compound 15 in place of intermediate 3e. Mass spec. 751.5 MH+. NMR (300MHz, CD₃CO₂D) 7.75-7.85 (1H, s), 7.65-7.75 (1H, d,d), 7.35-7.5 (1H, m), 7.1-7.2 (1H, d), 7.0-7.1 (1H, t), 5.5-5.6 (1H, t), 4.8-4.95
10 (1H, t), 3.9-4.1 (3H, s), 3.3-3.5 (2H, m), 3.2-3.3 (1H, s), 2.2-2.4 (2H, m), 2.0-2.2 (acetate signal), 1.2-1.6 (4H, m), 0.8-1.0 (3H, t).

Example 17: 7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazine (Compound 17).

15 a. 1'-Acetonaphthone (10.2 g, 60.0 mMole) and 0.1 ml of concentrated HCl were dissolved in acetic acid (100 ml) and bromine (9.6 g, 60.0 mMole) were added dropwise
20 with stirring over a three hour period. The reaction was concentrated under reduced pressure and dried to constant weight. The product was used without further purification.

b. Compound 17 was prepared in a manner analogous
25 to example 1 except Cbz-(L)-Leucine was used in place of Cbz-(L)-Norleucine, intermediate 17a was used in place of 2-Bromoacetophenone in step 1a, and 1M BH₃/THF was used for reduction of lactam intermediate in step d. Mass spec. 409.2 MH+. NMR (300MHz, DMSO-d₆) 8.5-8.9 (3H, s),
30 8.1-8.25 (1H, d), 7.9-8.15 (3H, m), 7.7-7.8 (1H, d), 7.5-7.7 (3H, m), 5.8-6.1 (1H, d), 4.7-4.85 (1H, s), 4.55-4.75 (1H, d), 4.2-4.45 (2H, m), 3.85-4.05 (1H, m), 3.0-3.4 (10H, H₂O), 2.9-3.1 (2H, q), 1.9-2.2 (1H, t), 1.7-1.9 (2H, m), 1.0-1.2 (3H, d), 0.8-1.0 (3H, d).

- 53 -

Example 18: 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methyl-propyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazine (Compound 18).

5 Compound 18 was prepared in a manner analogous to example 3 except Cbz-(L)-Isoleucine was used in place on Cbz-(L)-Norleucine in step a. Mass spec. 389.3 MH+. NMR (300MHz, DMSO-d6) 8.5-8.9 (3H, s), 8.05-8.2 (1H, d), 7.9-8.05 (1H, s), 7.35-7.5 (1H, t), 7.15-7.25 (1H, d), 7.0-7.15 (1H, t), 5.65-5.85 (1H, d), 4.65-4.8 (1H, s), 4.5-4.65 (1H, d,d), 4.3-4.45 (1H, d,d), 3.9-4.0 (3H, s), 3.8-4.0 (1H, m), 3.2-3.7 (8H, H2O), 2.8-3.0 (2H, m), 2.2-2.4 (1H, m), 1.4-1.6 (1H, m), 1.15-1.35 (1H, m), 1.0-1.15 (3H, d), 0.8-0.95 (3H, t).

15 Example 19: bis-1,1'-7-(2-amino-1-oxo-3-thiopropyl - (2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazin-7-yl) disulfide (Compound 19).

Compound 19 was prepared in a manner analogous to
20 example 10 except compound 17 was used in place of intermediate 3e. Mass spec. 815.5 MH+. NMR (300MHz, DMSO-d6) 8.7-9.2 (3H, s), 8.15-8.3 (1H, s), 8.0-8.1 (2H, m), 7.85-8.0 (1H, s), 7.7-7.8 (1H, d), 7.5-7.7 (3H, m), 5.8-6.0 (1H, s), 4.8-5.0 (1H, s), 4.5-4.54 (1H, d), 4.4-4.5 (1H, d), 4.2-4.4 (1H, t), 3.9-4.1 (1H, t), 3.0-3.9 (12H, m H2O obscures signal), 2.0-2.2 (1H, t), 1.7-2.0 (2H, m), 1.0-1.2 (3H, d), 0.85-1.0 (3H, d).

Example 20: bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(methoxy-phenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide (Compound 20).

Compound 20 was prepared in a manner analogous to example 10 except compound 18 was used in place of intermediate 3e. Mass spec. 775.5 MH+. NMR (300MHz, DMSO-d6) 8.7-9.0 (3H, s), 8.05-8.15 (1H, d), 7.9-8.1 (1H, s), 7.35-7.5 (1H, t), 7.15-7.25 (1H, d), 7.0-7.15 (1H,

- 54 -

t), 5.65-5.85 (1H, d), 4.8-5.0 (1H, s), 4.45-4.6 (1H, d), 4.35-4.5 (1H, d), 4.2-4.35 (1H, m), 3.8-4.1 (1H, m), 3.8-3.9 (3H, s), 3.4-3.8 (10H, H₂O), 3.2-3.4 (2H, d), 2.2-2.4 (1H, m), 1.4-1.65 (1H, m), 1.15-1.35 (1H, m), 1.0-1.15 (3H, d), 0.8-0.95 (3H, t).

Example 21: S-(dimethylethyl)-S'-[2-amino-3-oxo-3(8-butyl-2-(2-methoxyphenyl))-5,6,7,8-tetrahydroimidazo [1,2a]pyrazin-7-yl]propyl]disulfide (Compound 21)

10 Compound 21 was prepared in a manner analogous to example 3 except that Fmoc-(L)-Cys(tBuS)-OH was used in step e and final deprotection was accomplished by treatment with tris(aminoethyl)amine (1.5ml per mmole) in CH₂Cl₂ (10 ml per mmole) for 0.5 hour at room temperature.

15 The product was purified by preparative reverse phase column chromatography to provide pure compound 21. Mass spec. 477.3 MH⁺. NMR (300MHz, DMSO-d₆, 90°C) 8.0-8.1 (1H, d), 7.4-7.5 (1H, s), 7.1-7.3 (1H, t), 7.0-7.1 (1H, d), 6.9-7.0 (1H, t), 5.4-5.55 (1H, s), 4.3-4.7 (1H, m), 4.1-4.3 (1H, d), 3.8-4.1 (7H, m), 3.0-3.2 (2H, m + H₂O), 2.8-2.9 (1H, d,d), 2.1-2.3 (2H, m), 1.7-2.1 (2H, m), 1.2-1.7 (13H, m), 0.8-1.0 (3H, t).

20

Example 22: 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazine (Compound 22)

25

a. 2'-Methylacetophenone (25.0g, 186 mMole) was dissolved in glacial acetic acid (250 ml) and concentrated HCl (250 uL) was added followed by a dropwise addition of bromine (9.6 ml, 186 mMole) over 15 minutes. The mixture was stirred 3 hours and then concentrated under reduced pressure. The residue was taken up in ethyl ether and washed with saturated NaHCO₃ solution. The ether layer was dried over Na₂SO₄, filtered, and concentrated to yield 38.0g, (96%) of crude

30

- 55 -

2-bromo-2'-methylacetophenone which was used without further purification.

b. Compound 22 was prepared in a manner analogous to example 3 except 2-bromo-2'-methylacetophenone was
5 used in place of 2-bromo-2'-methoxyacetophenone in step a. Mass spec. 373.2 MH+. NMR (300MHz, DMSO-d₆) 8.6-8.8 (3H, s), 7.9-8.0 (1H, s), 7.6-7.75 (1H, d), 7.3-7.5 (3H, m), 5.8-6.0 (1H, d,d), 4.7-4.8 (1H, s), 4.55-4.7 (1H, d), 4.3-4.44 (1H, d,d), 4.1-4.3 (1H, m), 3.8-4.0 (1H, m),
10 3.4-3.55 (1H, t), 2.85-3.1 (2H, m), 2.4-2.5 (3H, s), 2.0-2.3 (2H, m), 1.2-1.6 (4H, m), 0.8-1.0 (3H, t).

Example 23: bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-
8-butyl-2-(2-methylphenyl)-5,6,7,8-
15 tetrahydroimidazo[1,2a] pyrazine]
disulfide (Compound 23)

Compound 23 was prepared in a manner analogous to example 10 except compound 23 was used in place of
intermediate 3e. Mass spec. 743.4 MH+. NMR (300MHz,
DMSO-d₆, 90°C) 7.6-7.8 (1H, d), 7.2-7.3 (1H, s), 7.0-7.2
20 (3H, m), 5.3-5.6 (1H, broad s), 4.3-4.8 (1H, broad s), 3.5-4.2 (4H, m), 3.0-3.3 (2H, broad s), 2.8-3.0 (1H, m), 2.4-2.5 (3H, s), 2.1-2.4 (2H, broad s), 1.7-2.1 (2H, m), 1.2-1.7 (4H, m), 0.8-1.0 (3H, t).

- 56 -

Example 24: 7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo-[1,2a]pyrazine (Compound 24)

5 Compound 24 was prepared in a manner analogous to example 3 except Boc-(L)-t-Leucine was used in place of Cbz-(L)-Norleucine in step a and deprotection was accomplished in step c by treatment with trifluoroacetic acid for 0.5 hours. Mass spec. 389.3 MH⁺. NMR (300MHz,
10 DMSO-d₆) 8.5-8.8 (3H, broad s), 7.95-8.1 (1H, d), 7.9-8.0 (1H, s), 7.3-7.5 (1H, t), 7.1-7.25 (1H, d), 7.0-7.15 (1H, t), 5.55-5.7 (1H, s), 4.65-4.8 (1H, broad s), 4.5-4.6 (1H, m), 4.35-4.5 (1H, m), 4.1-4.3 (1H, m), 3.9-4.1 (1H, m), 3.85-3.95 (3H, s), 3.3-3.4 (1H, t), 2.7-3.1 (2H, m),
15 1.0-1.2 (9H, s).

Example 25: 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methyl-propyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine
20 (Compound 25)

a. Intermediate 18d (3.36 g, 11.8 mMole) was dissolved in 10ml CH₂Cl₂ and a 1M solution of BBr₃ in CH₂Cl₂ (47 ml) was added dropwise. The mixture was heated at reflux for 2 hours, cooled and poured into saturated
25 NaHCO₃ solution (25 ml). The aqueous layer was extracted 3 times with CH₂Cl₂ (60 ml), dried over Na₂SO₄, filtered, and concentrated to 30 ml. Di-(tert) butyldicarbonate (2.57 g, 11.8 mMole) was added, and the reaction stirred at room temperature overnight. The crude product was
30 purified by column chromatography on silica gel using 1:1 / ethyl acetate:hexanes as eluant. The yield was 3.31g (75%) of white solid product.

b. Intermediate 25a (850 mg, 2.29 mMole) was dissolved in THF (20 ml) that contained sodium hydride

- 57 -

(96.1 mg, 2.4 mMole) and the mixture was treated with benzyl bromide (292 uL, 2.4 mMole) under N₂ at room temperature. The reaction was stirred overnight at room temperature and concentrated. The residue was
5 partitioned between CH₂Cl₂ (30 ml) and H₂O (15 ml). The CH₂Cl₂ layer was dried over Na₂SO₄, filtered, and concentrated. Crystallization from ethyl ether and hexanes yielded 887 mg (83.7%) of the product.

c. Intermediate 25b (887 mg, 1.92 mMole) was
10 treated with 90% Tfa/H₂O (50 ml) for 15 minutes at room temperature under N₂. Solvents were removed under reduced pressure and the residue was distributed between CH₂Cl₂ and saturated NaHCO₃ solution. The CH₂Cl₂ layer was dried over Na₂SO₄ solution, filtered and concentrated.
15 The crude intermediate was acylated in a manner analogous to example 1, step 1e, and then deprotected in a manner analogous to example 1, step f. Mass spec. 465.3 MH⁺.
NMR (300MHz, DMSO-d₆) 8.3-8.8 (3H, broad s), 8.0-8.1 (1H, d, d), 7.8-8.0 (1H, s), 7.45-7.55 (2H, m), 7.3-7.45 (4H, m),
20 7.15-7.3 (1H, d), 7.0-7.15 (1H, t), 5.6-5.8 (1H, d), 5.3-5.4 (2H, s), 4.65-4.8 (1H, broad s), 4.45-4.6 (1H, m), 4.25-4.4 (1H, m), 4.1-4.25 (1H, m), 3.75-3.95 (1H, m), 3.25-3.4 (1H, t), 2.8-3.0 (2H, m), 2.15-2.4 (1H, m), 1.4-1.6 (1H, m), 1.1-1.35 (1H, m), 0.95-1.1 (3H, d), 0.8-
25 1.0 (3H, t).

Example 26: 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine (Compound 26).

30 a. A solution of H-(L)-Phe-OH (10.0 g, 60.6 mMole) in acetic acid (60 ml) and 5% aqueous HCl (60 ml) was hydrogenated over PtO₂ (430 mg) until hydrogen was no longer consumed. Solvents were removed under reduced pressure, and the residue was dissolved in methanol (50

- 58 -

ml) and H₂O (20 ml). A 10% NaOH solution was added with vigorous stirring to pH = 4.4, the solution was cooled, and the product was filtered off and washed with H₂O.

b. Crude intermediate 26a (60.6 mMole) was
5 suspended in 100 ml H₂O containing K₂CO₃ (8.36 g, 60.6 mMole), and a solution of Cbz-Osu (15.1 g, 60.6 mMole) in CH₃CN (150 ml) was added with vigorous stirring for 45 minutes at room temperature. The CH₃CN was distilled off at reduced pressure and the aqueous layer was washed with
10 ethyl ether. The aqueous layer was acidified with concentrated HCl to pH = 1 and the product extracted with ethyl acetate (2 X 50 ml). The ethyl acetate layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield 17.27 g (93%) of Cbz-(L)-
15 cyclohexylalanine (26b).

c. Compound 26 was prepared in a manner analogous to example 3 except Cbz-(L)-Cyclohexylalanine (26b) was used in place of Cbz-(L)-Norleucine in step a. Mass spec. 429.3 (MH⁺). NMR (300MHz, DMSO-d₆) 8.6-8.9 (3H,
20 s), 8.1-8.3 (1H, d,d), 7.9-8.1 (1H, s), 7.35-7.5 (1H, m), 7.15-7.25 (1H, d), 7.05-7.15 (1H, t), 6.0-6.1 (1H, t), 4.7-4.8 (1H, m), 4.55-4.7 (1H, m), 4.3-4.45 (1H, m), 4.1-4.3 (1H, m), 3.9-4.0 (3H, s), 3.8-3.95 (1H, m), 3.35-3.5 (1H, t), 2.8-3.1 (2H, m), 2.05-2.2 (1H, d), 1.9-2.1 (2H,
25 t), 0.8-1.7 (10H, m).

- 59 -

Example 27: 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine (Compound 27).

5 Compound 27 was prepared in a manner analogous to example 3 except Cbz-(L)-Valine was used in place of Cbz-(L)-Norleucine in step a. Mass spec. 375.1 MH+. NMR (300MHz, DMSO-d6) 8.6-8.8 (3H, broad s), 8.1-8.3 (1H, d), 8.0-8.1 (1H, s), 7.35-7.5 (1H, t), 7.15-7.25 (1H, d),
10 7.05-7.15 (1H, t), 5.6-5.8 (1H, d), 4.65-4.8 (1H, broad s), 4.5-4.7 (1H, m), 4.3-4.45 (1H, m), 4.1-4.3 (1H, m), 3.9-4.0 (3H, s), 3.8-3.95 (1H, m), 3.35-3.5 (1H, t), 2.8-3.05 (2H, m), 2.5-2.7 (1H, m), 1.1-1.2 (3H, d), 0.9-1.05 (3H, d).

15 Example 28: bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [1,2a]]pyrazine] disulfide (Compound 28).

Compound 28 was prepared in a manner analogous to
20 ~~example 10~~ except compound 27 was used in place of intermediate 3e. Mass spec. 747.4 MH+. NMR (300MHz, DMSO-d6) 8.8-9.0 (3H, broad s), 8.05-8.2 (1H, d), 7.9-8.1 (1H, s), 7.35-7.5 (1H, t), 7.15-7.25 (1H, d), 7.0-7.15 (1H, t), 5.55-5.75 (1H, broad s), 4.8-5.0 (1H, broad s),
25 4.45-4.65 (1H, m), 4.35-4.5 (1H, m), 4.2-4.35 (1H, m), 3.85-3.95 (3H, s), 3.9-4.05 (1H, m), 3.2-3.4 (2H, d), 2.45-2.65 (1H, m partially obscured by solvent), 1.05-1.2 (3H, d), 0.9-1.05 (3H, d).

30 Example 29: 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro[1,2a]pyrazine (Compound 29).

a. Bromine (3.19 ml, 61.9 mMole) was added dropwise to a mixture of 2',6'-dimethoxysacetophenone (11.15 g, 61.9 mMole) and concentrated HCl (100 uL) in acetic acid
35 (50 mL) over 20 minutes. The reaction was stirred at

- 60 -

room temperature for 2 hours, and the solvents were evaporated under reduced pressure. The residue was dissolved in ethyl acetate (100 ml) and washed with saturated NaHCO_3 solution (100) and with saturated NaCl solution (100 ml). The ethyl acetate layer was dried over Na_2SO_4 , filtered, and concentrated to an oil (14.9 g). Crystallization from ethyl acetate and hexanes yields 4.87 g (30%) of 2-bromo-2',6'-dimethoxyacetophenone (29a).

- 10 b. Compound 29 was prepared in a manner analogous to example 3 except 2-bromo-2',6'-dimethoxyacetophenone (29a) was used in place of 2-bromoacetophenone in step a. One methyl ether group is cleaved efficiently during BH_3 reduction of lactam 29d. Mass spec. 405.3.

- 15 Example 30: bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a]pyrazine] disulfide (Compound 30)

- Compound 30 was prepared in a manner analogous to
20 example 10 except compound 24 was used in place of intermediate 3e. Mass spec. 775.5 (MH⁺). NMR (300MHz, DMSO-d₆) 8.7-9.1 (3H, broad s), 8.0-8.1 (1H, d), 7.8-8.0 (1H, s), 7.3-7.5 (1H, t), 7.1-7.2 (1H, d), 7.0-7.1 (1H, t), 5.55-5.65 (1H, s), 4.8-5.0 (1H, s), 4.4-4.6 (2H, m),
25 4.2-4.4 (1H, m), 3.9-4.1 (1H, m), 3.8-4.0 (3H, s), 3.2-3.4 (2H, d), 1.0-1.2 (9H, s).

- 61 -

Example 31: 2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydro-7-((thiazolidin-4-yl)carbonyl)-imidazo[1,2a]pyrazine (Compound 31)

5 Compound 31 was prepared in a manner analogous to example 18 except Boc-(L)-thiaproline was used for the coupling in step e. Mass spec. 401.3 (MH⁺). NMR (300MHz, DMSO-d₆, 90°C) 8.0-8.2 (1H, d), 7.85-8.0 (1H, s), 7.3-7.5 (1H, t), 7.15-7.25 (1H, d), 7.05-7.15 (1H, t), 5.7-5.85 (1H, d), 4.75-5.0 (1H, s), 4.45-4.7 (1H, m), 4.3-4.45 (2H, m), 4.15-4.3 (2H, m), 3.9-4.0 (3H, s), 3.8-3.95 (1H, m), 3.4-3.6 (1H, t), 3.1-3.25 (1H, m), 2.25-2.45 (1H, m), 1.4-1.6 (1H, m), 1.15-1.4 (1H, m), 1.0-1.23 (3H, t), 0.8-1.0 3H, t).

15 Antiproliferative activity of farnesyl-transferase inhibitors on human tumoral cells

The assays were performed using either A-427 lung carcinomas (expressing mutated Ki-ras gene), HT-29 colon adenocarcinomas (expressing wild type ras gene), Calu-1 lung carcinomas (expressing mutated Ki-ras gene), and MIA-PaCa pancreatic cancer cells (expressing mutated Ki-ras gene). These tumoral cells were seeded on 96 well plates at day 0 and maintained at 37°C in 5% CO₂ atmosphere. At day 1, cells were treated with increased concentrations of test compounds ranging from 0 to 100 μM for 96 hrs. At the end of this period, the quantification of cell proliferation was evaluated by the colorimetric assay based on the cleavage of the tetrazolium salt WST-1 by mitochondrial dehydrogenases in viable cells leading to the formazan formation (Cell Proliferation Reagent WST-1 Kit, Boehringer Mannheim, Germany). These experiments, done in octuplicate, were repeated twice. The results, shown in Table I, depict the concentration range (μM) of test compound required to

- 62 -

inhibit proliferation as compared to control cells in which no test compound was added.

TABLE I

	COMPOUND	CELL TYPE			
		A-427	HT-29	Calu-1	MIA PaCa-2
5	3	6.25 - 12.5	12.5	10 - 30	12.5 - 25
	4	12.5 - 25	50 - 100	10 - 30	
	5	6.25 - 25	50 - 100	12.5 - 25	
	6		50 - 100		
10	8	12.5 - 25	25 - 50	25 - 50	
	10	3.12 - 125	25 - 50	3 - 10	
	11	6.25 - 12.25	50 - 100	30 - 100	
	12	3.12 - 6.25	50	10 - 30	
15	13	6.25 - 12.5	25 - 50	12.5 - 50	
	14	3.12 - 12.5	50 - 100	10 - 30	
	15	6.25 - 12.5	25 - 50	12.5 - 25	
	16	3.12 - 12.5	25 - 50	12.5 - 25	
20	17	6.25 - 12.5	6 - 12.5	12.5 - 25	
	18	6.25	50 - 100	12.5 - 25	
	19	0.78 - 1.56		6.25 - 12.5	
	20	0.78	50 - 100	6.25 - 12.5	12.5
25	21	12.5 - 25	25 - 50	25 - 50	
	22	6.25 - 12.5		12.5 - 25	
	23	3.12 - 6.25	12.5 - 25	6.25 - 12.5	
	24	6.25 - 12.5	50 - 100		25 - 50
30	25	0.78 - 1.56	12.5 - 25	12.5 - 25	6.25 - 12.5
	26	0.39 - 1.56	12.5	12.5 - 25	6.25 - 12.5
	27	6.25	50 - 100	12.5 - 25	
	28	12.5 - 25		50 - 100	
30	29	3.12 - 6.25	25 - 50		6.25 - 12.5
	30	3.12 - 6.25	25 - 50		12.5 - 25
	31		25 - 50		

- 63 -

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.

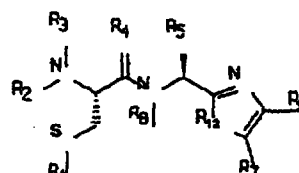
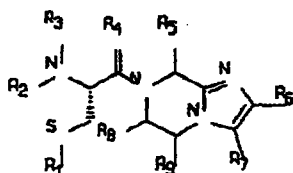
What is claimed is:



- 64 -

Claims

1. A compound having the formula (I) or formula (II):



5

I

II

wherein:

R_1 is H, lower alkyl, cycloalkylthio, or lower alkylthio, or, together with R_2 , form $-\text{CH}_2-$, $-\text{CO}-$, or $-\text{C}(\text{CH}_3)_2-$;

10 each of R_2 and R_3 , independently, is H or lower alkyl;

R_4 is H_2 or O;

R_5 is H, or substituted or unsubstituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, 15 cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is lower alkyl, $-\text{O}-\text{R}_{10}$, $-\text{S}(\text{O})_m\text{R}_{10}$ (where m is 0, 1, or 2), $-\text{N}(\text{R}_{10})(\text{R}_{11})$, $-\text{N}-\text{C}(\text{O})-\text{R}_{10}$, $-\text{NH}-(\text{SO}_2)-\text{R}_{10}$; $-\text{CO}_2-\text{R}_{10}$, $-\text{C}(\text{O})-$ 20 $\text{N}(\text{R}_{10})(\text{R}_{11})$, or $-(\text{SO}_2)-\text{N}(\text{R}_{10})(\text{R}_{11})$;

each of R_6 and R_7 , independently, is H, $-\text{C}(\text{O})\text{NHCHR}_{13}\text{CO}_2\text{R}_{14}$, or substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, 25 heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is OH, lower alkyl, lower alkoxy, aryloxy,



- 65 -

aryl lower alkoxy, $-N(R_{10})(R_{11})$, $-COOH$, $-C(O)-N(R_{10})(R_{11})$, or halo; or R_6 and R_7 , together, form aryl or heterocyclyl;

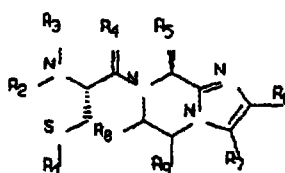
each of R_8 and R_9 , independently, is H, or
5 substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cycloalkenyl, cycloalkenyl lower alkyl, aryl, aryl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl, wherein the substituent is OH, lower alkyl, lower alkoxy, $-N(R_{10})(R_{11})$, $-COOH$, $-C(O)-$
10 $N(R_{10})(R_{11})$, or halo; or R_8 and R_9 , together, form aryl or heterocyclyl; and

each of R_{10} and R_{11} , independently, is H, lower alkyl, aryl, aryl lower alkyl, cycloalkyl, cycloalkyl lower alkyl, heterocyclyl, or heterocyclyl lower alkyl;
15 R_{12} is NR_9 , S, or O;

R_{13} is substituted or unsubstituted lower alkyl wherein the substituent is lower alkyl, $-OR_{10}$, $-S(O)_mR_{10}$ (wherein m is 0, 1, or 2) or $-N(R_{10})(R_{11})$; and

R_{14} is H or lower alkyl;
20 or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein said compound is of the formula:

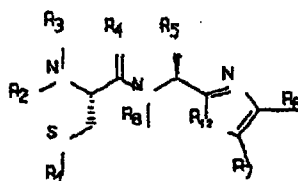


or a pharmaceutically acceptable salt thereof.



THIS SHEET HAS BEEN
REPLACED

3. A compound of claim 1, wherein said compound is of the formula:



or a pharmaceutically acceptable salt thereof.

5 4. A compound of claim 2, wherein each of R_8 and R_9 , independently, is H; or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4, wherein R_7 is H; or a pharmaceutically acceptable salt thereof.

10 6. A compound of claim 5, wherein R_6 is substituted or unsubstituted aryl or cycloalkyl, and R_5 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a pharmaceutically acceptable salt thereof.

15 7. A compound of claim 6, wherein each of R_1 , R_2 , and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.

This Sheet Has Been Replaced





THIS SHEET HAS BEEN
REPLACED

8. A compound of claim 7, wherein R_6 is phenyl, 1-naphthyl, or phenyl substituted with halo, lower alkyl or lower alkoxy, and R_5 is lower alkyl, cycloalkyl, cycloalkyl lower alkyl or lower alkyl substituted with -
5 O- R_{10} (where R_{10} is aryl); or a pharmaceutically acceptable salt thereof.

9. A compound of claim 4, wherein R_6 is H; or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9, wherein R_7 is
10 substituted or unsubstituted aryl or cycloalkyl, and R_5 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10, wherein each of R_1 , R_2 ,
15 and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11, wherein R_7 is phenyl, 1-naphthyl, or phenyl substituted or unsubstituted with halo, lower alkyl, or lower alkoxy, and R_5 is lower
20 alkyl, cycloalkyl, cycloalkyl lower alkyl; or lower alkyl substituted with -O- R_{10} (where R_{10} is aryl); or a pharmaceutically acceptable salt thereof.

13. A compound of claim 3, wherein R_6 is H or substituted or unsubstituted lower alkyl; or a
25 pharmaceutically acceptable salt thereof.

14. A compound of claim 13, wherein R_6 is H or -C(O)NHCHR₁₃CO₂R₁₄; or a pharmaceutically acceptable salt thereof.

This Sheet Has Been Replaced





- 68 -

15. A compound of claim 14, wherein R_7 is substituted or unsubstituted aryl or cycloalkyl, and R_5 is H or substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a
5 pharmaceutically acceptable salt thereof.

16. A compound of claim 15, wherein each of R_1 , R_2 , and R_3 , independently, is H and R_{12} is S; or a pharmaceutically acceptable salt thereof.

17. A compound of claim 16, wherein R_7 is phenyl or
10 phenyl substituted with halo, lower alkyl, or lower alkoxy; R_8 is H or lower alkyl, R_5 is lower alkyl, cycloalkyl, or cycloalkyl lower alkyl, and R_6 is H or $-C(O)NHCH(CH_2CH_2SCH_3)CO_2R_{14}$; or a pharmaceutically acceptable salt thereof.

18. A compound of claim 13, wherein R_7 is H or
15 $-C(O)NHCHR_{13}CO_2R_{14}$; or a pharmaceutically acceptable salt thereof.

19. A compound of claim 18, wherein R_6 is substituted or unsubstituted aryl or cycloalkyl, and R_5
20 is H or substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a pharmaceutically acceptable salt thereof.

20. A compound of claim 19, wherein each of R_1 , R_2 , and R_3 , independently, is H, and R_{12} is S; or a
25 pharmaceutically acceptable salt thereof.



THIS SHEET HAS BEEN REPLACED

21. A compound of claim 20, wherein R_6 is phenyl or phenyl substituted or unsubstituted with halo, lower alkyl, or lower alkoxy, R_8 is H or lower alkoxy; R_9 is lower alkyl, cycloalkyl, or cycloalkyl lower alkyl, and
5 R_7 is H or $-C(O)NHCHR_{13}CO_2R_{14}$; or a pharmaceutically acceptable salt thereof.
22. A compound of claim 4, wherein R_5 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl, R_6 is halo or substituted or
10 unsubstituted cycloalkyl or aryl, and R_7 is halo or substituted or unsubstituted cycloalkyl or aryl.
23. A compound of claim 22, wherein each of R_1 , R_2 , and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.
- 15 24. A compound of claim 23, wherein R_5 is lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; R_6 is phenyl, naphthyl, or phenyl substituted with halo, lower alkyl, or lower alkoxy, and R_7 is halo, phenyl, 1-naphthyl, or phenyl substituted with halo, lower alkyl,
20 or lower alkoxy.
25. A compound of claim 1, wherein said compound is of the formula:
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 25 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

This Sheet Has Been Replaced



THIS SHEET HAS BEEN
REPLACED

- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-methyl)-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 10 7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl)-5-phenyl-imidazole;
- 2-((2-amino-1-oxo-3-mercapto-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine;
- 15 7-(2-amino-1-oxo-3-thio-propyl)-2-(2-methoxyphenyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 20 ~~methoxyphenyl~~-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 25 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl-5-(2-methoxyphenyl)-imidazole;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- 30 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- S-(dimethylethyl)-s'-[2-amino-3-oxo-3(8-butyl-2-(2-methoxyphenyl))-5,6,7,8-
- 35 tetrahydroimidazo[1,2a]pyrazin-7-yl)propyl]disulfide;

This Sheet Has Been Replaced





THIS SHEET HAS BEEN REPLACED

- 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-
- 5 (2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 10 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-
- 15 tetrahydroimidazo[1,2a]]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro[1,2a]pyrazine;
2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-
- 20 ~~tetrahydro~~-7-((thiazolidin-4-yl)carbonyl)-imidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- 25 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo-[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-cyclohexyl-8-
- 30 (cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

This Sheet Has Been Replaced





THIS SHEET HAS BEEN
REPLACED

- 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-phenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- [S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl)-propyl]-S'-cyclohexyl]disulfide;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl) methyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine (cis isomer);
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(4-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(3-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

This Sheet Has Been Replaced





THIS SHEET HAS BEEN
REPLACED

- [S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-propyl]-S'-ethyl]disulfide;
- 5 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-methylthio)-ethyl-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(3-indolinylmethyl)-2-(2-methoxyphenyl)-8-5,6,7,8-
- 10 tetrahydroimidazo[1,2a] pyrazine; and
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylimidazol-3-yl) methyl-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine; or
- 8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-7-(2-
- 15 oxo-thiazolidin-4-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine; and
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine or
- 20 a pharmaceutically acceptable salt thereof.

26. A compound consisting of a first compound and a second compound of claim 1, wherein R_1 in said first compound and R_1 in said second compound, in combination, form a disulfide bond; or a pharmaceutically

25 acceptable salt thereof.

27. A compound of claim 26, said first and second compounds are identical; or a pharmaceutically acceptable salt thereof.

28. A compound of claim 27, wherein said

30 compound is of the formula:

This Sheet Has Been Replaced





THIS SHEET HAS BEEN
REPLACED

bis-1,1'-[2-amino-3-(7-butyl-2-(2-methoxyphenyl)-4,5,6,7-tetrahydro-imidazo[1,2a]piperazine-6-yl)-3-oxo]propyl disulfide; or

bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-7-(2-methylpropyl)-4,5,6,7-tetrahydro-imidazo[1,2a]piperazine-6-yl)-3-oxo]propyl disulfide;

bis-1,1'-[2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methylamino)-pentyl)-5-(2-methoxyphenyl)imidazole]disulfide;

10 bis-1,1'-7-(2-amino-1-oxo-3-thiopropyl)-(2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl) disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

15 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine, disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

25 bis-1,1'-[2-amino-3-(8-butyl-2-cyclohexyl-5,6,7,8-tetrahydro-imidazo-[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide;

bis-1,1'-[2-amino-3-(3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo[1,2a]-pyrazin-7-yl)-3-oxo-propyl]disulfide;

30 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide;

This Sheet Has Been Replaced





THIS SHEET HAS BEEN REPLACED

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine]disulfide ;

5 bis-1,1'-[2-amino-3-(2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

10 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine] disulfide;

15 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide; or

20 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine] disulfide;

bis-1,1'-[2-amino-33-(2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-3-oxopropyl]-disulfide;

25 or a pharmaceutically acceptable salt thereof.

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

30 30. A method of treating tumor or restenosis in a subject, which comprises administering to said subject a therapeutically effective amount of the compound or salt of claim 26.

This Sheet Has Been Replaced



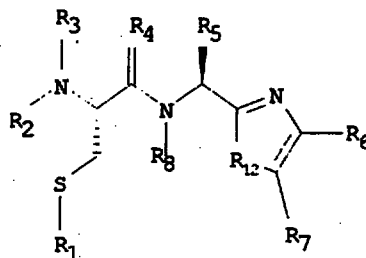


PCT/US 97/02651

IP/EE/... MAR 1998

- 66 -

3. A compound of claim 1, wherein said compound is of the formula:



or a pharmaceutically acceptable salt thereof.

5 4. A compound of claim 2, wherein each of R_8 and R_9 , independently, is H; or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4, wherein R_7 is H; or a pharmaceutically acceptable salt thereof.

10 6. A compound of claim 5, wherein R_6 is substituted or unsubstituted aryl or cycloalkyl, and R_5 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a pharmaceutically acceptable salt thereof.

15 7. A compound of claim 6, wherein each of R_1 , R_2 , and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.

AMENDED SHEET



* C L M S *

PC/US 97/02651

JP/US 11 MAR 1998

- 67 -

8. A compound of claim 7, wherein R_6 is phenyl, 1-naphthyl, or phenyl substituted with halo, lower alkyl or lower alkoxy, and R_5 is lower alkyl, cycloalkyl, cycloalkyl lower alkyl or lower alkyl substituted with -
5 O- R_{10} (where R_{10} is aryl); or a pharmaceutically acceptable salt thereof.

9. A compound of claim 4, wherein R_6 is H; or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9, wherein R_7 is
10 substituted or unsubstituted aryl or cycloalkyl, and R_5 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10, wherein each of R_1 , R_2 ,
15 and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11, wherein R_7 is phenyl, 1-naphthyl, or phenyl substituted or unsubstituted with halo, lower alkyl, or lower alkoxy, and R_5 is lower alkyl,
20 cycloalkyl, cycloalkyl lower alkyl; or lower alkyl substituted with -O- R_{10} (where R_{10} is aryl); or a pharmaceutically acceptable salt thereof.

13. A compound of claim 3, wherein R_5 is H or substituted or unsubstituted lower alkyl; or a
25 pharmaceutically acceptable salt thereof.

14. A compound of claim 13, wherein R_5 is H or -C(O)NHCHR₁₃CO₂R₁₄; or a pharmaceutically acceptable salt thereof.

AMENDED SHEET



- 69 -

21. A compound of claim 20, wherein R_6 is phenyl or phenyl substituted or unsubstituted with halo, lower alkyl, or lower alkoxy, R_8 is H or lower alkoxy; R_9 is lower alkyl, cycloalkyl, or cycloalkyl lower alkyl, and R_7 is H or $-C(O)NHCHR_{13}CO_2R_{14}$; or a pharmaceutically acceptable salt thereof.

22. A compound of claim 4, wherein R_3 is substituted or unsubstituted lower alkyl, cycloalkyl, or cycloalkyl lower alkyl, R_6 is halo or substituted or unsubstituted cycloalkyl or aryl, and R_7 is halo or substituted or unsubstituted cycloalkyl or aryl.

23. A compound of claim 22, wherein each of R_1 , R_2 , and R_3 , independently, is H; or a pharmaceutically acceptable salt thereof.

24. A compound of claim 23, wherein R_3 is lower alkyl, cycloalkyl, or cycloalkyl lower alkyl; R_6 is phenyl, naphthyl, or phenyl substituted with halo, lower alkyl, or lower alkoxy, and R_7 is halo, phenyl, 1-naphthyl, or phenyl substituted with halo, lower alkyl, or lower alkoxy.

25. A compound of claim 1, wherein said compound is of the formula:

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;



- 70 -

- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-
- 5 pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-methyl)-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-
- 10 tetrahydro-imidazo-[1,2a]-pyrazine;
- 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino-pentyl)-5-phenyl-imidazole;
- 2-(((2-amino-1-oxo-3-mercapto-propyl)-amino)-methyl)-5-phenyl-thiazole-4-carbonyl-methionine;
- 15 7-(2-amino-1-oxo-3-thio-propyl)-2-(2-methoxyphenyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-
- 20 pyrazine;
- 7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;
- 2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methyl)-amino)-pentyl-5-(2-methoxyphenyl)-imidazole;
- 25 7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-
- 30 methylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- S-(dimethylethyl)-s'-[2-amino-3-oxo-3(8-butyl-2-(2-methoxyphenyl))-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl)propyl]disulfide;



IPEA/US 11 MAR 1998

- 71 -

- 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-
- 5 (2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- 10 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-
- 15 tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro[1,2a]pyrazine;
2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-
- 20 tetrahydro-7-((thiazolidin-4-yl)carbonyl)-imidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
- 25 7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo-[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-cyclohexyl-8-
- 30 (cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

AMENDED SHEET



- 72 -

7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

5 7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

10 7-((2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-phenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

15 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

[S-[(2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-propyl]-S'-cyclohexyl]disulfide;

20 7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl) methyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine (cis isomer);

25 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(4-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

30 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(3-piperidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;



- 73 -

- [S-[(2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-propyl]-S'-ethyl]disulfide;
- 5 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-methylthio)-ethyl-5,6,7,8-tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(3-indolinylmethyl)-2-(2-methoxyphenyl)-8-5,6,7,8-
- 10 tetrahydroimidazo[1,2a] pyrazine;
- 7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylimidazol-3-yl) methyl-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
- 8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-7-(2-
- 15 oxo-thiazolidin-4-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine; or
- 7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine or
- 20 a pharmaceutically acceptable salt thereof.

26. A compound consisting of a first compound and a second compound of claim 1, wherein R₁ in said first compound and R₁ in said second compound, in combination, form a disulfide bond; or a pharmaceutically acceptable

25 salt thereof.

27. A compound of claim 26, said first and second compounds are identical; or a pharmaceutically acceptable salt thereof.

28. A compound of claim 27, wherein said

30 compound is of the formula:

AMENDED SHEET



* C L M S *

PCT/U 97/02651

IPEA/US 11 MAR 1998

- 74 -

bis-1,1'-[2-amino-3-(7-butyl-2-(2-methoxyphenyl)-4,5,6,7-tetrahydro-imidazo[1,2a]piperazine-6-yl)-3-oxo]propyl disulfide; or

5 bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-7-(2-methylpropyl)-4,5,6,7-tetrahydro-imidazo[1,2a]piperazine-6-yl)-3-oxo]propyl disulfide;

bis-1,1'-[2-(1-(N-(2-amino-1-oxo-3-thiopropyl)-N-methylamino)-pentyl)-5-(2-methoxyphenyl)imidazole] disulfide;

10 bis-1,1'-7-(2-amino-1-oxo-3-thiopropyl)-(2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl) disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

15 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

25 bis-1,1'-[2-amino-3-(8-butyl-2-cyclohexyl-5,6,7,8-tetrahydro-imidazo-[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide;

bis-1,1'-[2-amino-3-(3-bromo-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo[1,2a]-pyrazin-7-yl)-3-oxo-propyl]disulfide;

30 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide;

RECEIVED SMT



PAT/US 97/02651

IPEA/US 11 MAR 1998

- 75 -

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide;

5 bis-1,1'-[2-amino-3-(2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazin-7-yl)-3-oxo-propyl]disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

10 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide;

15 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;

20 bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine] disulfide; or

bis-1,1'-[2-amino-3-(2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydro-imidazo[1,2a]pyrazin-7-yl)-3-oxopropyl]-disulfide;

25 or a pharmaceutically acceptable salt thereof.

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

30 30. A method of treating tumor or restenosis in a subject, which comprises administering to said subject a therapeutically effective amount of the compound or salt of claim 26.

PENDING SHEET

98 04493-6
RTMP's
copy



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : C07D 487/04, 277/20, 277/28, 277/38, 263/30, 263/34, 233/54, A61K 31/495, 31/425, 31/42, 31/415	A1	(11) International Publication Number: WO 97/30053 (43) International Publication Date: 21 August 1997 (21.08.97)
(21) International Application Number: PCT/US97/02651 (22) International Filing Date: 14 February 1997 (14.02.97) (30) Priority Data: 08/602,438 16 February 1996 (16.02.96) US 08/752,546 20 November 1996 (20.11.96) US (71) Applicant: BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Milford, MA 01757 (US). (72) Inventors: GORDON, Thomas, D.; 6 Rainbow Drive, Med- way, MA 02053 (US). MORGAN, Barry, A.; 237 Prospect Street, Franklin, MA 02038 (US). (74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).	(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, 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, UZ, VN, ARIPO patent (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). Published With international search report.	
(54) Title: FARNESYL TRANSFERASE INHIBITORS (57) Abstract A family of compounds capable of inhibiting the activity of farnesyl transferase.		