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(54) **INHIBITEURS DE LA FARNESYLE TRANSFERASE**

(54) **INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE**

(57) La présente invention comporte des analogues du motif structural CA^1A^2X de la protéine Ras, laquelle est modifiée par farnésylation in vivo. Ces analogues de CA^1A^2X inhibent la farnésyle transférase ainsi que la farnésylation de certaines protéines. En outre, ces analogues de CA^1A^2X diffèrent de ceux précédemment décrits en tant qu'inhibiteurs de la farnésyle transférase, en ce qu'ils sont dépourvus d'une fraction thiol. Cette absence de fraction thiol offre des avantages uniques, en termes d'un meilleur comportement pharmacocinétique de ces analogues chez les animaux, d'une prévention de réactions chimiques dépendant des thiols, telles qu'une autoxydation rapide et une formation de disulfure avec les thiols endogènes, et d'une toxicité systématique réduite. Les composés selon l'invention comprennent également une fraction amine cyclique en position A^2 du motif structural. On décrit encore dans cette invention des compositions chimiothérapeutiques contenant ces inhibiteurs de farnésyle transférase, ainsi que des procédés de production de ceux-ci.

(57) The present invention comprises analogs of the CA^1A^2X motif of the protein Ras that is modified by farnesylation in vivo. These CA^1A^2X analogs inhibit the farnesyl-protein transferase and the farnesylation of certain proteins. Furthermore, these CA^1A^2X analogs differ from those previously described as inhibitors of farnesyl-protein transferase in that they do not have a thiol moiety. The lack of the thiol offers unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. The compounds of the instant invention also incorporate a cyclic amine moiety in the A^2 position of the motif. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.



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(57) Abstract			
The present invention comprises analogs of the CA¹A²X motif of the protein Ras that is modified by farnesylation <i>in vivo</i>. These CA¹A²X analogs inhibit the farnesyl-protein transferase and the farnesylation of certain proteins. Furthermore, these CA¹A²X analogs differ from those previously described as inhibitors of farnesyl-protein transferase in that they do not have a thiol moiety. The lack of the thiol offers unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. The compounds of the instant invention also incorporate a cyclic amine moiety in the A² position of the motif. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.			

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

RELATED APPLICATION

5 The present patent application is a continuation-in-part application of copending application Serial No. 08/412,828, filed March 29, 1995.

BACKGROUND OF THE INVENTION

10 The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon
15 growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen,
20 *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory
25 signal.

 Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus
30 contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which

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catalyze the alkylation of the cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to
5 undergo post-translational farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also
10 suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been
15 demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-
20 dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has
25 been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl
30 pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis

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by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational

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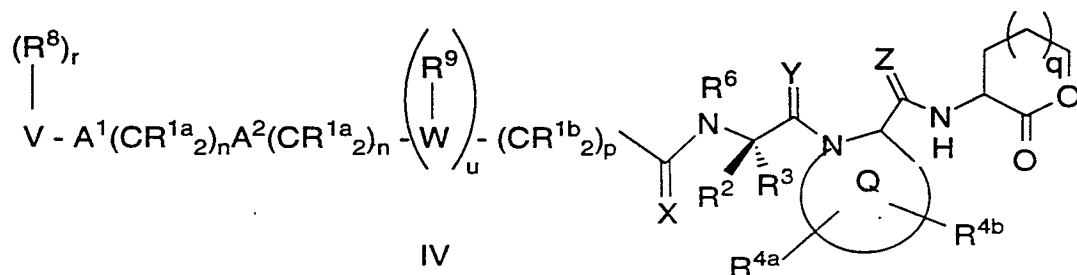
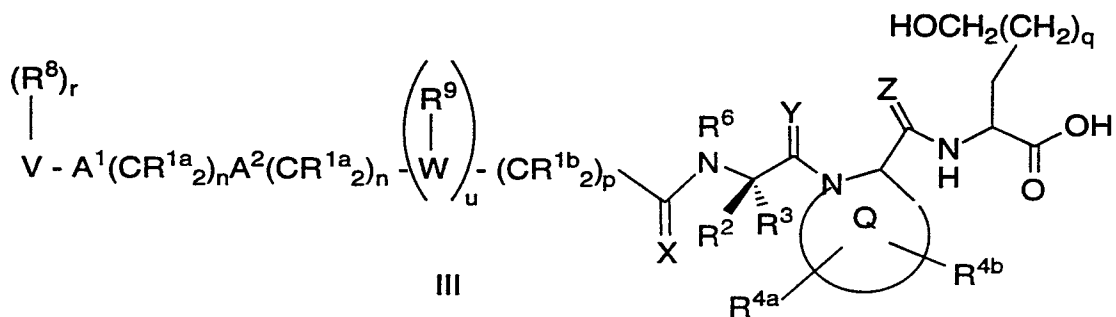
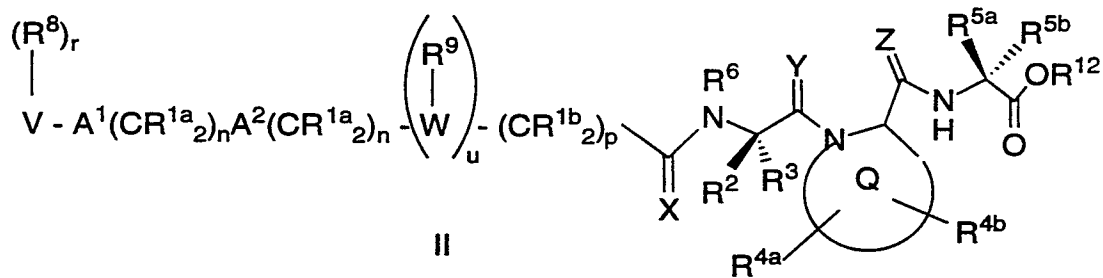
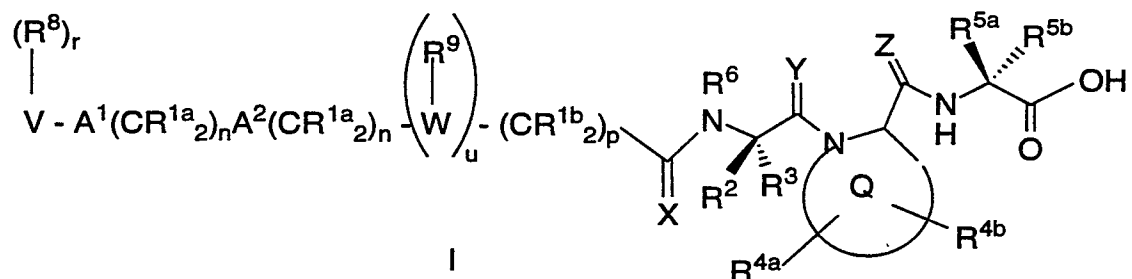
farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

5 SUMMARY OF THE INVENTION

The present invention comprises analogs of the CA¹A²X motif of the protein Ras that is modified by farnesylation *in vivo*. These CA¹A²X analogs inhibit the farnesylprotein transferase. Furthermore, these CA¹A²X analogs differ from those previously described as
10 inhibitors of farnesyl-protein transferase in that they do not have a thiol moiety. The lack of the thiol offers unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. The
15 compounds of the instant invention also incorporate a cyclic amine moiety in the A² position of the motif. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

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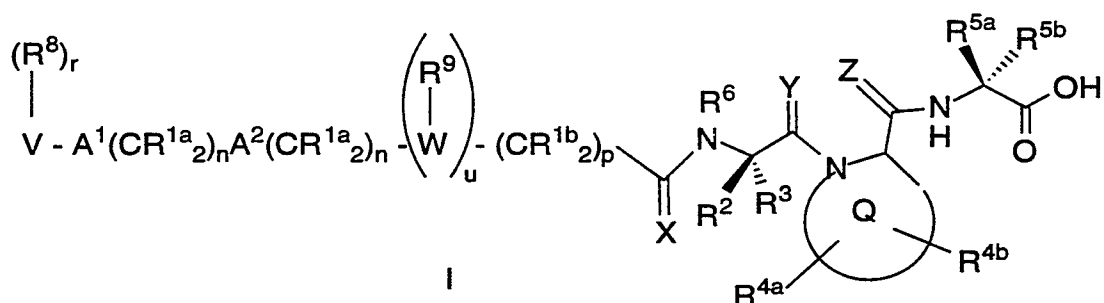
The compounds of this invention are illustrated by the formulae:



DETAILED DESCRIPTION OF THE INVENTION

- 5 The compounds of this invention inhibit the farnesyl-protein transferase. In a first embodiment of this invention, the farnesyl-protein transferase inhibitors are illustrated by the formula I:

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wherein:

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- 5 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;
- 15 R² and R³ are independently selected from:
 - a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 20 i) methionine sulfoxide, or
 - ii) methionine sulfone, and
 - c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,

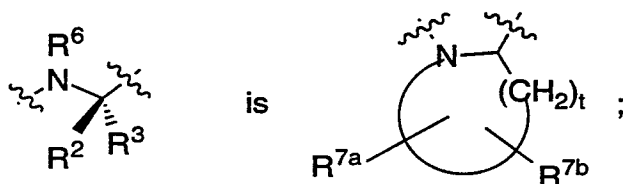
25 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

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- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



10

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

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wherein the substituent is selected from F, Cl, Br, (R¹⁰)₂NC(O)-, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,

5

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

- 10 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m-, -NC(O)-, and -N(COR¹⁰)-;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

15

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 25

R⁹ is selected from:

- a) hydrogen,
- 30 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

10

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

15

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

20

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

25

- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

30

X, Y and Z are independently H₂ or O;

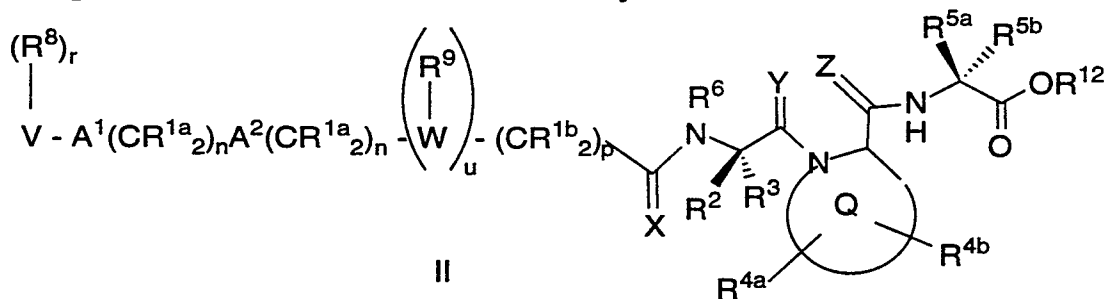
m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

- 10 -

- p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 4 or 5;
 t is 3, 4 or 5; and
 5 u is 0 or 1;
 or the pharmaceutically acceptable salts thereof.

In a second embodiment of this invention the prodrugs of compounds of formula I are illustrated by the formula II:



wherein:

R^{1a} and R^{1b} are independently selected from:

- 15 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-,
 20 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-
 NR¹⁰-;

R² and R³ are independently selected from:

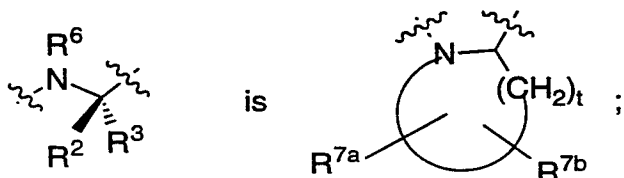
- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone, and

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- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 5 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
 20 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-
 C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 25 or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

30 R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid.

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- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 5 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, (R¹⁰)₂NC(O)-, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or
- 15 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;
- 20 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;
- R⁸ is independently selected from:
- a) hydrogen,
 - b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 25
- 30

R⁹ is selected from:

- 13 -

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

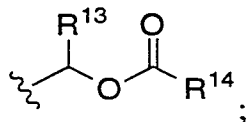
R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is

- a) substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_5-C_8 cycloalkyl, or substituted or unsubstituted cyclic amine, wherein the substituted alkyl, cycloalkyl or cyclic amine is substituted with 1 or 2 substituents independently selected from:

- 1) C_1-C_6 alkyl,
- 2) aryl,
- 3) heterocycle,
- 4) $-N(R^{11})_2$,
- 5) $-OR^{10}$, or

b)



R^{13} is independently selected from hydrogen and C_1-C_6 alkyl;

R^{14} is independently selected from C_1-C_6 alkyl;

- 14 -

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
-S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

- 5 Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

- 10 a) hydrogen,
b) heterocycle,
c) aryl,
d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
15 e) C₂-C₂₀ alkenyl,
provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

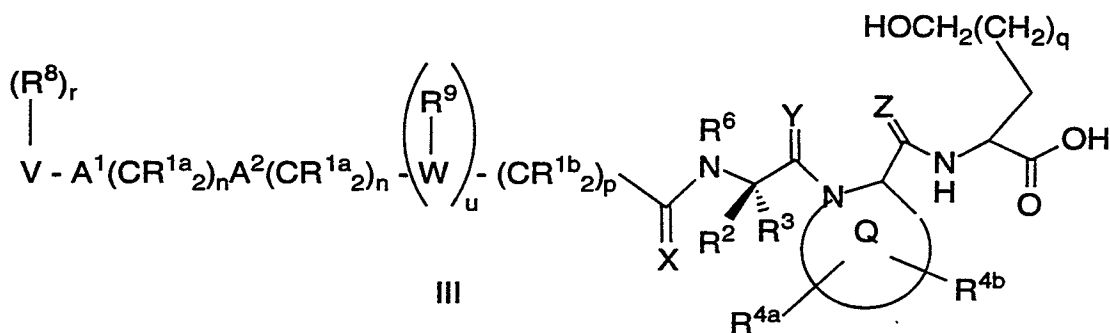
20

X, Y and Z are independently H₂ or O;

- m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
25 p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;
30 or the pharmaceutically acceptable salts thereof.

In a third embodiment of this invention, the inhibitors of farnesyl transferase are illustrated by the formula III:

- 15 -



wherein:

R^{1a} and R^{1b} are independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-
C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-
NR¹⁰-;

R² and R³ are independently selected from:

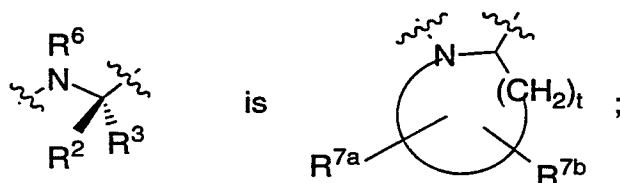
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring
amino acid which is:
 - 20 i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl,
C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 - 25 • wherein the substituent is selected from F, Cl, Br,
N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
-N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

- 16 -

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



10

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

15

20

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

25

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

30

- 17 -

- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,

- 18 -

- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,
- provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if
- 5 A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

X, Y and Z are independently H₂ or O;

10

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2;

15 r is 0 to 5, provided that r is 0 when V is hydrogen;

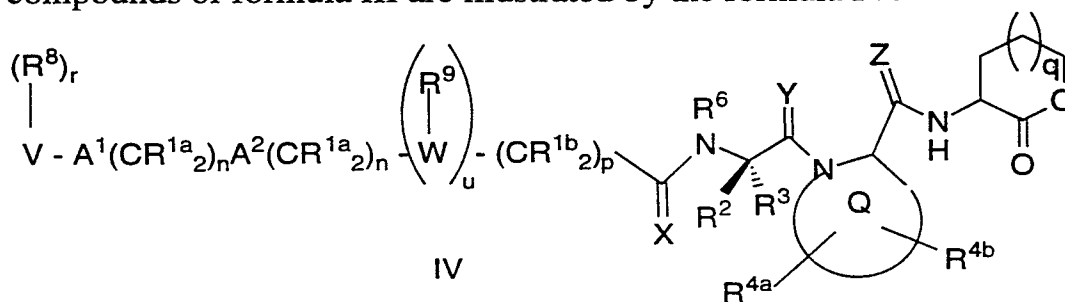
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

20 or the pharmaceutically acceptable salts thereof.

In a fourth embodiment of this invention the prodrugs of compounds of formula III are illustrated by the formula IV:



25 wherein:

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

- 19 -

- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 5 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

10

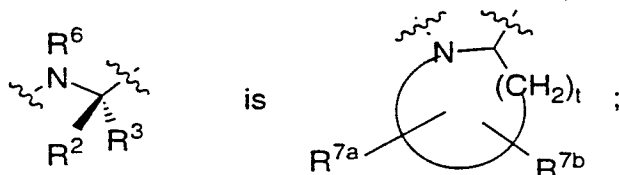
R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 15 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclic group,
- 20 wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
- d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or
- 25

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that

30



- 20 -

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
 5 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-
 10 C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclic and
 C₃-C₁₀ cycloalkyl;

15 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl,
 20 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F,
 25 Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-
 C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 30 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-
 (NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and

- 21 -

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

10

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

- 15 Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

20

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,

25

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

30

X, Y and Z are independently H₂ or O;

m is 0, 1 or 2;

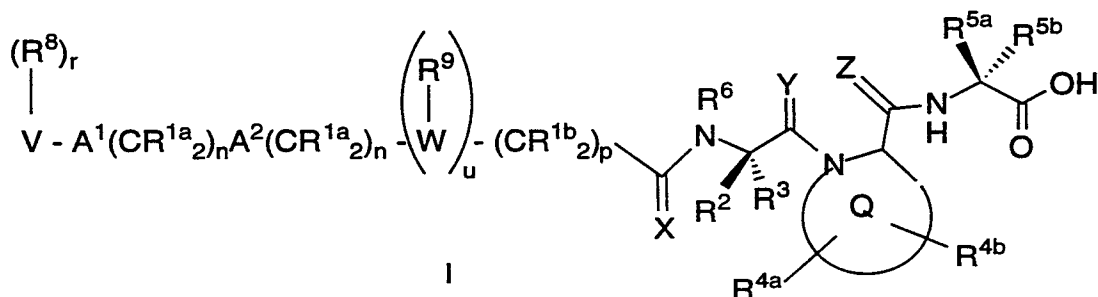
n is 0, 1, 2, 3 or 4;

- 22 -

- p is 0, 1, 2, 3 or 4;
 q is 0, 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 4 or 5;
 5 t is 3, 4 or 5; and
 u is 0 or 1;

or the pharmaceutically acceptable salts thereof.

- 10 In a more preferred embodiment of this invention, the Ras farnesyl transferase inhibitors are illustrated by the Formula I:



wherein:

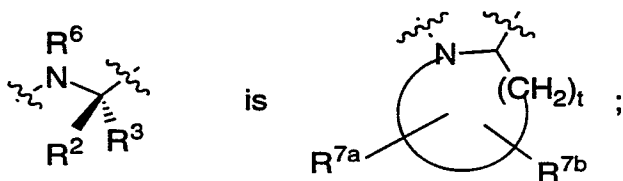
- 15 R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;
- R^{1b} is independently selected from:
- 20 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;
- R² and R³ are independently selected from:
- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- i) methionine sulfoxide, or
 ii) methionine sulfone.

- 23 -

- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a} and R^{7a} are independently selected from:

- a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-
 C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclic and C₃-
 C₁₀ cycloalkyl;

R^{4b} and R^{7b} are hydrogen;

- 24 -

R5a is selected from:

- a) a side chain of a naturally occurring amino acid, wherein the amino acid is selected from methionine and glutamine,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R5b is selected from:

- a) hydrogen, and
- b) C₁-C₃ alkyl;

R6 is independently selected from hydrogen or C₁-C₆ alkyl;

R8 is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

- 25 -

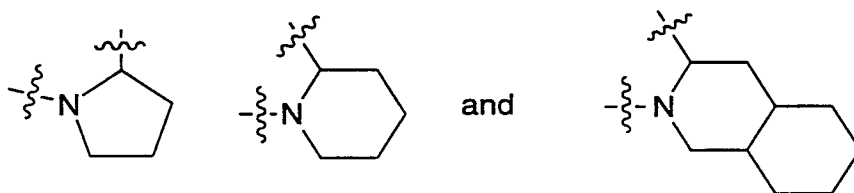
R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

Q is selected from:



A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
- c) aryl,

- 26 -

- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 e) C₂-C₂₀ alkenyl, and
 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if
 5 A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

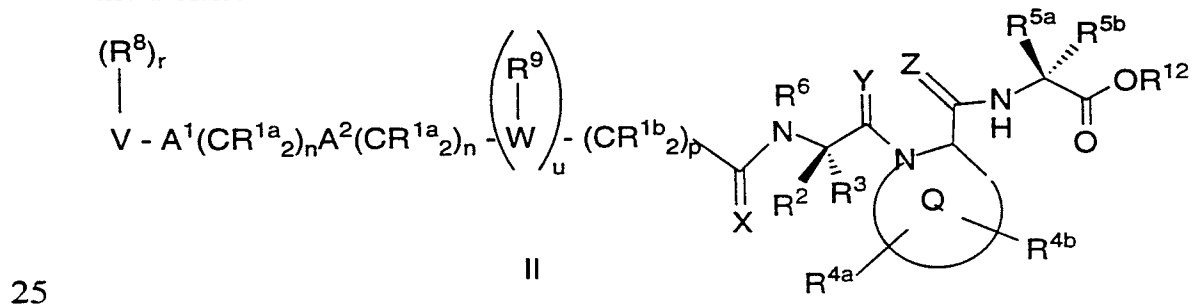
10

X, Y and Z are independently H₂ or O;

- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 15 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 t is 3, 4 or 5; and
 u is 0 or 1;

- 20 or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention, the prodrugs of the preferred compounds of Formula I are illustrated by the Formula II:



wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

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R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or alkenyl,
- 5 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

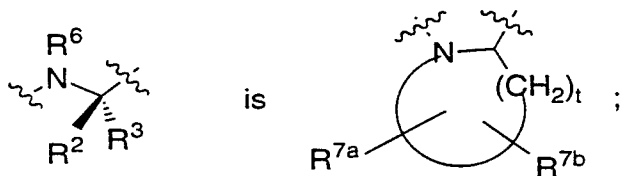
R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- 10 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 15 c) substituted or unsubstituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
- 20 d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

25

R^2 or R^3 are combined with R^6 to form a ring such that



30 R^{4a} and R^{7a} are independently selected from:

- a) hydrogen,

- 28 -

- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 5 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-
10 C₁₀ cycloalkyl;

R^{4b} and R^{7b} are hydrogen;

R^{5a} is selected from:

- 15 a) a side chain of a naturally occurring amino acid, wherein the amino acid is selected from methionine and glutamine,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 20 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
wherein the substituent is selected from F, Cl, Br,
NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
25 (R¹⁰)₂NC(O)-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-
30 C₁₀ cycloalkyl;

R^{5b} is selected from:

- a) hydrogen, and
- b) C₁-C₃ alkyl;

- 29 -

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- 5 a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R⁹ is selected from:

- 15 a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

- 25 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

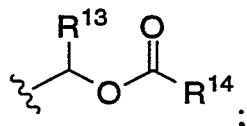
R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

- 30 R¹² is
 - a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:
 - 1) aryl,

- 30 -

- 2) heterocycle,
- 3) $-N(R^{11})_2$,
- 4) $-OR^{10}$, or

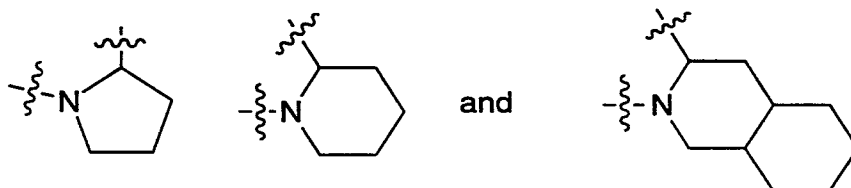
b)



R^{13} is independently selected from hydrogen and C_1 - C_6 alkyl;

R^{14} is independently selected from C_1 - C_6 alkyl;

Q is selected from:



A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{10}-$, O, $-\text{N}(\text{R}^{10})-$, or $\text{S}(\text{O})_m$;

V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
- c) aryl,
- d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C_2 - C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $\text{S}(\text{O})_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $\text{S}(\text{O})_m$;

- 31 -

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

5

X, Y and Z are independently H₂ or O;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

10 p is 0, 1, 2, 3 or 4;

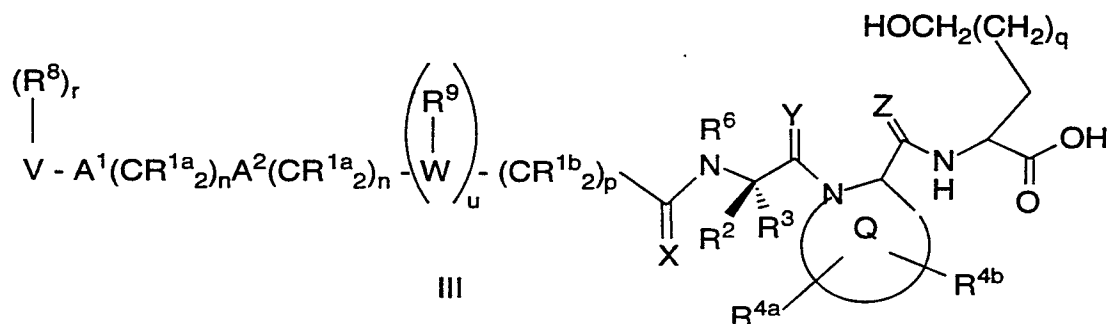
r is 0 to 5, provided that r is 0 when V is hydrogen;

t is 3, 4 or 5; and

u is 0 or 1;

15 or the pharmaceutically acceptable salts thereof.

In a third more preferred embodiment of this invention, the inhibitors of farnesyl transferase are illustrated by the formula III:



wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

25

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or alkenyl.

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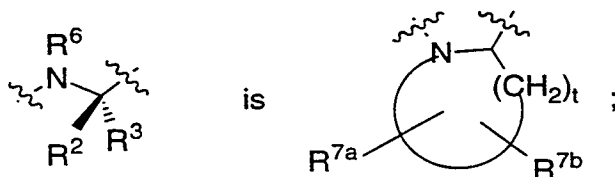
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

R² and R³ are independently selected from:

- 5 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 10 c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 15 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

- 20 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



25

R^{4a} and R^{7a} are independently selected from:

- a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 30 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

- 33 -

- c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 5 d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3 - C_{10} cycloalkyl;

R^{4b} and R^{7b} are hydrogen;

10

R^6 is independently selected from hydrogen or C_1 - C_6 alkyl;

R^8 is independently selected from:

- a) hydrogen,
- 15 b) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 20 c) C_1 - C_6 alkyl substituted by C_1 - C_6 perfluoroalkyl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

R^9 is selected from:

- a) hydrogen,
- 25 b) C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 30 c) C_1 - C_6 alkyl unsubstituted or substituted by C_1 - C_6 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

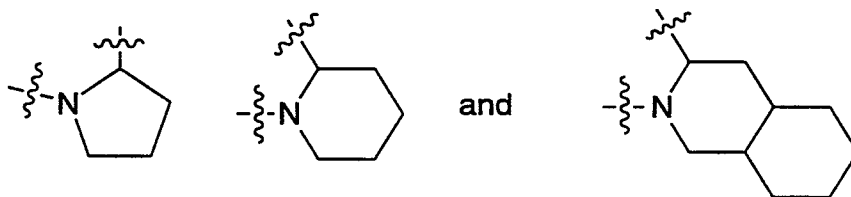
R^{10} is independently selected from hydrogen, C_1 - C_6 alkyl, benzyl and

- 34 -

aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

5 Q is selected from:



10 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

- 15 a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,
thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl,
isoquinolinyl, and thienyl,
c) aryl,
d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced
20 with a heteroatom selected from O, S, and N, and
e) C₂-C₂₀ alkenyl, and

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if
A¹ is a bond, n is 0 and A² is S(O)_m;

25 W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,
thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or
isoquinolinyl;

X, Y and Z are independently H₂ or O;

30

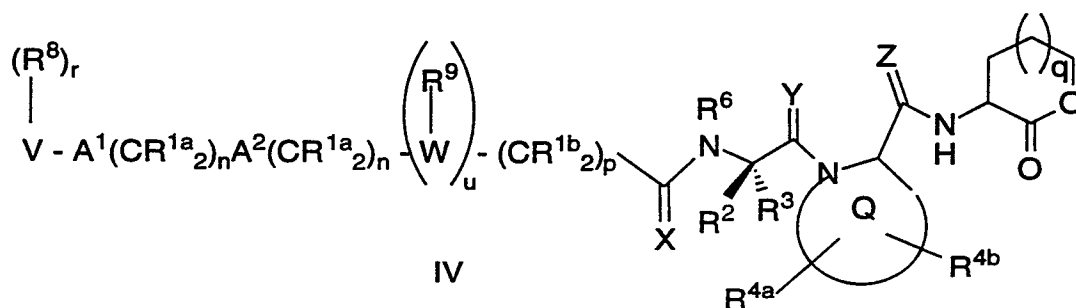
m is 0, 1 or 2;

- 35 -

- n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 q is 0, 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 5 t is 3, 4 or 5; and
 u is 0 or 1;

or the pharmaceutically acceptable salts thereof.

- 10 In a fourth more preferred embodiment of this invention, the prodrugs of the preferred compounds of Formula III are illustrated by the Formula IV:



- 15 wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

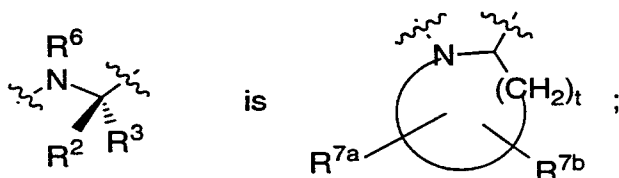
- 20 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;
- 25 R² and R³ are independently selected from:
 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:

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- i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
 C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 5 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 10 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

15 R² or R³ are combined with R⁶ to form a ring such that



R^{4a} and R^{7a} are independently selected from:

- 20 a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-,
 25 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-
 C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 30 substituted group selected from aryl, heterocyclic and C₃-
 C₁₀ cycloalkyl;

- 37 -

R^{4b} and R^{7b} are hydrogen;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

5 R⁸ is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

15 R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

25

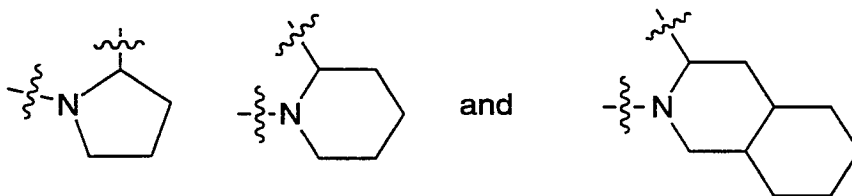
R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

30

Q is selected from:

- 38 -



5 A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{10}-$, O, $-\text{N}(\text{R}^{10})-$, or $\text{S}(\text{O})_m$;

V is selected from:

- 10 a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
 c) aryl,
 d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 15 e) C_2 - C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $\text{S}(\text{O})_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $\text{S}(\text{O})_m$;

20 W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X, Y and Z are independently H_2 or O;

25 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 q is 0, 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 30 t is 3, 4 or 5; and
 u is 0 or 1;

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or the pharmaceutically acceptable salts thereof.

The preferred compounds of this invention are as follows:

5

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-
prolyl-methionine methyl ester

10

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-
prolyl-methionine

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

15

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone isopropyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine sulfoxide

20

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine sulfoxide isopropyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone

25

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

30

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-
prolyl-methionine methyl ester

35

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-
prolyl-methionine

- 40 -

N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

5 N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

10 N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

15

N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

20

N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester

N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine

25

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

30

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

35

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

- 41 -

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

- 5 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

10

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

- 15 N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

- 20 N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

25

N-[1-[1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

- 30 N-[1-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(1-(1-Farnesyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine

- 42 -

N-[1-(1-(1-Geranyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-methionine

5 N-[1-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-methionine

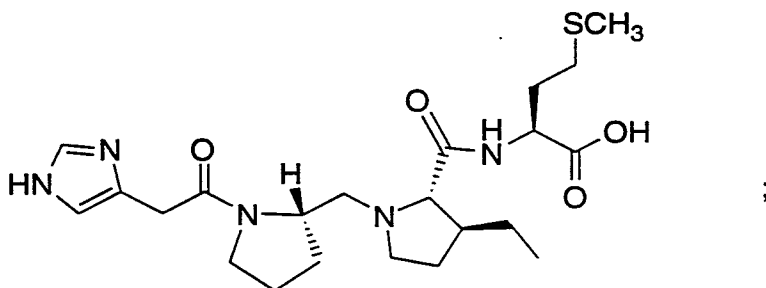
N-[1-[1-(2-Naphthylmethyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-methionine and

10 N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-(β -acetyl-amino)alanine

or the pharmaceutically acceptable salts thereof.

15 Specific examples of compounds of the invention are:

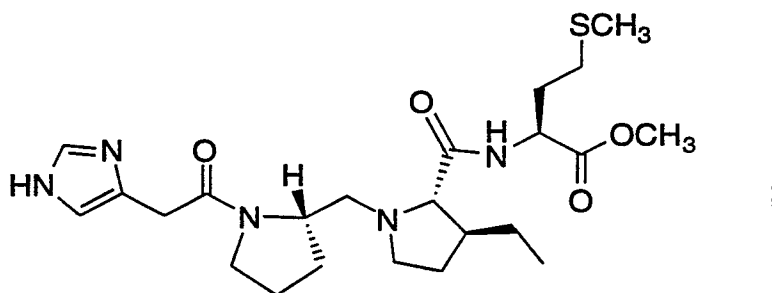
N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-methionine



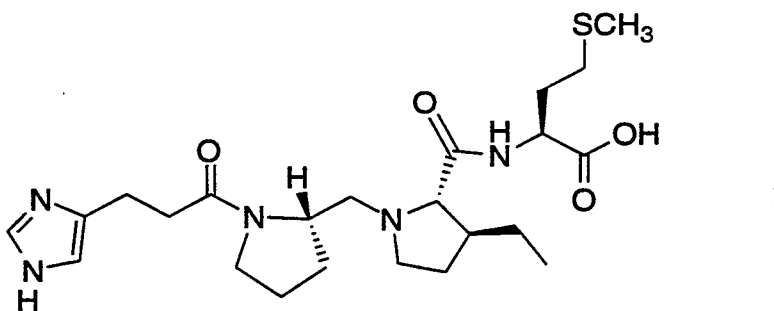
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N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-propyl-methionine methyl ester

- 43 -

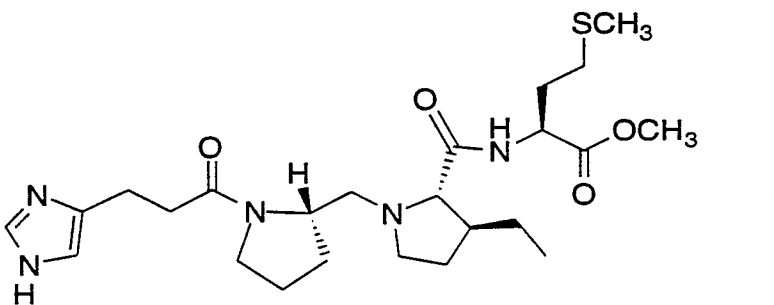


N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine



5

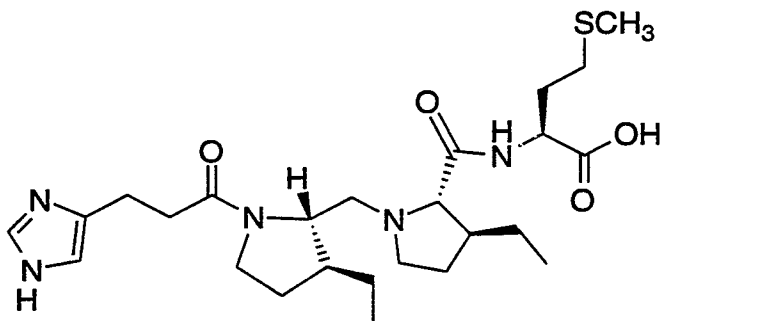
N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester



10

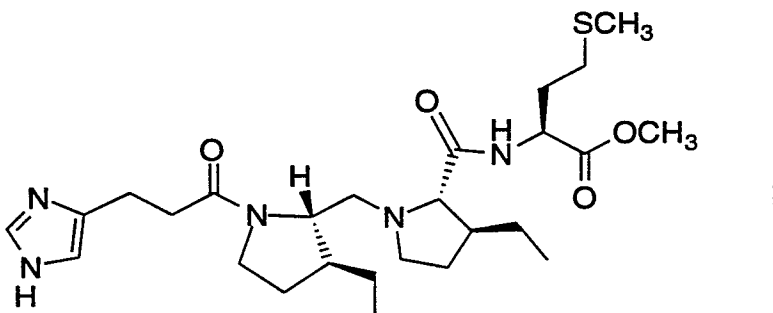
N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

- 44 -

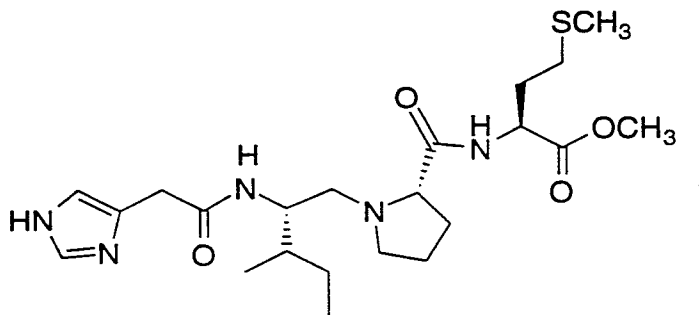


N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

5



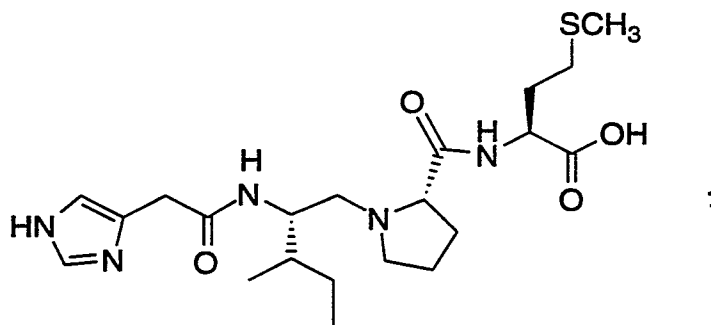
N-[2(S)-(1H-Imidazol-4-yl)acetyl-amino]-3(S)-methylpentyl]-prolyl-methionine methyl ester



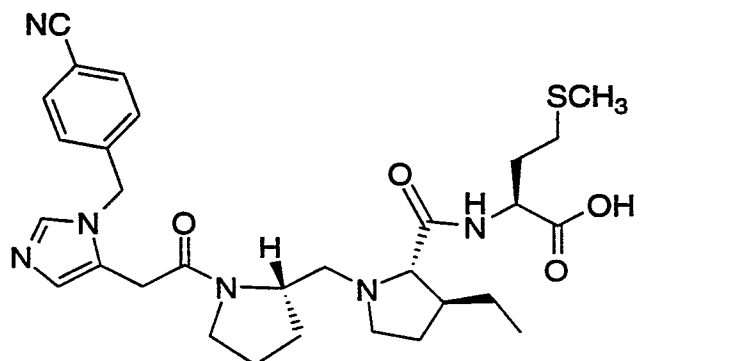
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N-[2(S)-(1H-Imidazol-4-yl)acetyl-amino]-3(S)-methylpentyl]-prolyl-methionine

- 45 -

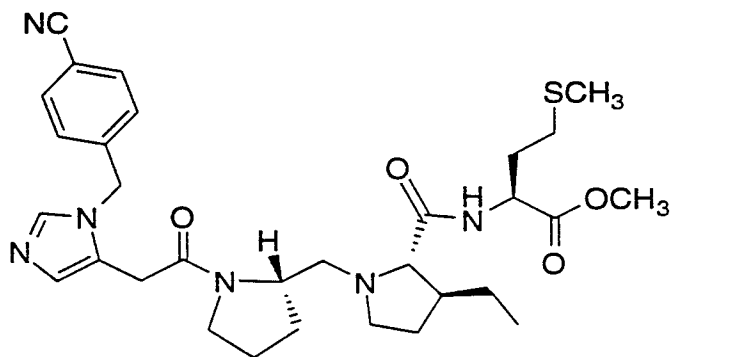


N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine



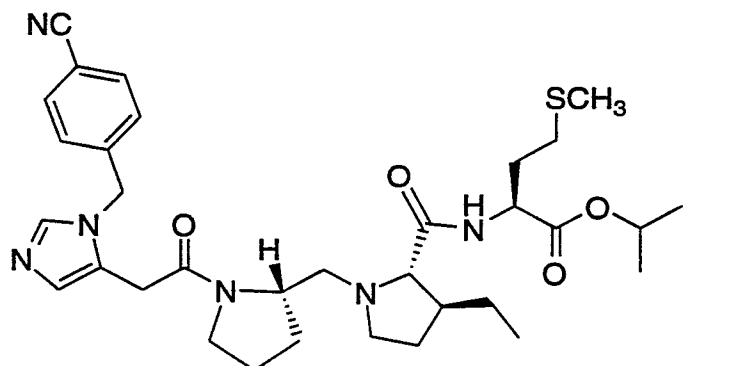
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N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester



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N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester



5 or the pharmaceutically acceptable salts thereof.

In the present invention, the amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

10

15

20

25

Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Asparagine or		
Aspartic acid	Asx	B
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glutamine or		
Glutamic acid	Glx	Z
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L

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	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
5	Serine	Ser	S
	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V

10

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention.

15

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

20

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

25

"Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

30

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

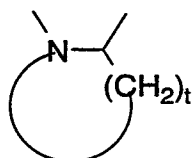
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The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists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

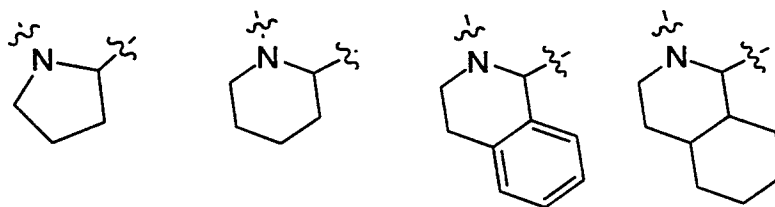
As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆ alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH- and C₁-C₂₀ alkyl.

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The following structure:



represents a cyclic amine moiety having 5 or 6 members in the ring, such
 5 a cyclic amine which may be optionally fused to a phenyl or cyclohexyl
 ring. Examples of such a cyclic amine moiety include, but are not limited
 to, the following specific structures:



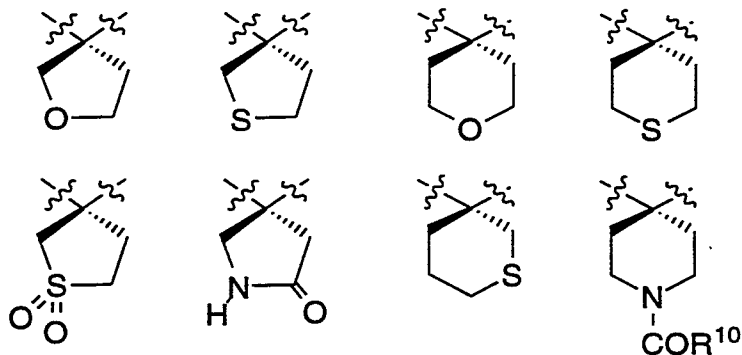
10 It is also understood that substitution on the cyclic amine moiety by R^{8a}
 and R^{8b} may be on different carbon atoms or on the same carbon atom.

When R³ and R⁴ are combined to form - (CH₂)_s -, cyclic
 moieties are formed. Examples of such cyclic moieties include, but are
 15 not limited to:

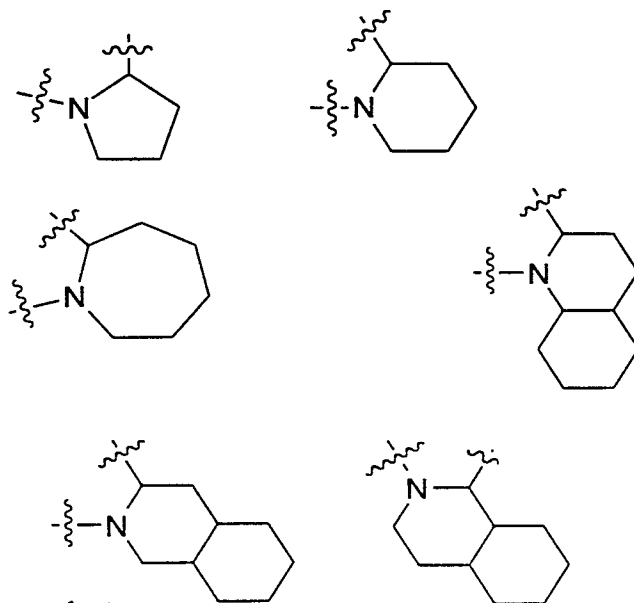


When R^{5a} and R^{5b} are combined to form - (CH₂)_s -, cyclic
 moieties as described hereinabove for R³ and R⁴ are formed. In addition,
 20 such cyclic moieties may optionally include a heteroatom(s). Examples
 of such heteroatom-containing cyclic moieties include, but are not limited
 to:

- 50 -



- As used herein, the phrase "nitrogen containing C4-C9 mono
 5 or bicyclic ring system wherein the non-nitrogen containing ring may be
 a C5-C7 saturated ring" which defines moiety "Q" of the instant invention
 includes but is not limited to the following ring systems:



10

The pharmaceutically acceptable salts of the compounds of
 this invention include the conventional non-toxic salts of the compounds
 of this invention as formed, e.g., from non-toxic inorganic or organic

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acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{10} , Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents $-NHH$, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^8)_2$, $R^8C(O)NR^8-$ or C_1-C_6 alkyl unsubstituted or substituted by $-N(R^8)_2$, R^8O- or $R^8C(O)NR^8-$.

Preferably, R^2 is the sidechain of glycine (hydrogen).

Preferably, R^3 is selected from:

- a) a side chain of a naturally occurring amino acid,
- b) substituted or unsubstituted C_1-C_{20} alkyl,
 - wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
- c) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^3 is combined with R^6 to form pyrrolidinyl ring.

Preferably, R^{4a} , R^{4b} , R^{7a} and R^{7b} are independently selected from: hydrogen, C_1-C_6 alkyl, aryl and benzyl.

Preferably, R^{5a} and R^{5b} are independently selected from:

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a side chain of a naturally occurring amino acid, methionine sulfoxide, methionine sulfone and unsubstituted or substituted C₁-C₆ alkyl.

Preferably, R⁶ is: hydrogen or is combined with R³ to form pyrrolidiny ring.

5 Preferably, R⁸ is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰- and C₁-C₆ alkyl.

Preferably, R⁹ is hydrogen.

Preferably, R¹⁰ is selected from H, C₁-C₆ alkyl and benzyl.

10 Preferably, R¹² is selected from C₁-C₆ alkyl and benzyl.

Preferably, A¹ and A² are independently selected from: a bond, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)- and -N(R¹⁰)S(O)₂-.

Preferably, Q is a pyrrolidiny ring.

15 Preferably, V is selected from hydrogen, heterocycle and aryl.

Preferably, n, p and r are independently 0, 1, or 2.

Preferably t is 3.

20 The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety conventional chemical methods. Generally, the salts are prepared by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

25 The compounds of the invention can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "The Peptides", Vol. I, Academic Press 1965, or Bodanszky *et al.*, "Peptide Synthesis", Interscience Publishers, 1966, or McOmie (ed.) "Protective Groups in Organic Chemistry", Plenum Press, 1973, or Barany *et al.*, "The Peptides: Analysis, Synthesis, Biology" 2, Chapter 1, Academic Press, 1980, or Stewart *et al.*, "Solid Phase Peptide

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Synthesis", Second Edition, Pierce Chemical Company, 1984. The teachings of these works are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

5	Ac ₂ O	Acetic anhydride;
	Boc	t-Butoxycarbonyl;
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
	DMAP	4-Dimethylaminopyridine;
10	DME	1,2-Dimethoxyethane;
	DMF	Dimethylformamide;
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
	HOBT	1-Hydroxybenzotriazole hydrate;
15	Et ₃ N	Triethylamine;
	EtOAc	Ethyl acetate;
	FAB	Fast atom bombardment;
	HOBT	3-Hydroxy-1,2,2-benzotriazin-4(3H)-one;
	HPLC	High-performance liquid chromatography;
20	MCPBA	m-Chloroperoxybenzoic acid;
	MsCl	Methanesulfonyl chloride;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
	Py	Pyridine;
	TFA	Trifluoroacetic acid;
25	THF	Tetrahydrofuran.

Compounds of this invention are prepared by employing the reactions shown in the following Reaction Schemes A-J, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key bond-forming and peptide modifying reactions are:

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Reaction A Amide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

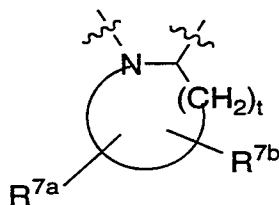
5 Reaction B Preparation of a reduced peptide subunit by reductive alkylation of an amine by an aldehyde using sodium cyanoborohydride or other reducing agents.

Reaction C Deprotection of the reduced peptide subunit

10 Reaction D Peptide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

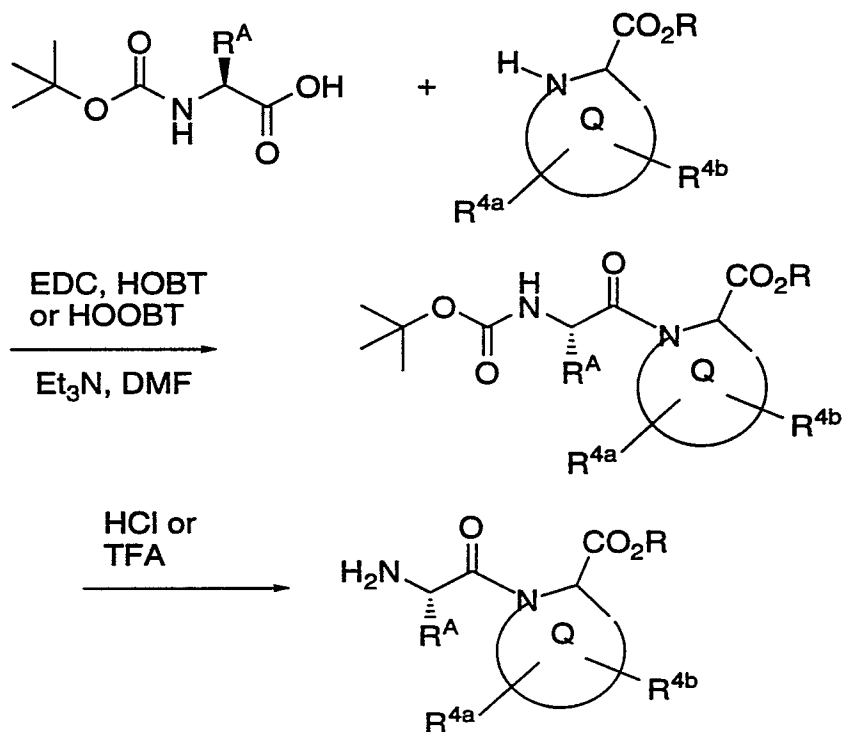
15 Reaction E Preparation of a reduced subunit by borane reduction of the amide moiety.

20 Reaction Schemes A-E illustrate bond-forming and peptide modifying reactions incorporating acyclic peptide units. It is well understood that such reactions are equally useful when the - NHC(R^A) - moiety of the reagents and compounds illustrated is replaced with the following moiety:



25 These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the reactions described in the Reaction Schemes.

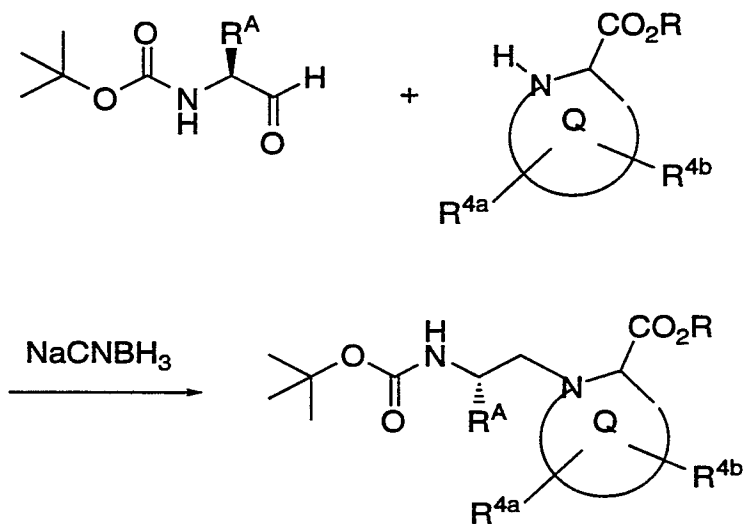
- 55 -

REACTION SCHEME AReaction A. Coupling of residues to form an amide bond

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REACTION SCHEME B

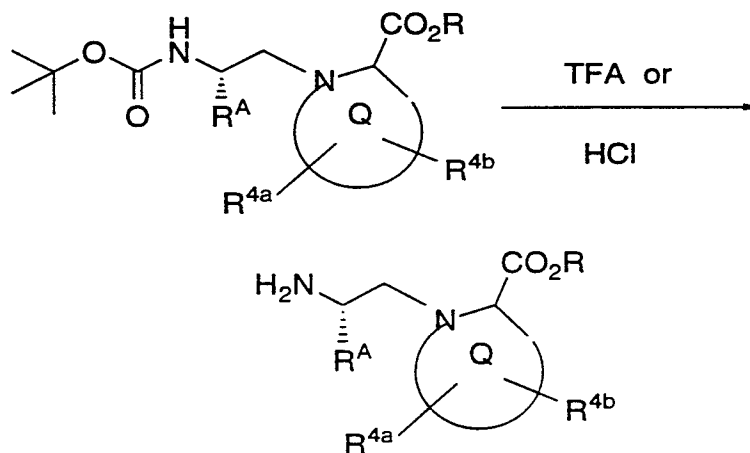
Reaction B. Preparation of reduced peptide subunits by reductive alkylation



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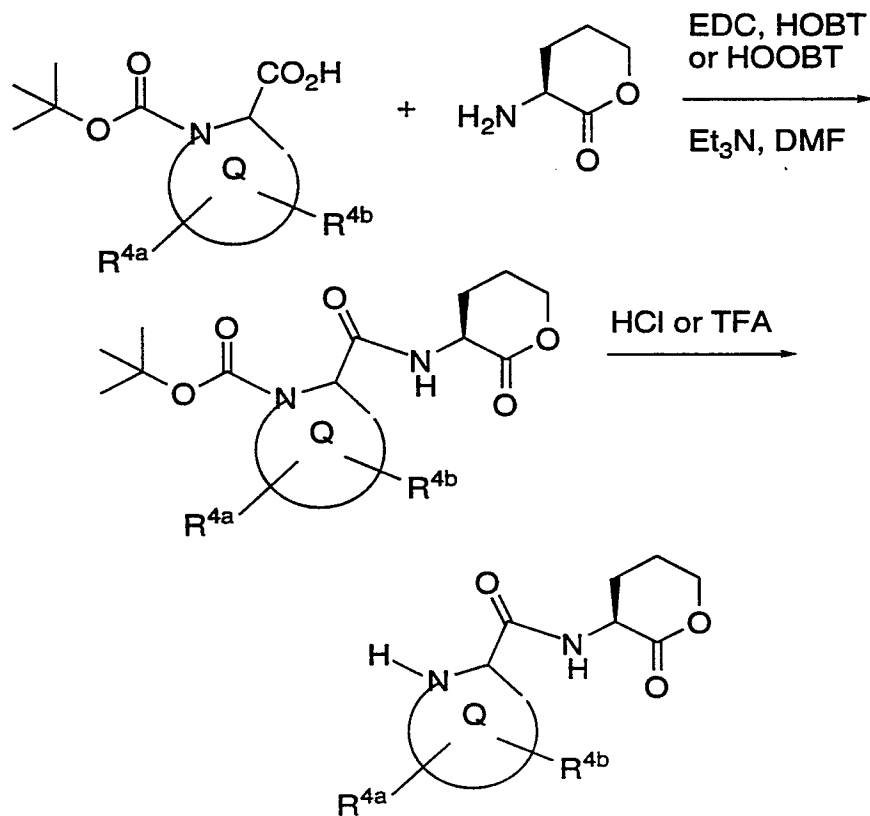
REACTION SCHEME C

Reaction C. Deprotection of reduced peptide subunits

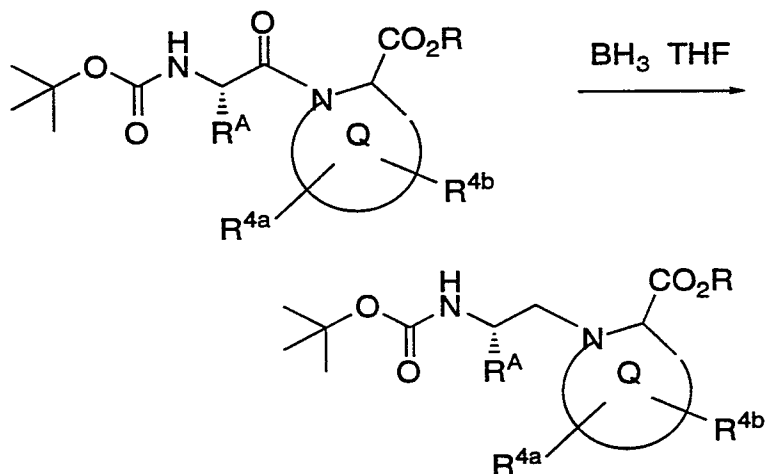


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REACTION SCHEME DReaction D. Coupling of residues to form an amide bond

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REACTION SCHEME EReaction E. Preparation of reduced dipeptides from peptides

5

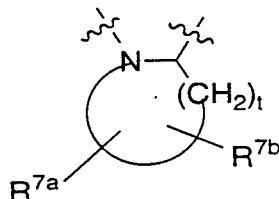
where R^A is R^2 , R^3 , R^{5a} or R^{5b} as previously defined; R^{4a} and R^{4b} are as previously defined; and R is an appropriate protecting group for the carboxylic acid.

10

Reaction Schemes F - M illustrate reactions wherein the non-sulfhydryl-containing moiety at the N-terminus of the compounds of the instant invention is attached to an acyclic peptide unit which may be further elaborated to provide the instant compounds. It is well understood that such reactions are equally useful when the $-NHC(R^A)-$ moiety of

15

the reagents and compounds illustrated is replaced with the following moiety:



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These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the reactions described in Reaction Schemes A - E.

5 The intermediates whose synthesis are illustrated in Reaction Schemes A and C can be reductively alkylated with a variety of aldehydes, such as **I**, as shown in Reaction Scheme F. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75, 10 from the appropriate amino acid (Reaction Scheme F). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product **II** can be deprotected to give the final 15 compounds **III** with trifluoroacetic acid in methylene chloride. The final product **III** is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **III** can further be selectively protected to obtain **IV**, which can subsequently be reductively alkylated with a second aldehyde to obtain **V**. Removal of 20 the protecting group, and conversion to cyclized products such as the dihydroimidazole **VII** can be accomplished by literature procedures.

Alternatively, the protected dipeptidyl analog intermediate can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products 25 such as **VIII** (Reaction Scheme G). The trityl protecting group can be removed from **VIII** to give **IX**, or alternatively, **VIII** can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole **X**. Alternatively, the dipeptidyl analog intermediate can be acylated or sulfonylated by standard techniques.

30 The imidazole acetic acid **XI** can be converted to the acetate **XIII** by standard procedures, and **XIII** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **XIV**. Hydrolysis and reaction with the protected dipeptidyl analog intermediate in the

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presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as **XV**.

If the protected dipeptidyl analog intermediate is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as **XVI** in Reaction Scheme I, the protecting groups can be subsequently removed to unmask the hydroxyl group (Reaction Schemes I, J). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as **XX**. In addition, the fully deprotected amino alcohol **XXI** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXII** (Reaction Scheme K), or tertiary amines.

The Boc protected amino alcohol **XVIII** can also be utilized to synthesize 2-aziridinylmethylpiperazines such as **XXIII** (Reaction Scheme L). Treating **XVIII** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXIII**. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXIV**.

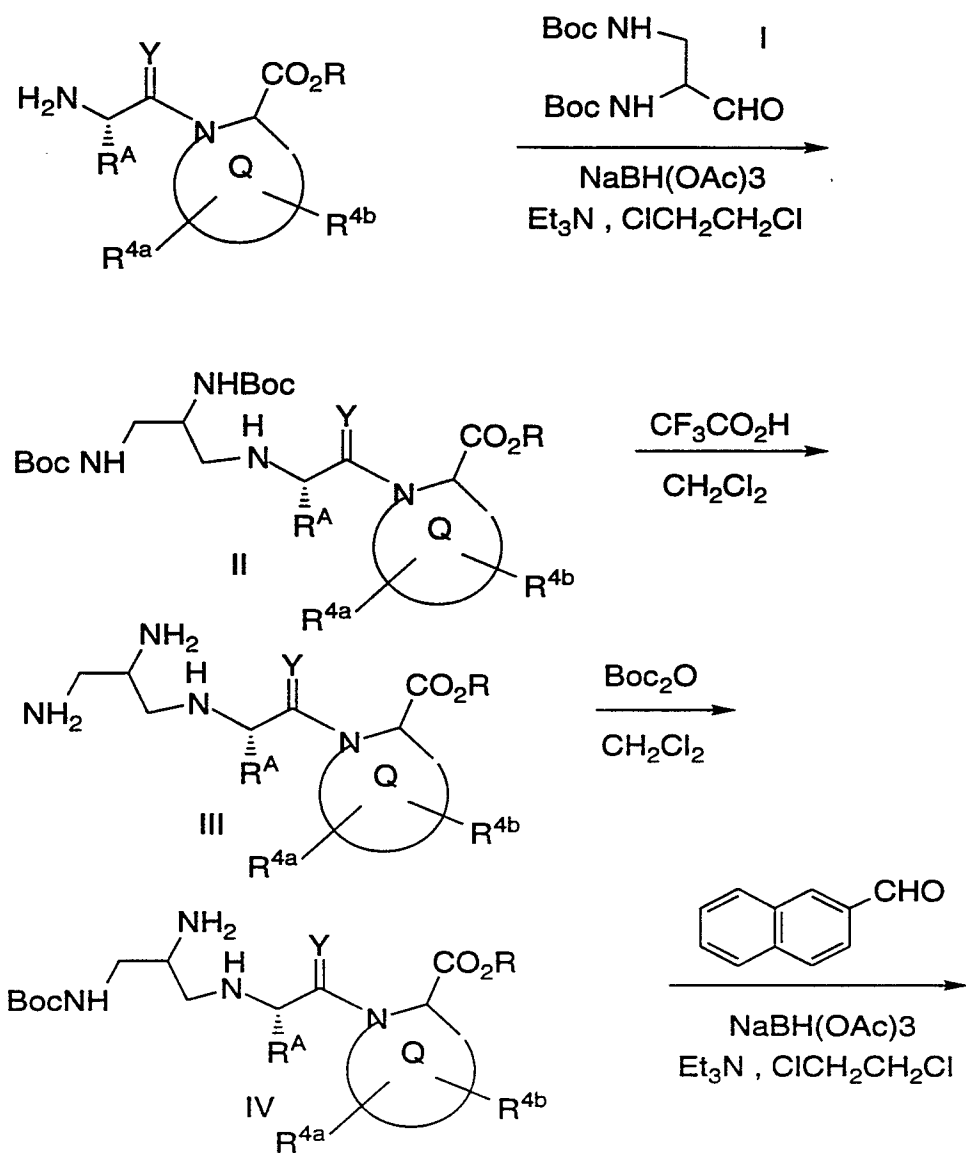
In addition, the protected dipeptidyl analog intermediate can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XXX**, as shown in Reaction Scheme M. When R' is an aryl group, **XXX** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XXXI**. Alternatively, the amine protecting group in **XXX** can be removed, and O-alkylated phenolic amines such as **XXXII** produced.

Similar procedures as are illustrated in Reaction Schemes F-M may be employed using other peptidyl analog intermediates such as those whose synthesis is illustrated in Reaction Schemes B - E.

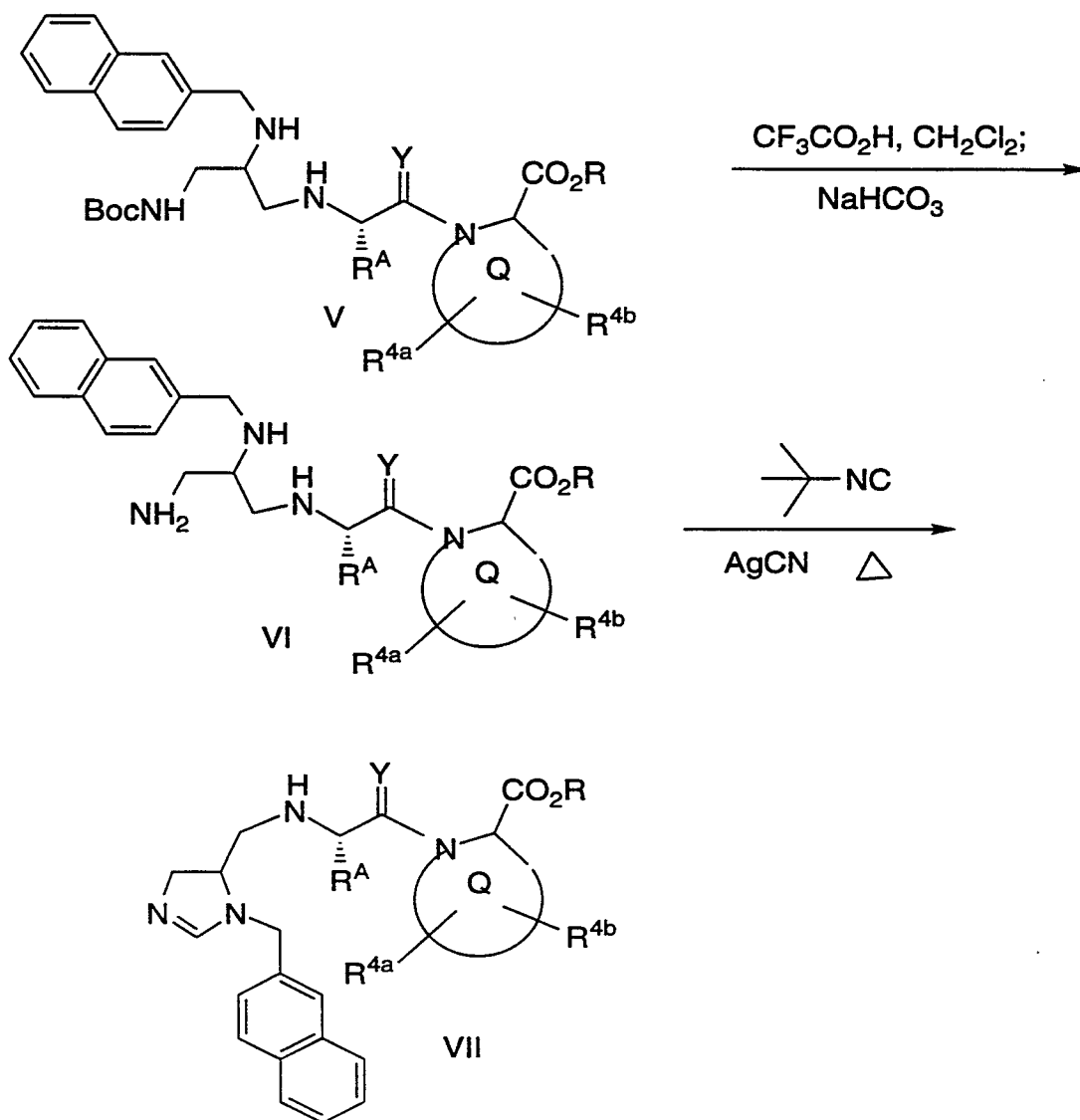
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Reaction Schemes N-R illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic
5 moieties for variable W are also well known in the art.

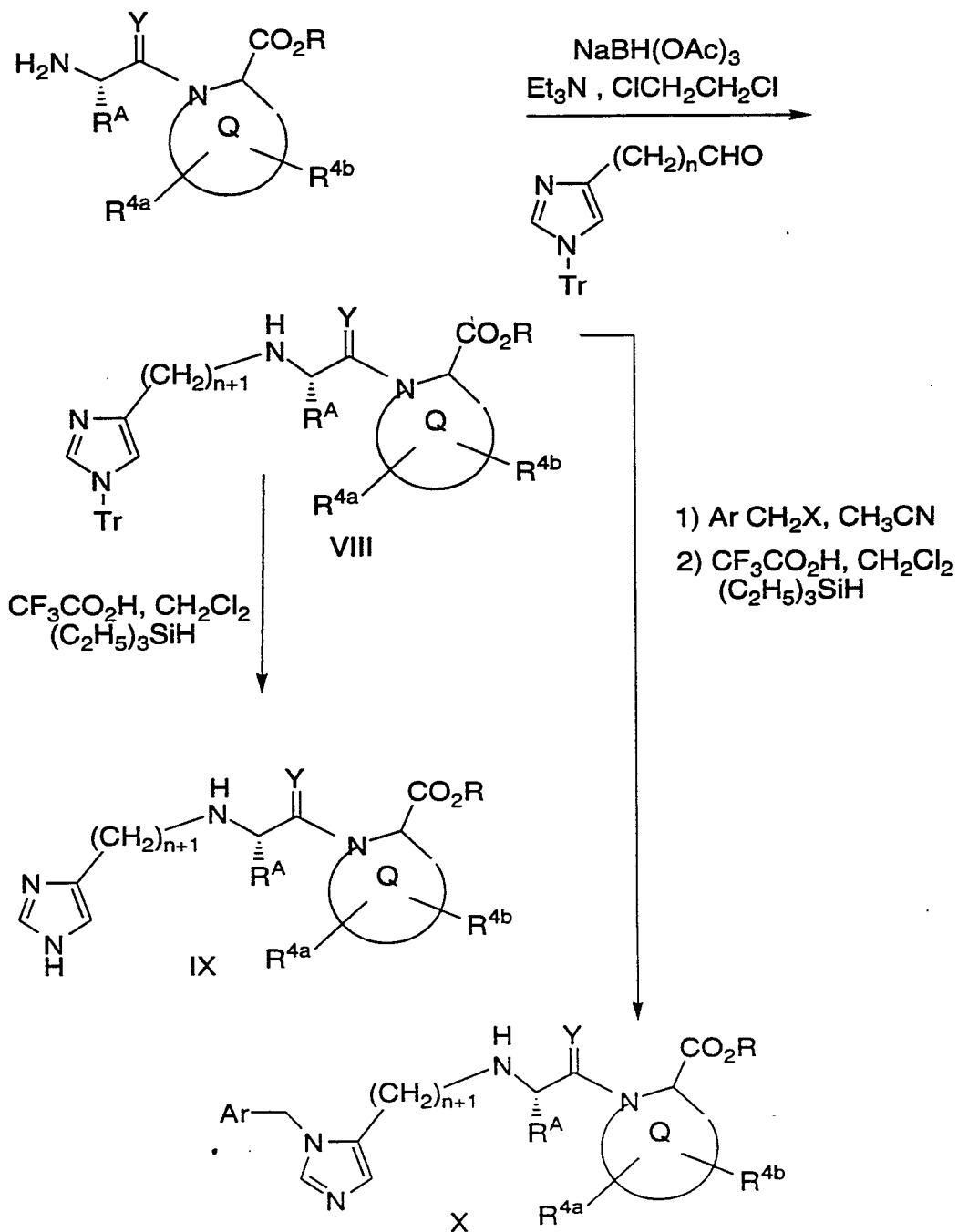
- 62 -

REACTION SCHEME F

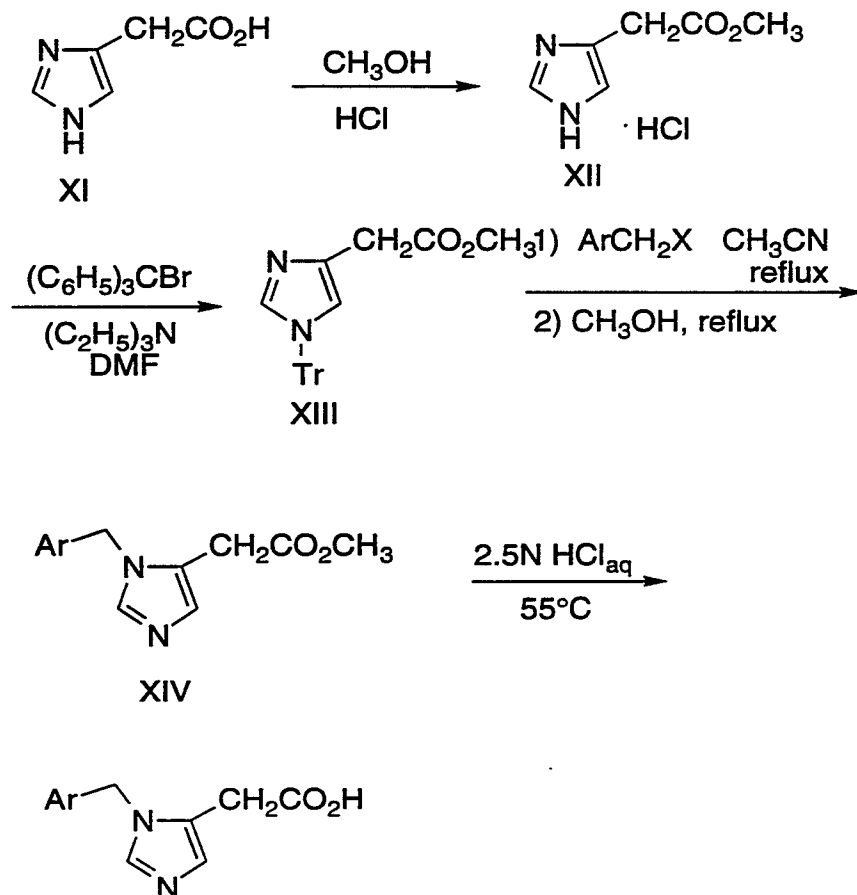
- 63 -

REACTION SCHEME F (continued)

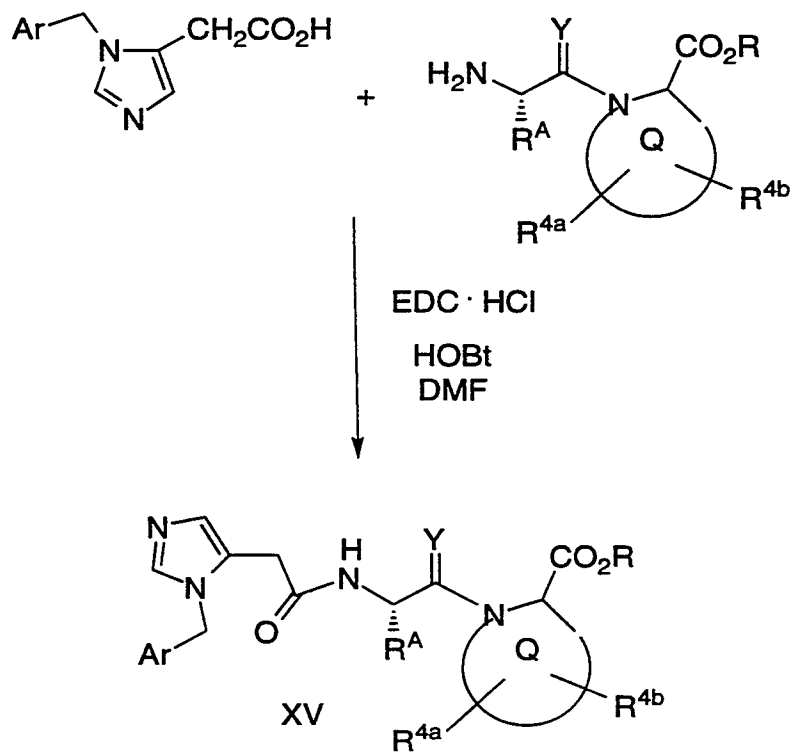
- 64 -

REACTION SCHEME G

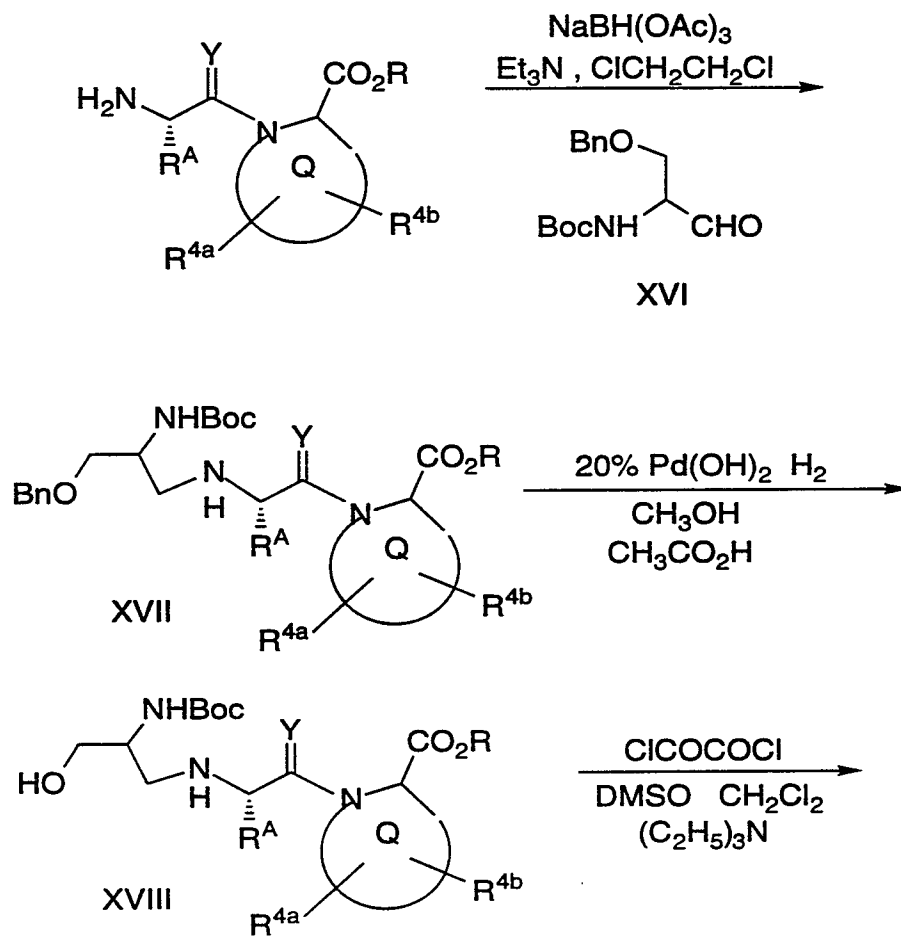
- 65 -

REACTION SCHEME H

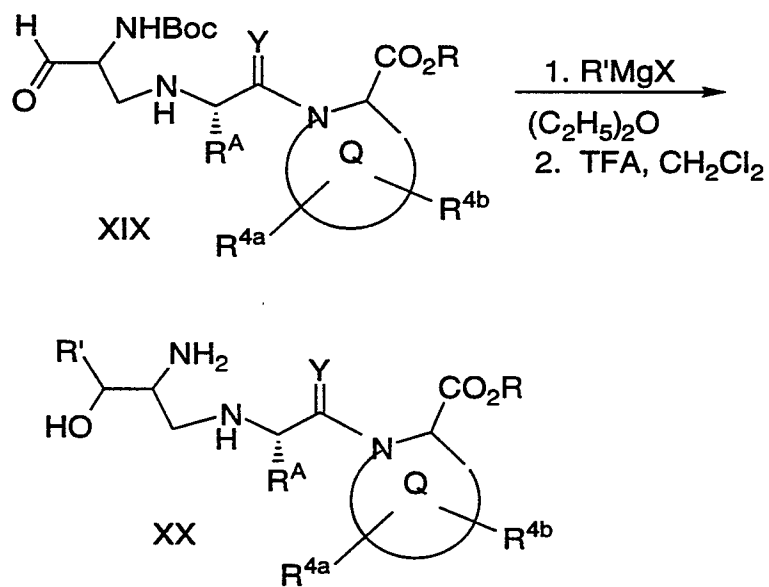
REACTION SCHEME I



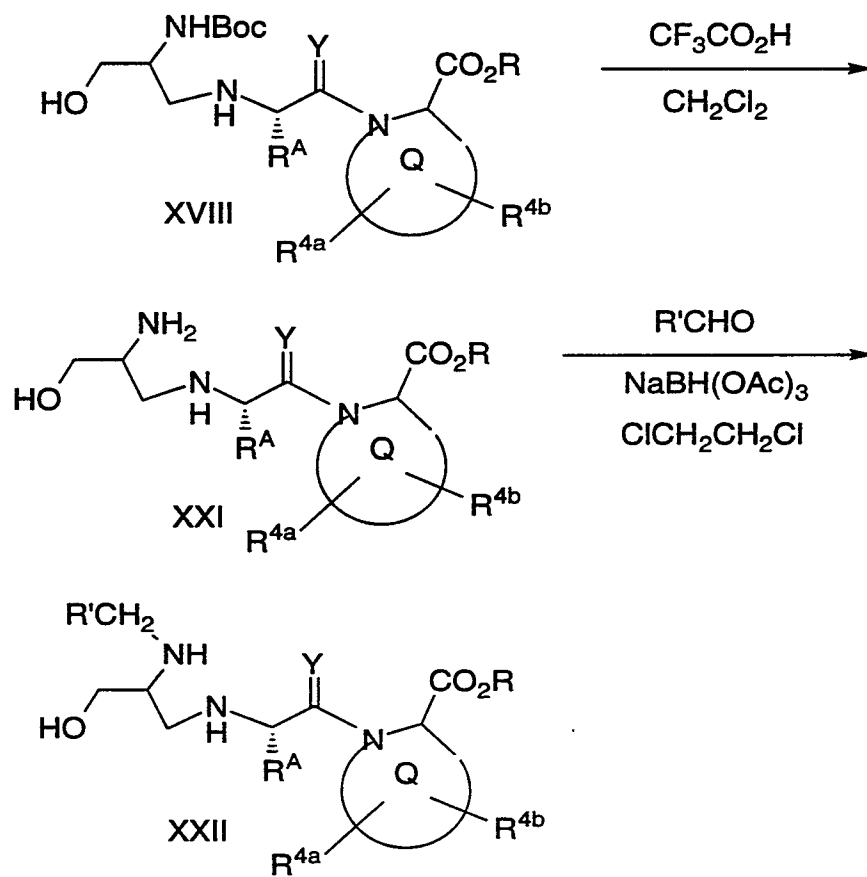
- 67 -

REACTION SCHEME J

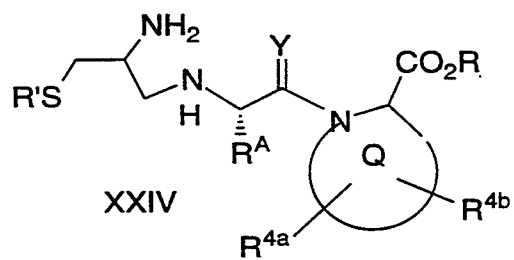
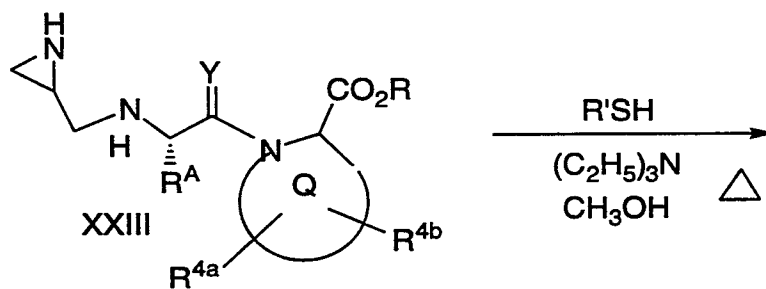
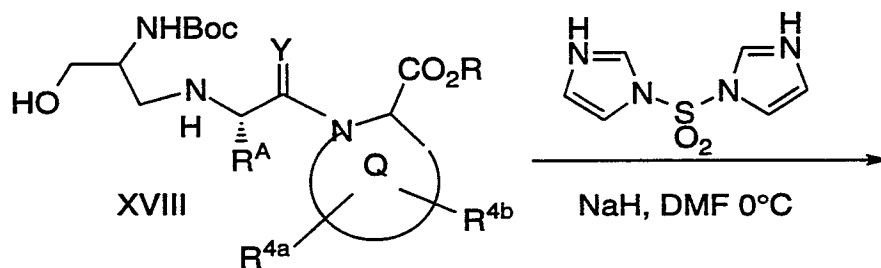
- 68 -

REACTION SCHEME J (CONTINUED)

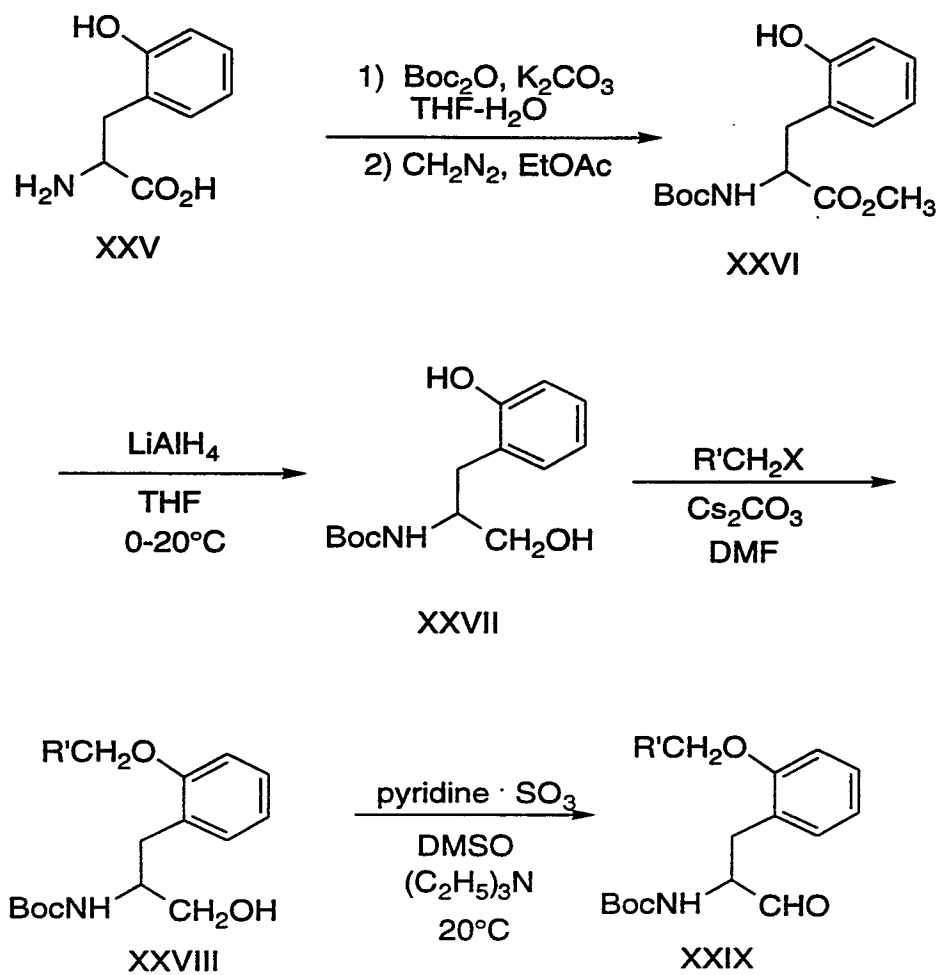
- 69 -

REACTION SCHEME K

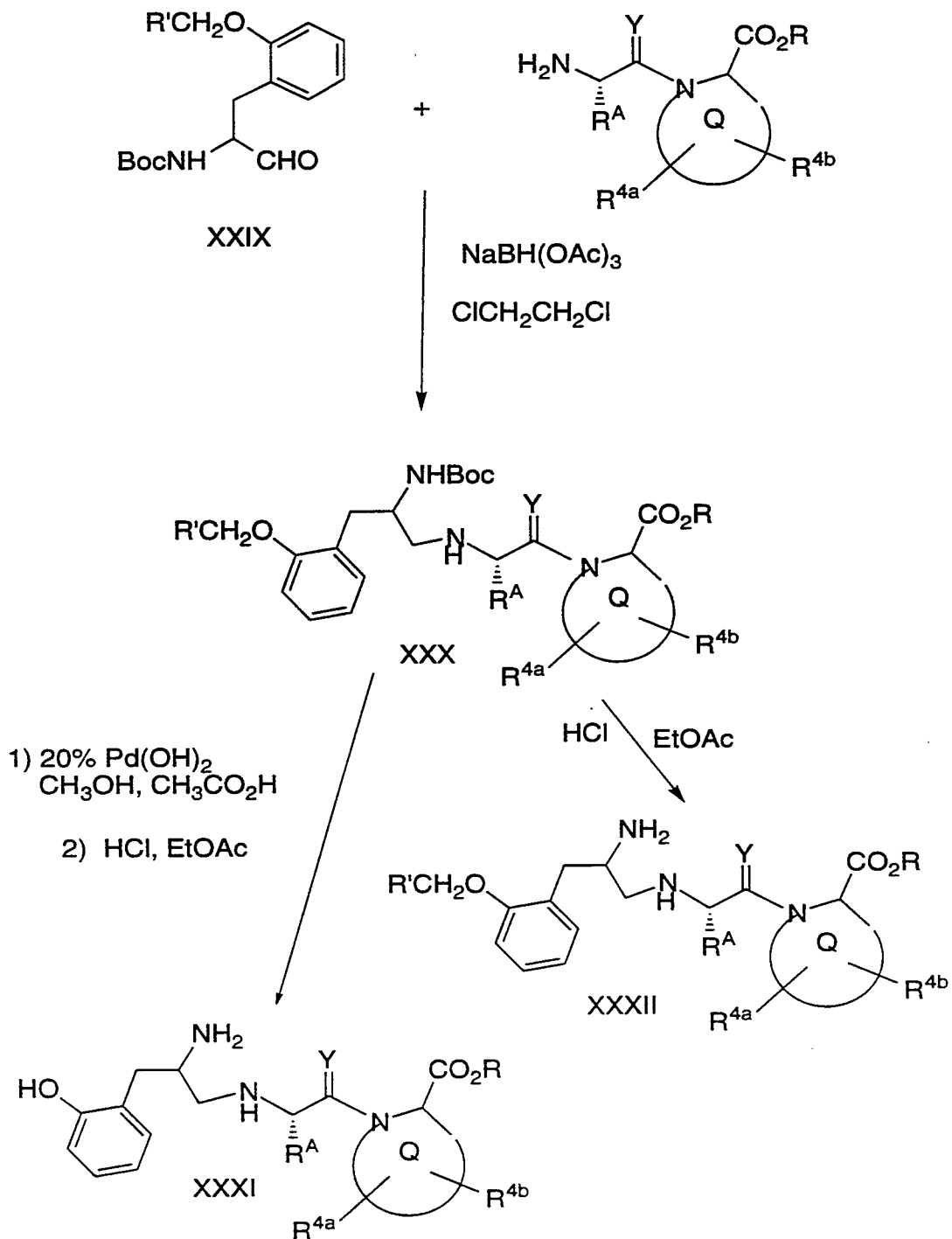
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REACTION SCHEME L

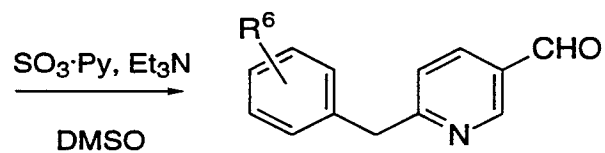
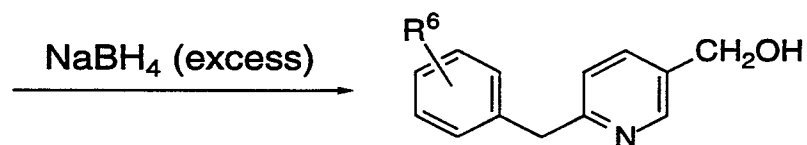
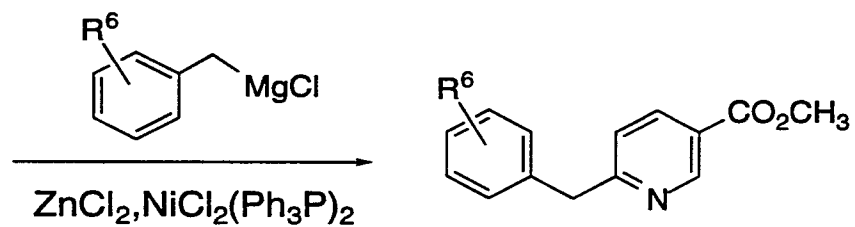
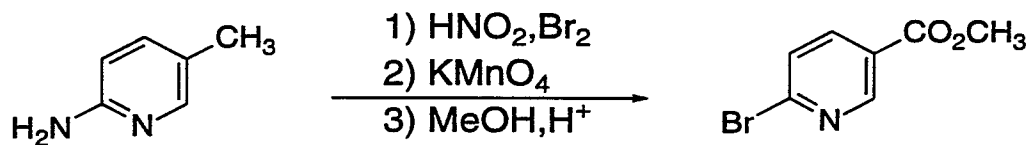
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REACTION SCHEME M

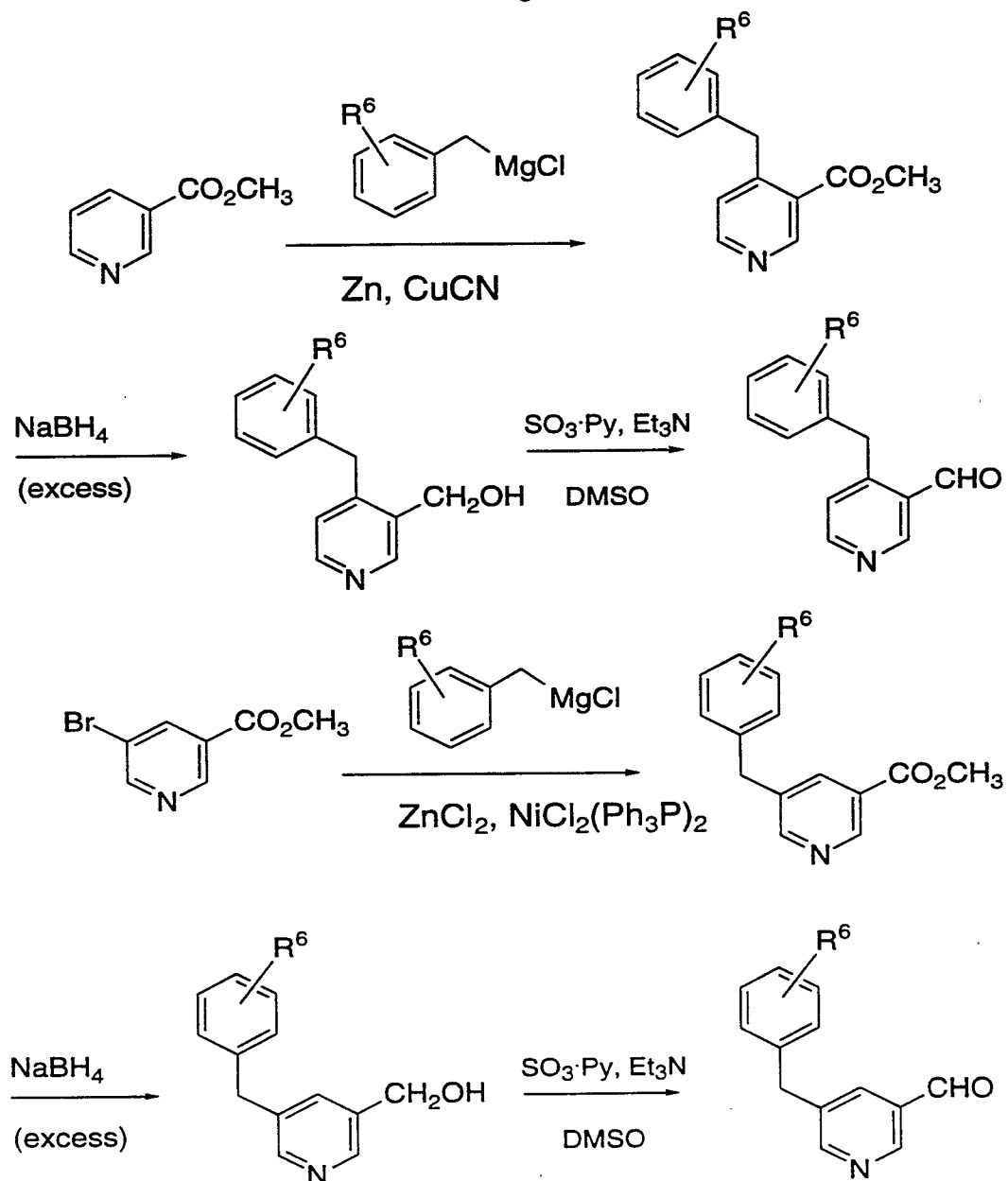
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REACTION SCHEME M (continued)

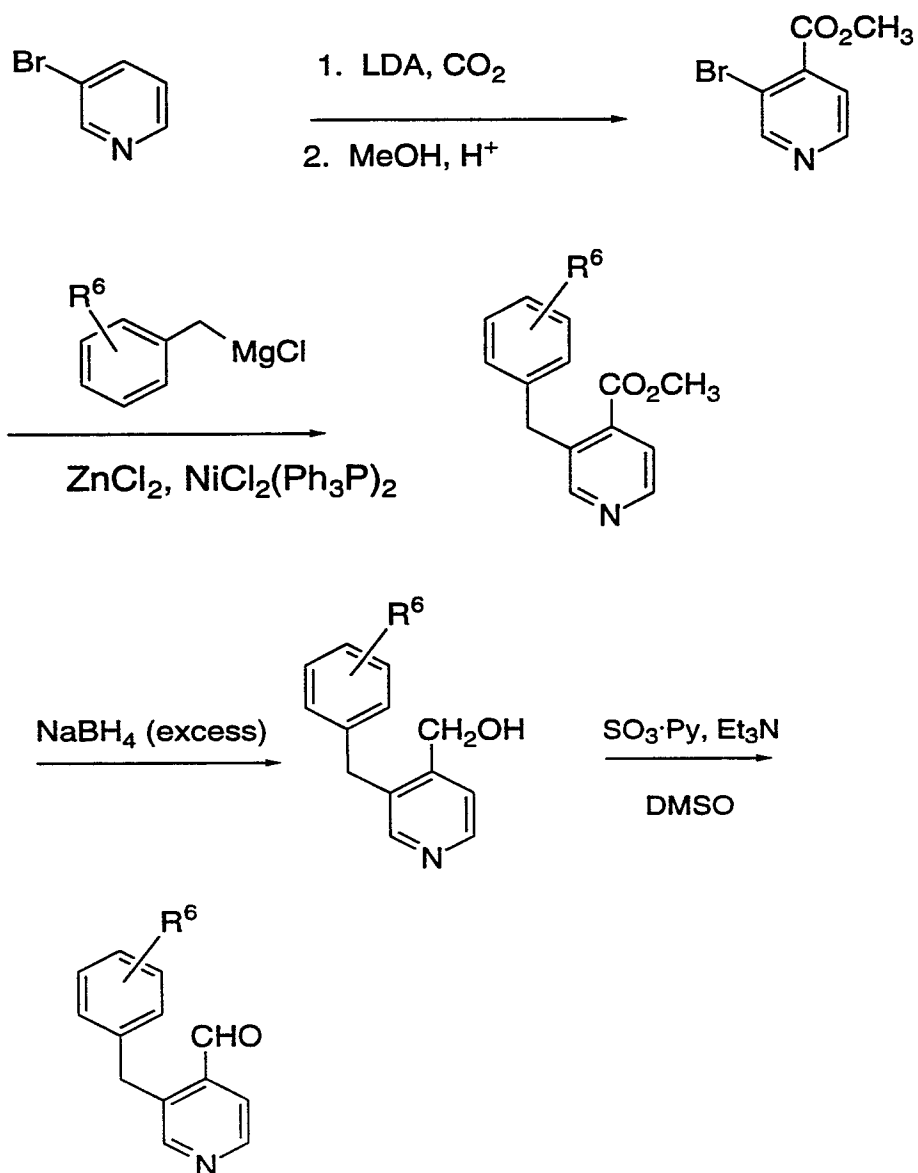
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REACTION SCHEME N

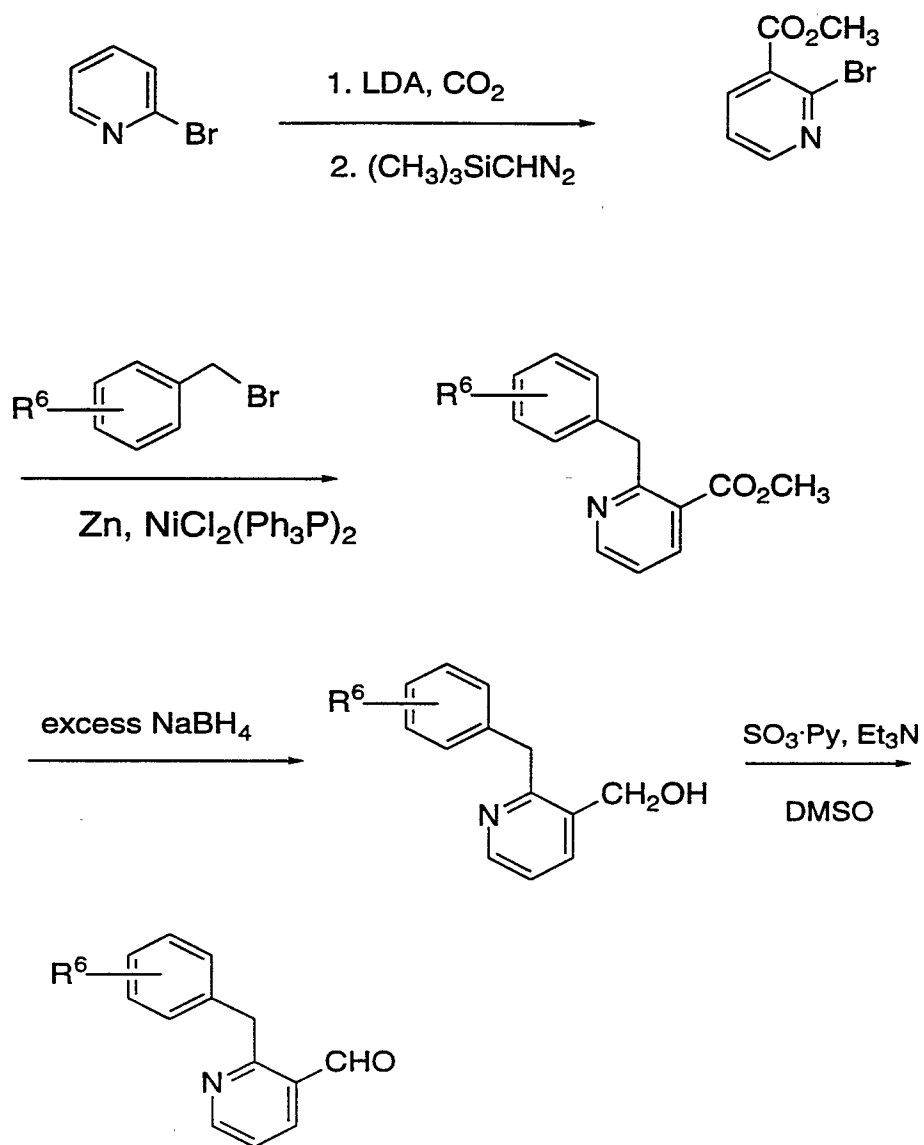
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REACTION SCHEME P

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REACTION SCHEME Q

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REACTION SCHEME R

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The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras formation (i.e., neurofibromin (NF-1), neu, scr, ab1, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

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American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination
5 with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous,
10 intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or
15 suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the
20 active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use,
25 the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or
30 diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

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When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 20 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 10 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-

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protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a K_i substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

The standard workup referred to in the examples refers to solvent extraction and washing the organic solution with 10% citric acid, 10% sodium bicarbonate and brine as appropriate. Solutions were dried over sodium sulfate and evaporated *in vacuo* on a rotary evaporator.

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EXAMPLE 1

Preparation of N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester and
5 N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-
prolyl-methionine trifluoroacetate

10 Step A: Preparation of Diethyl 1-acetyl-5-hydroxy-3-
ethylpyrrolidine-2,2-dicarboxylate

Sodium (4.02 g, 0.175 mol) was dissolved in a stirred solution of diethyl acetamidomalonate (235.4 g, 1.19 mol) in abs EtOH (1.4 L) at ambient temperature under argon. The reaction mixture was cooled to 0°C, and trans-2-pentenal (100 g, 1.08 mol) was added
15 dropwise maintaining the reaction temperature at <5°C. After the addition, the reaction was allowed to warm to room temperature, stirred for 4 h, then quenched with acetic acid (28 mL). The solution was concentrated *in vacuo*, and the residue dissolved in EtOAc (1.5 L), washed with 10% NaHCO₃ solution (2 x 300 mL), brine, and dried
20 (MgSO₄). The solution was filtered and concentrated to 700 mL, then heated to reflux and treated with hexane (1 L). On cooling, the title compound precipitated and was collected, mp 106 - 109°C. ¹H NMR (CD₃OD) δ 5.65 (d, 1H, J= 5 Hz), 4.1 - 4.25 (m, 4H), 2.7-2.8 (m, 1H), 2.21 (s, 3H), 2.10 (dd, 1H, J = 6, 13, Hz), 1.86- 1.97 (m, 2H), 1.27 (t, 3H,
25 J= 7 Hz), 1.23 (t, 3H, J= 7 Hz), 1.1- 1.25 (m, 1H), 0.97 (t, 3H, J= 7 Hz).

Step B: Preparation of Diethyl 1-acetyl-3-ethylpyrrolidine-2,2-dicarboxylate

To a solution of diethyl 1-acetyl-5-hydroxy-3-ethylpyrrolidine-2,2-dicarboxylate (287 g, 0.95 mol) and triethylsilane (228 mL, 1.43 mol) in CH₂Cl₂ (3 L) under argon was added
30 trifluoroacetic acid (735 mL, 9.53 mol) dropwise with stirring while maintaining the internal temperature at 25 °C by means of an ice bath. After stirring for 3 h at 23°C, the solution was concentrated *in vacuo*.
35 the residue diluted with CH₂Cl₂ (1.5 L), then treated with H₂O (1 L) and

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solid Na₂CO₃ with vigorous stirring until the solution was basic. The organic layer was separated, dried (Na₂SO₄), filtered, then concentrated to give the title compound as a yellow oil which was used without further purification.

5

Step C: Preparation of 3-Ethylproline hydrochloride (Cis:Trans Mixture)

Diethyl 1-Acetyl-3-ethylpyrrolidine-2,2-dicarboxylate (373 g, 0.95 mol) was suspended in 6N HCl (2 L) and HOAc (500 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (1L), then concentrated *in vacuo* to give an oil which crystallized upon trituration with ether to give the title compound. ¹H NMR (D₂O) δ 4.23 (d, 1H, J= 8 Hz), 3.84 (d, 1H, J= 8 Hz), 3.15- 3.4 (m, 4H), 2.33- 2.44 (m, 1H), 2.19-2.4 (m, 1H), 2.02- 2.15 (m, 2H), 1.53- 1.72 (m, 3H), 1.23- 1.43 (m, 2H), 1.0- 1.15 (m, 1H), 0.75 - 0.83 (m, 6H).

15

Step D: Preparation of N-[(*tert*-Butyloxy)carbonyl]-*cis:trans*-3-ethylproline methyl ester

3-Ethylproline hydrochloride (Cis:Trans Mixture) (20 g, 0.11 mol) was dissolved in CH₃OH (200 mL), and the solution was saturated with HCl gas, then stirred at 23°C for 24 h. Argon was bubbled through the solution to remove excess HCl. The solution was treated with NaHCO₃ (>84 g) to a pH of 8, then di-*tert*-butyl dicarbonate (25.1 g, 0.115 mol) dissolved in CH₃OH (20 mL) was added slowly. After stirring for 18 h at 23°C, the mixture was filtered, the filtrate concentrated, and the residue triturated with EtOAc, filtered again, and concentrated to give the title compound as an oil.

20

25

Step E: Preparation of N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline and N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester

30

N-[(*tert*-Butyloxy)carbonyl]-*cis,trans*-3-ethylproline methyl ester (29.1 g, 0.113 mol) was dissolved in CH₃OH (114 mL) with cooling to 0°C, then treated with 1 N NaOH (114 mL). After stirring for 20 h at

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23°C, the solution was concentrated to remove the CH₃OH and then extracted with EtOAc (3 x). The organic layers were combined, dried (MgSO₄), filtered, and concentrated to give 12.8 g of N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester as an oil. The aqueous layer was acidified with solid citric acid and extracted with EtOAc (2 x), the organic layers combined, dried (MgSO₄), filtered, and concentrated to give N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline as an oil. ¹H NMR (CD₃OD) δ 3.86 and 3.78 (2 d, 1H, J = 6 Hz), 3.33 - 3.58 (m, 2H), 2.01 - 2.22 (m, 2H), 1.5 - 1.74 (m, 2H), 1.33 - 1.5 (m, 1H), 1.45 and 1.42 (2 s, 9H), 0.98 (t, 3H, J = 8 Hz).

Step F: Preparation of 3(S)-Ethyl-2(S)-proline hydrochloride

N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline (15.5 g, 0.064 mol), S-α-methylbenzylamine (9.03 mL, 0.070 mol), HOBT (10.73 g, 0.070 mol), and N-methylmorpholine (8 mL, 0.076 mol) were dissolved in CH₂Cl₂ (150 mL) with stirring in an ice-H₂O bath, treated with EDC (13.4 g, 0.070 mol) stirred at 23°C for 48 h. The reaction mixture was partitioned between EtOAc and 10% citric acid solution, the organic layer washed with satd NaHCO₃ solution, brine and dried (MgSO₄), filtered, and concentrated to give an oil. This oil was dissolved in a minimum amount of ether (10 mL) to crystallize the desired S,S,S diastereomer (4.2 g), mp 118-121°C. A solution of this product in 8N HCl (87 mL) and glacial acetic acid (22 mL) was heated at reflux overnight. The solution was concentrated on a rotary evaporator, and the residue taken up in H₂O and extracted with ether. The aqueous layer was concentrated to dryness to give a 1:1 mixture of 3(S)-ethyl-2(S)-proline hydrochloride and α-methylbenzylamine.

3(S)-Ethyl-2(S)-proline containing α-methylbenzylamine (2.0 g, 0.0128 mol) was dissolved in dioxane (10 mL) and H₂O (10 mL) with stirring and cooling to 0°C. N,N-diisopropylethylamine (2.2 mL, 0.0128 mol) and di-*tert*-butyl-dicarbonate (2.79 g, 0.0128 mol) were added and stirring was continued at 23°C for 48 h. The reaction mixture was partitioned between EtOAc (60 mL) and H₂O (30 mL), the organic layer washed with 0.5N NaOH (2 x 40 mL), the aqueous layers

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combined and washed with EtOAc (30 mL) and this layer back-extracted with 0.5 N NaOH (30 mL). The aqueous layers were combined and carefully acidified at 0°C with 1N HCl to pH 3. This mixture was extracted with EtOAc (3 x 40 mL), the organics combined, dried (MgSO₄), filtered and concentrated to give N-[(*tert*-Butyloxy)carbonyl-3(S)-ethyl-2(S)-proline as a colorless oil. N-[(*tert*-Butyloxy)carbonyl-3(S)-ethyl-2(S)-proline was dissolved in EtOAc (50 mL) and the solution was saturated with HCl gas with cooling in an ice-H₂O bath. The solution was stoppered and stirred at 0°C. for 3 hr. Argon was bubbled through the solution to remove excess HCl, and the solution was concentrated to dryness to give 3(S)-ethyl-2(S)-proline hydrochloride.

Step G: N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-prolinol
3(S)-Ethyl-2(S)-proline hydrochloride containing α -methylbenzylamine (2.0 g, 0.0128 mol) was dissolved in dioxane (10 mL) and H₂O (10 mL) with stirring and cooling to 0°C. N,N-diisopropylethylamine (2.2 mL, 0.0128 mol) and di-*tert*-butyl-dicarbonate (2.79 g, 0.0128 mol) were added and stirring was continued at 23°C for 48 h. The reaction mixture was partitioned between EtOAc (60 mL) and H₂O (30 mL), the organic layer washed with 0.5N NaOH (2 x 40 mL), the aqueous layers combined and washed with EtOAc (30 mL) and this layer back-extracted with 0.5 N NaOH (30 mL). The aqueous layers were combined and carefully acidified at 0°C with 1N HCl to pH 2. This mixture was extracted with EtOAc (3 x 40 mL), the organics combined, dried (MgSO₄), filtered and concentrated to give N-[(*tert*-Butyloxy)carbonyl--3(S)-ethyl-2(S)-proline as a colorless oil which was used without purification.

N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-proline (1.6 g, 6.58 mmol) was dissolved in dry THF (10 mL) and treated with borane (1M in THF, 12.5 mL, 12.5 mmol) with stirring at 0 °C for 2 h, then 23°C for 1 h. The solution was cooled to 0°C, treated with H₂O (20 mL), and extracted with EtOAc (2 x 30 mL). The organics were washed with brine, satd NaHCO₃, H₂O, dried (MgSO₄), filtered and concentrated to give a viscous oil. The oil was dissolved in CH₂Cl₂, filtered through dry SiO₂.

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and the filtrate concentrated to give the title compound as an oil. ^1H NMR (CDCl_3) δ 4.97 (d, 1H, $J = 7$ Hz), 3.71 (t, 1H, $J = 8$ Hz), 3.51-3.62 (m, 3H), 3.18 - 3.26 (m, 1H), 1.9 - 2.0 (m, 1H), 1.53-1.7 (m, 2H), 1.47 (s, 9H), 1.26 - 1.43 (m, 2H), 0.95 (t, 3H, $J = 7$ Hz).

5

Step H: N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-prolinal

N-[(*tert*-Butyloxy)carbonyl-3(S)-ethyl-2(S)-prolinol (0.638 g, 2.78 mmol) and Et_3N (1.4 mL, 9.74 mmol) were dissolved in dry CH_2Cl_2 (10 mL) with stirring and cooling to -10°C and treated dropwise with a solution of $\text{SO}_3\cdot\text{pyr}$ (1.33 g, 8.35 mmol) in dry DMSO (5 mL) keeping the reaction mixture temperature at $< 0^\circ\text{C}$. The mixture was stirred at 0°C for 20 min then at 5°C for 20 min, and at 15°C for 1 h, then poured into ice-cold 0.5 N HCl and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), organics combined, washed with H_2O , aq satd NaHCO_3 solution, brine, and dried (Na_2SO_4). Filtration and concentration to dryness gave the title compound which was used without purification.

20 Step I: N-[(*tert*-Butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-proline methyl ester

N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-prolinal (0.315 g, 0.0014 mol) and proline methyl ester hydrochloride (0.233 g, 0.0014 mol) were dissolved in MeOH (5 mL) at ambient temperature under argon with cooling in an ice- H_2O bath, and treated with sodium cyanoborohydride (0.131 g, 0.002 mol) with stirring. After 18 h the mixture was poured into 5% NaHCO_3 solution (20 mL), the CH_3OH removed and the aq layer washed with EtOAc (3 x 30 mL), the organics combined, washed with brine, and dried (MgSO_4). Filtration and concentration to dryness gave the title compound as a colorless oil after chromatography (SiO_2 , hexane: EtOAc, 6:1). ^1H NMR (CDCl_3) δ 3.70 (s, 3H), 3.1 - 3.7 (m, 5H), 2.2 - 2.65 (m, 4H), 1.7 - 2.15 (m, 5H), 1.5 - 1.65 (m, 1H), 1.46 (s, 9H), 1.2 - 1.5 (m, 2H), 0.93 (t, 3H, $J = 7$ Hz).

30

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Step J: N-[(*tert*-Butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-proline

N-[(*tert*-Butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-proline methyl ester 0.081 g, 0.238 mmol) was dissolved in
 5 CH₃OH (2 mL), cooled to 0°C and treated with 1N NaOH solution (0.952 mL, 0.952 mmol). After stirring at 23°C for 3h, the solution was neutralized with 1N HCl (0.952 mL, 0.952 mmol), concentrated to remove the CH₃OH, then lyophilized and the residue used as is.

10 **Step K:** N-[(*tert*-Butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[(*tert*-Butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-proline (0.238 mmol), HOBT (0.048 g, 0.262 mmol), EDC (0.068 g, 0.0357 mmol), and methionine methyl ester hydrochloride
 15 (0.048 g, 0.238 mmol) were dissolved in CH₂Cl₂ (10 mL) and stirred at 23°C for 18 h. EtOAc (100 mL) was added, and the mixture washed with satd NaHCO₃ solution, H₂O, brine, and dried (MgSO₄). Filtration and concentration to dryness gave 0.085 g of title compound. ¹H NMR (CD₃OD) δ (major rotamer) 4.63 (t, 1H, J = 7 Hz), 3.73 (s, 3H), 3.55 -
 20 3.7 (m, 1H), 3.0-3.5 (m, 4H), 2.3 - 2.7 (m, 5H), 1.9 - 2.2 (m, 3H), 2.08 (s, 3H), 1.6 - 1.9 (m, 4H), 1.46 (s, 9H), 1.3 - 1.45 (m, 2H), 0.92 - 1.02 (m, 3H).

25 **Step L:** N-[3(S)-Ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester hydrochloride

HCl gas was bubbled into a solution of N-[(*tert*-butyloxy)carbonyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester (0.085 g, 0.18 mmol) in EtOAc (5 mL) with stirring and cooling in an ice-H₂O bath until saturation. The solution was
 30 stoppered and stirred at 0°C for 2 h, then purged with Ar and concentrated to give the title compound as a yellow foam.

Step M: N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

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N-[3(S)-Ethylpyrrolidin-2(S)-ylmethyl]-prolyl methionine methyl ester hydrochloride (0.075 g, 0.169 mmol), 1H-imidazol-4-ylacetic acid (0.052 g, 0.253 mmol), HOBt (0.34 g, 0.253 mmol), EDC (0.49 g, 0.253 mmol) and Et₃N (0.176 mL, 1.27 mmol) were dissolved in DMF (4 mL) and stirred at 23°C for 18 h. The solvent was removed *in vacuo*, EtOAc (60 mL) was added, and the solution was washed sequentially with satd NaHCO₃ solution, H₂O, brine, and dried (MgSO₄). Filtration and concentration to dryness gave the title compound after chromatography (SiO₂, 5 - 10% CH₃OH/CH₂Cl₂). ¹H NMR (CD₃OD) δ (major rotamer) 7.62 (s, 1H), 6.93 (s, 1H), 4.6 - 4.67 (m, 1H), 4.1-4.16 (m, 1H), 3.74 (s, 3H), 3.65 (s, 2H), 3.5 - 3.68 (m, 2H), 3.2 - 3.25 (m, 1H), 3.04 - 3.1 (m, 1H), 2.44 - 2.7 (m, 5H), 2.05 - 2.26 (m, 4H), 2.08 (s, 3H), 1.68 - 1.87 (m, 4H), 1.26 - 1.5 (m, 3H), 0.99 (t, 3H, J = 7 Hz). FAB MS 480 (M + 1).

15

Step N: N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine trifluoroacetate

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester (0.020 g, 0.042 mmol) was dissolved in CH₃OH (2 mL) at 0°C and treated with 1N NaOH solution (0.167 mL, 0.167 mmol) with stirring. After 5 h at 23°C 1N HCl (0.167 mL, 0.167 mmol) was added and the mixture was purified by preparative RP HPLC on a Vydac column eluting with 0.1% TFA/CH₃CN: 0.1% TFA/ H₂O gradient to give the title compound.

¹H NMR (CD₃OD) δ 8.88 (d, 1H, J = 1Hz), 7.43 (d, 1H, J = 1Hz), 4.53 - 4.58 (m, 1H), 4.25-4.31 (m, 1H), 3.96 (ABq, 2H), 3.7 - 3.85 (m, 3H), 3.58 - 3.66 (m, 1H), 3.50 (dd, 1H, J = 3, 14 Hz), 3.39 (dd, 1H, J = 3, 14 Hz), 3.23 - 3.42 (m, 1H), 2.45 - 2.67 (m, 3H), 2.12 - 2.28 (m, 4H), 2.08 (s, 3H), 1.98 - 2.05 (m, 3H), 1.54 - 1.68 (m, 2H), 1.26 - 1.4 (m, 1H), 1.03 (t, 3H, J = 7 Hz). FAB MS 466 (M + 1).

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EXAMPLE 2

Preparation of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

Step A: N-[(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline

3(S)-Ethyl-2(S)-proline hydrochloride (from Example 1, Step F) (2.33 g, 0.013 mol) was dissolved in CH₃OH (20 mL), treated with 3A molecular sieves (2 g) and KOAc (1.27 g, 0.013 mol) to adjust the pH of the reaction mixture to 4.5-5, then N-[(*tert*-Butyloxy)carbonyl-prolinal (Pettit et al., J. Org. Chem. (1994) **59**, [21] 6287-95) (3.36 g, 0.017 mol) was added, and the mixture was stirred for 16 hrs at room temperature. The reaction mixture was filtered, quenched with aq satd NaHCO₃ (5 mL) and concentrated to dryness. The residue was extracted with CHCl₃. The extract was dried (MgSO₄), filtered, and concentrated to give the title compound and inorganic salts.

Step B: N-[(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

N-[(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline (2.4 g, 0.008 mol), methionine isopropyl ester hydrochloride (2.21 g, 0.0097 mol), HOBt (1.49 g, 0.0097 mol) and EDC (1.86 g, 0.0097 mol) were dissolved in DMF (15 mL) at room temperature and treated with N-methylmorpholine (3 mL, 0.024 mol). The reaction mixture was stirred overnight at room temperature, then concentrated and partitioned between EtOAc and H₂O. The organic layer was washed with aq satd NaHCO₃ solution, brine, and dried (MgSO₄). The crude product was chromatographed on a flash silica gel column eluting with hexane: EtOAc, 7:3 to give N-(t-butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester.

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Step C: N-(Pyrrolidin-2(S)-ylmethyl)-3(S)-ethyl-prolyl methionine
isopropyl ester hydrochloride

5 N-[(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-
ethyl-prolyl-methionine isopropyl ester (1.38 g, 0.0028 mol) was
dissolved in EtOAc (40 mL), cooled to -20°C, saturated with HCl gas,
and stirred at 0°C. for 1.25 hr, and room temperature for 0.25 hr.
Concentration to dryness gave the title compound.

Step D: 1H-Imidazole-4- acetic acid methyl ester hydrochloride

10 A solution of 1H-imidazole-4-acetic acid hydrochloride
(4.00g, 24.6 mmol) in methanol (100 ml) was saturated with gaseous
hydrogen chloride. The resulting solution was allowed to stand at room
temperature (RT) for 18hr. The solvent was evaporated in vacuo to afford
the title compound as a white solid.
15 ¹H NMR(CDCl₃, 400 MHz) δ 8.85(1H, s), 7.45(1H, s), 3.89(2H, s) and
3.75(3H, s) ppm.

Step E: 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl
ester

20 To a solution of 1H-Imidazole-4- acetic acid methyl ester
hydrochloride (24.85g, 0.141mol) in dimethyl formamide (DMF)
(115ml) was added triethylamine (57.2 ml, 0.412mol) and tribenzyl
bromide(55.3g, 0.171mol) and the suspension was stirred for 24hr. After
this time, the reaction mixture was diluted with ethyl acetate (EtOAc) (1
25 l) and water (350 ml). The organic phase was washed with sat. aq.
NaHCO₃ (350 ml), dried (Na₂SO₄) and evaporated in vacuo. The
residue was purified by flash chromatography (SiO₂, 0-100% ethyl
acetate in hexanes; gradient elution) to provide the title compound as a
white solid.
30 ¹H NMR (CDCl₃, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m),
6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

Step F: [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl
ester

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To a solution of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (8.00g, 20.9mmol) in acetonitrile (70 ml) was added bromo-p-toluenitrile (4.10g, 20.92 mmol) and heated at 55°C for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18hr. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 ml) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 ml) and heated to reflux for 30min. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75ml) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq NaHCO₃ (300ml) and CH₂Cl₂ (300ml) and stirred at room temperature for 2 hr. The organic layer was separated, dried (MgSO₄) and evaporated in vacuo to afford the title compound as a white solid :

¹H NMR(CDCl₃, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

20 Step G: [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid

A solution of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (4.44g, 17.4mmol) in THF (100ml) and 1 M lithium hydroxide (17.4 ml, 17.4 mmol) was stirred at RT for 18 hr. 1 M HCl (17.4 ml) was added and the THF was removed by evaporation in vacuo.

25 The aqueous solution was lyophilized to afford the title compound containing lithium chloride as a white solid.

¹H NMR(CD₃OD, 400 MHz) δ 8.22(1H, s), 7.74(1H, d, J=8.4Hz), 7.36(1H, d, J=8.4Hz), 7.15(1H, s), 5.43(2H, s) and 3.49(2H, s) ppm.

30 Step H: N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid • LiCl (0.416 g, 1.47 mmol), N-(pyrrolidin-2(S)-ylmethyl)-3(S)-ethyl-prolyl-

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methionine isopropyl ester hydrochloride (Step I) (0.63 g, 1.33 mmol),
HOObt (0.239 g, 1.47 mmol), and EDC (0.281 g, 1.47 mmol) were
dissolved in degassed DMF (20 mL) with stirring at room temperature,
N-methylmorpholine (0.8 mL, 5.32 mmol) was added to achieve a pH of
5 7, and stirring was continued overnight. The reaction mixture was
concentrated to remove most of the DMF, and the residue was partitioned
between EtOAc and aq satd NaHCO₃ solution. The aq layer was washed
with EtOAc, the organics combined, washed with brine and dried
(MgSO₄). Filtration and concentration to dryness gave the title
10 compound after chromatography on silica gel eluting with
CH₂Cl₂:CH₃OH, 95:5.

Anal. calcd for C₃₃H₄₆N₆O₄S • 0.7 H₂O: C, 62.38; H, 7.52; N, 13.23;
found: C, 62.40; H, 7.17; N, 13.11.

FAB MS 623 (M+1)

15

Following the procedures outlined above, but substituting methionine
sulfone isopropyl ester for methionine isopropyl ester, the following
compound was prepared:

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-
20 ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone isopropyl ester

Anal. calcd for C₃₃H₄₆N₆O₆S • 0.9 H₂O: C, 59.07; H, 7.18; N, 12.52;
found: C, 58.99; H, 6.87; N, 12.86.

FAB MS 655 (M+1)

25

EXAMPLE 3

Preparation of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-
ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine
30 sulfoxide

30

To a solution of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-
ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine (0.15 g,
0.186 mM) in 3 mL of MeOH:H₂O 1:1 was added sodium periodate
(0.048 g, 0.223 mM). The mixture was stirred for 1 h, diluted with 3 mL

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of H₂O and purified by prep HPLC (Delta-pak, C-18). The pure fractions were pooled and lyophilized to yield the title compound.

Anal. calcd for C₃₀H₄₀N₆O₅S • 4.2 CF₃CO₂H • 0.5 H₂O:

C, 42.52; H, 4.20; N, 7.75;

5 found: C, 42.51; H, 4.21; N, 8.11.

FAB MS 597 (M+1)

Following the procedure above the following compound was prepared:

10 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfoxide isopropyl ester

Anal. calcd for C₃₃H₄₆N₆O₅S • 1.0 H₂O:

C, 60.34; H, 7.37; N, 12.80;

found: C, 60.32; H, 7.19; N, 12.42.

15

EXAMPLE 4

Preparation of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone

20 To a solution of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine (0.15 g, 0.186 mM) in 5 mL of MeOH:H₂O 1:1 was added Oxone (1.1 g, 0.372 mM). After stirring for 0.5 h, the mixture was partially evaporated and diluted with 5 mL of H₂O and purified by prep HPLC (Vydac, C-18).

25 The pure fractions were pooled and lyophilized to yield the title compound.

Anal. calcd for C₃₀H₄₀N₆O₆S • 3.2 CF₃CO₂H • 1.2 H₂O:

C, 43.75; H, 4.60; N, 8.41;

found: C, 43.75; H, 4.59; N, 8.45.

30 FAB MS 613 (M+1)

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EXAMPLE 5

Preparation of N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester and N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

Step A: N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

Following the procedures described for Example 2, but substituting methionine methyl ester hydrochloride for methionine isopropyl ester hydrochloride in Step B, the title compound was prepared. Anal. calcd for $C_{31}H_{42}N_6O_4S \cdot 3.7 CF_3CO_2H \cdot 0.3 H_2O$:

C, 45.13; H, 4.57; N, 8.22;
found: C, 45.10; H, 4.53; N, 8.39.

Step B: N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine trifluoroacetate

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester (0.016 g, 0.02 mmol) was dissolved in CH_3OH (1 mL) and H_2O (1 mL) at ambient temperature and treated with 1 N NaOH (0.3 mL, 0.3 mmol) with stirring. After 1 hr the reaction mixture was neutralized with 1N HCl (0.3 mL) and purified on a VYDAC preparative RP HPLC column and lyophilized to give the title compound.

Anal. calcd for $C_{30}H_{40}N_6O_4S \cdot 3.9 CF_3CO_2H \cdot 0.6 H_2O$:
C, 43.81; H, 4.39; N, 8.11;
found: C, 43.79; H, 4.39; N, 8.27.

Following the procedures outlined in Examples 2 and 3, but substituting the appropriate carboxylic acid in Example 2, Step H; the following compounds were prepared:

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N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

5 ^1H NMR (CD_3OD) δ 8.88 (s, 1H), 7.43 (s, 1H), 4.64 - 4.71 (m, 1H), 4.19-4.27 (m, 1H), 3.94 (s, 2H), 3.75 - 3.88 (m, 2H), 3.74 (s, 3H), 3.57 - 3.61 (m, 2H), 3.34 - 3.5 (m, 3H), 3.15 - 3.25 (m, 1H), 2.45 - 2.67 (m, 2H), 1.98 - 2.37 (m, 6H), 2.08 (s, 3H), 1.83 - 1.98 (m, 3H), 1.4 - 1.56 (m, 1H), 1.01 (t, 3H, $J = 7$ Hz).

Anal. calcd for $\text{C}_{23}\text{H}_{37}\text{N}_5\text{O}_4\text{S} \cdot 2.8 \text{ CF}_3\text{CO}_2\text{H} \cdot 1.3 \text{ H}_2\text{O}$:

10 C, 41.88; H, 4.96; N, 8.54;

Found: C, 41.85; H, 4.95; N, 8.54.

FAB MS 480 ($M + 1$).

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

15 ^1H NMR (CD_3OD) δ 8.87 (s, 1H), 7.43 (s, 1H), 4.61 - 4.71 (m, 1H), 4.2-4.3 (m, 1H), 3.94 (brs, 2H), 3.75 - 3.88 (m, 2H), 3.6 - 3.73 (m, 1H), 3.16 - 3.48 (m, 5H), 2.5 - 2.7 (m, 2H), 2.0 - 2.38 (m, 6H), 2.10 (s, 3H), 1.83 - 1.98 (m, 3H), 1.4 - 1.55 (m, 1H), 1.01 (t, 3H, $J = 7$ Hz).

20 Anal. calcd for $\text{C}_{22}\text{H}_{35}\text{N}_5\text{O}_4\text{S} \cdot 2.8 \text{ CF}_3\text{CO}_2\text{H}$:

C, 42.24; H, 4.85; N, 8.92;

Found: C, 42.18; H, 4.86; N, 8.95.

FAB MS 466 ($M + 1$).

25 N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

FAB MS 429 ($M + 1$).

N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

30 Anal. calcd for $\text{C}_{19}\text{H}_{34}\text{N}_4\text{O}_4\text{S} \cdot 3.0 \text{ CF}_3\text{CO}_2\text{H} \cdot 0.5 \text{ H}_2\text{O}$:

C, 39.22; H, 5.00; N, 7.32;

Found: C, 39.21; H, 5.02; N, 7.68.

FAB MS 415 ($M + 1$).

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N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S-yl)methyl]-3(S)-ethyl-prolyl-methionine methyl ester

Anal. calcd for $C_{24}H_{39}N_5O_4S \cdot 0.75 H_2O$:

C, 56.84; H, 8.05; N, 13.81;

5 Found: C, 56.79; H, 7.95; N, 13.90.

FAB MS 494 (M + 1).

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S-yl)methyl]-3(S)-ethyl-prolyl-methionine

10 FAB MS 480(M + 1).

N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S-yl)methyl]-3(S)-ethyl-prolyl-methionine methyl ester

Anal. calcd for $C_{32}H_{44}N_6O_4S \cdot 2.0 HCl \cdot 0.4 H_2O$:

15 C, 55.79; H, 6.85; N, 12.20;

Found: C, 55.86; H, 6.85; N, 11.95.

FAB MS 609 (M + 1).

N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S-yl)methyl]-3(S)-ethyl-prolyl-methionine

20 Anal. calcd for $C_{31}H_{42}N_6O_4S \cdot 2.9 CF_3CO_2H \cdot 0.8 H_2O$:

C, 47.03; H, 4.99; N, 8.94;

Found: C, 47.05; H, 4.96; N, 9.31.

FAB MS 595 (M + 1).

25

EXAMPLE 6

Preparation of N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester and N-[2(S)-(1H-

30 Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine

Step A: N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester

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Following the methods outlined in Example 1, but substituting N-(t-Butyloxycarbonyl)-isoleucinal for N-[(t-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-prolinal in Step I, the title compound was prepared.

5 Anal. calcd for $C_{22}H_{37}N_5O_4S \cdot 0.5 H_2O$: C, 55.43; H, 8.04; N, 14.69;

Found: C, 55.75; H, 7.82; N, 14.36.

FAB MS 468 (M + 1).

10 Step B: N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine

The title compound was prepared following the method described in Example 1, Step N.

Anal. calcd for $C_{21}H_{35}N_5O_4S \cdot 2.5 CF_3CO_2H$:

C, 42.27; H, 5.12; N, 9.48;

15 Found: C, 41.91; H, 5.17; N, 9.51.

FAB MS 454 (M + 1).

EXAMPLE 7

20 Preparation of N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester and N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

25 Step A: N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

Following the methods outlined in Example 1, but substituting N-(t-Butyloxycarbonyl)-prolinal for N-[(t-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-prolinal in Step I, the title compound was prepared.

30 Anal. calcd for $C_{21}H_{33}N_5O_4S \cdot 1.9 CF_3CO_2H \cdot 2.2 HCl$:

C, 39.80; H, 5.00; N, 9.36;

Found: C, 39.82; H, 5.01; N, 9.33.

FAB MS 452 (M + 1).

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Step B: N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

The title compound was prepared following the method described in Example 1, Step N.

5 Anal. calcd for $C_{20}H_{31}N_5O_4S \cdot 2.6 CF_3CO_2H \cdot 1.1 HCl$:

C, 40.15; H, 4.79; N, 9.29;

Found: C, 40.15; H, 4.85; N, 9.02.

FAB MS 438 (M + 1).

10 Following the procedures outlined in Examples 1, 2, and 7, the following compounds were prepared:

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

15 Anal. calcd for $C_{29}H_{38}N_6O_4S \cdot 1.2 H_2O$: C, 59.20; H, 6.92; N, 14.28;

Found: C, 59.25; H, 6.81; N, 14.14.

FAB MS 567 (M + 1).

20 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

Anal. calcd for $C_{28}H_{36}N_6O_4S \cdot 3.4 CF_3CO_2H \cdot 1.0 H_2O$:

C, 43.61; H, 4.35; N, 8.77;

Found: C, 43.59; H, 4.35; N, 8.91.

FAB MS 553 (M + 1).

25

EXAMPLE 8

Using the procedures described in Example 1, but substituting 3(S)-Ethyl-2(S)-proline hydrochloride for proline methyl ester in Step I, the
30 following compounds were prepared:

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

35 Anal. calcd for $C_{25}H_{41}N_5O_4S \cdot 0.5 H_2O$: C, 50.93; H, 7.52; N, 11.88;

Found: C, 50.90; H, 7.38; N, 11.87.

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N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine trifluoroacetate

Anal. calcd for $C_{24}H_{39}N_5O_4S \cdot 2.95 CF_3CO_2H$:

5 C, 43.27; H, 5.09; N, 8.44;
Found: C, 43.17; H, 5.16; N, 8.54.

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

10 Anal. calcd for $C_{33}H_{46}N_6O_4S$: C, 63.63; H, 7.45; N, 13.50;
Found: C, 63.53; H, 7.36; N, 13.39.

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine trifluoroacetate

15 Anal. calcd for $C_{32}H_{44}N_6O_4S \cdot 3.2 CF_3CO_2H \cdot 0.6 H_2O$:
C, 46.85; H, 4.96; N, 8.54;
Found: C, 46.86; H, 4.96; N, 8.78.

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

20 Anal. calcd for $C_{35}H_{50}N_6O_4S \cdot 0.25 H_2O$: C, 64.14; H, 7.77; N, 12.82;
Found: C, 64.16; H, 7.73; N, 12.82.

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

25 FAB MS 522 (M + 1).

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine trifluoroacetate

30 FAB MS 508 (M + 1).

N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

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N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine trifluoroacetate

EXAMPLE 9

5

Preparation of N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate and N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate.

10

Step A: 1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetic acid methyl ester and 1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetic acid methyl ester (3:1 mixture)

15

To a solution of sodium hydride (60% in mineral oil, 99 mg, 2.5 mmol) in dimethylformamide (2 ml) cooled to 0°C was added, via cannula, a solution of 1H-imidazole-4-acetic acid methyl ester hydrochloride (200 mg, 1.13 mmol) in dimethylformamide (3 ml). This suspension was allowed to stir at 0°C for 15 min. To this suspension was added 4-nitrobenzyl bromide (244 mg, 1.13 mmol) and stirred at room temperature for 2 h. After this time, the mixture was quenched with sat. aq. sodium bicarbonate (15 ml) and water (20 ml) and extracted with methylene chloride (2 x 50 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography using acetonitrile as eluent to give the title compounds as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (2H, d, J=8.5 Hz), 7.49 (1H, s), 7.27 (2H, d, J=8.5 Hz), 7.03 (0.25H, s), 6.87 (0.75H, s), 5.28 (0.5H, s), 5.18 (1.5H, s), 3.70 (2.25H, s), 3.65 (1.5H, s), 3.61 (0.75H, s) and 3.44 (0.5H, s) ppm.

30

Step B: 1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetic acid hydrochloride and 1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetic acid (3:1 mixture)

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To a solution of a mixture of 1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetic acid methyl ester and 1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetic acid methyl ester (3:1 mixture, 216 mg, 0.785 mmol) in methanol (3 ml) and tetrahydrofuran (3 ml) under argon was added 1.0 M sodium hydroxide (1.18 ml, 1.18 mmol) and stirred for 18 h. After this time, 1.0 N hydrochloric acid (2.36 ml, 2.36 mmol) was added and the mixture evaporated *in vacuo* to give the title compounds.

¹H NMR (CDCl₃, 400 MHz) δ 9.04 (0.75H, s), 8.83 (0.25H, s), 8.28 (2H, d, J=8.8 Hz), 7.61 (2H, d, J=8.8 Hz), 7.54 (0.75H, s), 7.43 (0.25H, s), 5.61 (0.5H, s), 5.58 (1.5H, s), 3.84 (0.5H, s) and 3.82 (1.5H, s) ppm.

Step C: N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester bis trifluoroacetate and N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester bis trifluoroacetate

To a solution of 1-(4-nitrobenzyl)-1H-imidazol-4-ylacetic acid hydrochloride and 1-(4-nitrobenzyl)-1H-imidazol-5-ylacetic acid hydrochloride (3:1 mixture, 0.392 mmol), N-[pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester hydrochloride (0.392 mmol), prepared as described in Example 1, Steps A-L (but utilizing the substitutions described in Example 2, Step A), and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOObt, 0.39 mmol) in methylene chloride (10 ml) are added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.392 mmol) and triethylamine (1.57 mmol) and the mixture is stirred overnight at room temperature. After this time, sat. aq. sodium bicarbonate (10 ml) is added and the mixture is extracted with methylene chloride. The combined extracts are washed with sat. aq. sodium bicarbonate (10 ml) and the solvent evaporated *in vacuo*. The regioisomers are separated by preparative HPLC using a Nova Prep 5000 Semi preparative HPLC system and a Waters PrepPak cartridge (47X300mm, C18, 15µm, 100 Å) eluting with 5-95% acetonitrile/water (0.1% TFA) at 100 ml/min (chromatography method A) to give the title compounds after lyophilization.

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Step D: N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis
trifluoroacetate

5 To a solution of N-[1-(1-(4-nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester bis trifluoroacetate (0.023 mmol) in methanol (1 ml) at room temperature is added 1.0N lithium hydroxide (135 μ l, 0.135 mmol). This solution is stirred for 4 h and treated with trifluoroacetic acid (100 μ l).
10 This mixture is purified by preparative HPLC using chromatography method A to give the title compound.

Step E: N-[1-(1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis
trifluoroacetate

15 To a solution of N-[1-(1-(4-nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester bis trifluoroacetate (0.031 mmol) in methanol (1 ml) is added 1.0N
20 lithium hydroxide (187 μ l, 0.187 mmol). This solution is stirred for 4 h and treated with trifluoroacetic acid (100 μ l). This mixture is purified by preparative HPLC using chromatography method A to give the title compound.

25 EXAMPLE 10

Preparation of N-[1-(1-(1-Farnesyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine bis trifluoroacetate

30 **Step A:** 1-(1-Farnesyl)-1H-imidazol-5-ylacetic acid methyl ester
To a solution of 1-(tribenzyl)-1H-imidazol-4-ylacetic acid methyl ester (200 mg, 0.523 mmol) in acetonitrile (5 ml) was added trans, trans-farnesyl bromide (156 μ l, 0.575 mmol) and heated at 55°C for 16 h. After this time, the reaction was heated at 80°C for 3 h and then the

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reaction mixture was evaporated *in vacuo*. The residue was dissolved in methanol (5 ml) and heated to reflux for 30 min and then evaporated *in vacuo*. The residue was purified by flash chromatography (2-4% methanol/methylene chloride gradient elution) to provide the title compound.

¹H NMR (CDCl₃, 400 MHz) δ 7.50 (1H, s), 6.92 (1H, s), 5.24 (1H, t, J=5.9 Hz), 5.09 (2H, m), 4.49 (2H, d, J=6.9 Hz), 3.69 (3H, s), 3.60 (2H, s), 1.91-2.15 (8H, m), 1.72 (3H, s), 1.65 (3H, s), 1.59 (3H, s) and 1.57 (3H, s) ppm.

Step B: N-[1-(1-(1-Farnesyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester bis trifluoroacetate

Following the procedure described in Example 9, Steps C-D, but using 1-farnesyl-1H-imidazol-5-ylacetic acid methyl ester described in Step A in place of 1-(4-nitrobenzyl)-1H-imidazol-5-ylacetic acid methyl ester provides the title compound.

Step C: N-[1-(1-(1-Farnesyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine bis trifluoroacetate

Following the procedure described in Example 1, Step N, but using the methyl ester prepared as described in Step B provides the title compound.

EXAMPLE 11

Preparation of N-[1-(1-(1-Geranyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate

Step A: N-[1-(1-(1-Geranyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester bis trifluoroacetate

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Following the procedure described in Example 10, Steps A-B, but using trans-geranyl bromide in place of farnesyl bromide provides the title compound.

5 Step B: N-[1-(1-(1-Geranyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate

Following the procedure described in Example 1, Step N, but using the methyl ester prepared as described in Step A provides the
10 title compound.

EXAMPLE 12

Preparation of N-[1-(1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis
15 trifluoroacetate

Step A: N-[1-(1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester bis trifluoroacetate

20 Following the procedure described in Example 9, Steps B-D, but using 4-methoxybenzyl chloride in place of 4-nitrobenzylbromide provides the title compound.

25 Step B: N-[1-(1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate

Following the procedure described in Example 1, Step N, but substituting the methyl ester from Step A provides the title compound.

30

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EXAMPLE 13

Preparation of N-[1-(1-(2-Naphthylmethyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis
5 trifluoroacetate

Step A: N-[1-(1-(2-Naphthylmethyl)-1H-imidazol-5-ylacetyl]3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl
ester bis trifluoroacetate
10 Following the procedure described in Example 9, Steps B-D, but using 2-(bromomethyl)naphthylene in place of 4-nitrobenzylbromide provided the title compound.

Step B: N-[1-(1-(2-Naphthylmethyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine bis trifluoroacetate
15 methionine bis trifluoroacetate
Following the procedure described in Example 1, Step N, but using the methyl ester prepared as described in Step A provided the title compound.

20

EXAMPLE 14

Preparation of N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-(β -acetyl amino)alanine trifluoroacetate
25 3(S)-ethyl-prolyl-(β -acetyl amino)alanine trifluoroacetate

Step A: Methyl 2(S)-benzyloxycarbonylamino-3-amino propionate
A solution of 2(S)-benzyloxycarbonylamino-3-aminopropionic acid (2.4 g) in methanol at 0° C was saturated with HCl gas. After stirring for 2 h at 20° C the solution was evaporated to obtain
30 the title compound. ¹H NMR (300 MHz, CD₃OD) δ 7.35 (5H, m), 5.13 (2H, s), 4.50 (1H, m), 3.77 (3H, s), 3.45 (1H, m), 3.22 (1H, m).

Step B: Methyl 2(S)-benzyloxycarbonylamino-3-acetyl amino-propionate

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To a solution of methyl 2(S)-benzyloxycarbonylamino-3-amino propionate (2.5 g) in methylene chloride was added pyridine (20 mL) and acetic anhydride (5 mL). After stirring for 2 h the solution was concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was extracted w/ 50 mL each of 2% potassium hydrogen sulfate, saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate and concentrated in vacuo. Upon evaporation pyridine hydrochloride precipitated and was removed by filtration. The filtrate was evaporated to obtain the title compound. ¹HNMR (300 MHz, CDCl₃) δ 7.28 (5H, s), 6.14 (1H, s), 5.97 (1H, d), 5.10 (2H, s), 4.41 (1H, m), 3.78 (3H, s), 1.93 (3H, s).

Step C: Methyl 2(S)-amino-3-acetylaminopropionate

To a solution of methyl 2(S)-benzyloxycarbonylamino-3-acetylaminopropionate (2.2 g) in ethanolic HCl was added 10% Pd/C (0.3 g) under nitrogen atmosphere. Hydrogen was applied to the mixture at 60 psi for 16 h. The mixture was filtered and concentrated in vacuo. The residue was triturated with diethyl ether to obtain the product. ¹HNMR (300 MHz, CD₃OD) δ 4.20 (1H, m), 3.88 (3H, s), 3.82 (1H, m), 3.60 (1H, m), 1.99 (3H, s).

Step D: N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-(β-acetyl amino)alanine methyl ester trifluoroacetate

Following the procedures outlined in Examples 1 and 2, but substituting the methyl 2(S)-amino-3-acetylaminopropionate of Step C for methionine methyl ester hydrochloride in Example 1, Step K, the title compound is prepared.

Step E: N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-(β-acetyl amino)alanine trifluoroacetate

The title compound is prepared following the method described in Example 1, Step N.

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EXAMPLE 15

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified
5 bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and RAS-
CAIL) were prepared as described by Schaber *et al.*, *J. Biol. Chem.*
265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992)
and Gibbs *et al.*, *PNAS U.S.A.* 86:6630-6634 (1989), respectively.
Bovine FPTase was assayed in a volume of 100 μ l containing 100 mM *N*-
10 (2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH
7.4, 5 mM MgCl₂, 5 mM dithiothreitol (DTT), 100 mM [³H]-farnesyl
diphosphate ([³H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM
Ras-CVLS and 10 μ g/ml FPTase at 31°C for 60 min. Reactions were
initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol.
15 Precipitates were collected onto filter-mats using a TomTec Mach II cell
harvester, washed with 100% ethanol, dried and counted in an LKB β -
plate counter. The assay was linear with respect to both substrates,
FPTase levels and time; less than 10% of the [³H]-FPP was utilized
during the reaction period. Purified compounds were dissolved in 100%
20 dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay.
Percentage inhibition is measured by the amount of incorporation of
radioactivity in the presence of the test compound when compared to the
amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer *et al.*,
25 *Biochemistry* 32:5167-5176 (1993). Human FPTase activity was assayed
as described above with the exception that 0.1% (w/v) polyethylene
glycol 20,000, 10 μ M ZnCl₂ and 100 nM Ras-CVIM were added to the
reaction mixture. Reactions were performed for 30 min., stopped with
100 μ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed
30 as described above for the bovine enzyme.

The compounds of the instant invention were tested for
inhibitory activity against human FPTase by the assay described above
and were found to have IC₅₀ of < 10 μ M.

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EXAMPLE 16

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, *Cancer Research* 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[³⁵S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, *J. Virol.* 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

30

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EXAMPLE 17

In vivo growth inhibition assay

5 To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

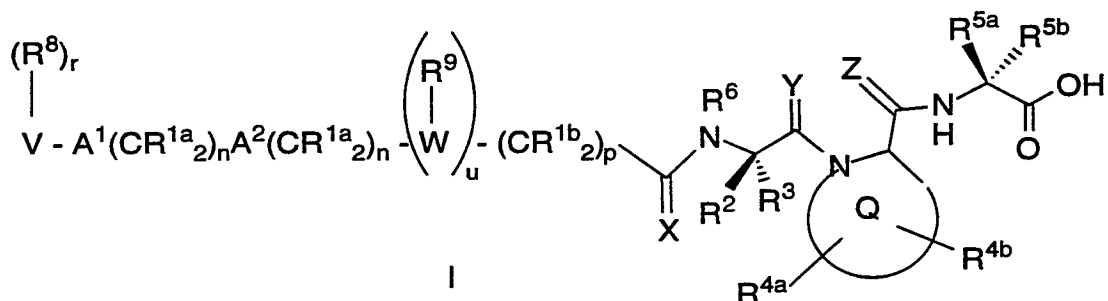
10 Rat 1 cells transformed with either v-*ras*, v-*raf*, or v-*mos* are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an
15 appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16
20 days after the cultures are seeded and comparisons are made.

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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase having the Formula I:

5



wherein:

R^{1a} and R^{1b} are independently selected from:

- 10 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-,
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-
 NR¹⁰-;

20 R² and R³ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
- 25 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl,
 C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-.

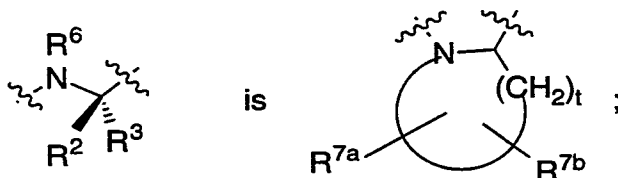
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CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and

- d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that



R^4a , R^4b , R^7a and R^7b are independently selected from:

- 15 a) hydrogen,
 b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$,
 20 or $R^{11}OC(O)NR^{10}-$, and
 d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

25 R^5a and R^5b are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 30 i) methionine sulfoxide, or
 ii) methionine sulfone,

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- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br,
 (R¹⁰)₂NC(O)-, NO₂, R¹⁰O-, R¹¹S(O)_m-,
 5 R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and
 C₁-C₂₀ alkyl,
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 10 C₁₀ cycloalkyl; or

R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon
 atoms is optionally replaced by a moiety selected from: O, S(O)_m,
 -NC(O)-, and -N(COR¹⁰)- ;

15 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- a) hydrogen,
 20 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl,
 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 25 heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F,
 Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-
 C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹⁰OC(O)NH-;
 30 R⁹ is selected from:
 a) hydrogen,
 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-

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(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

X, Y and Z are independently H₂ or O;

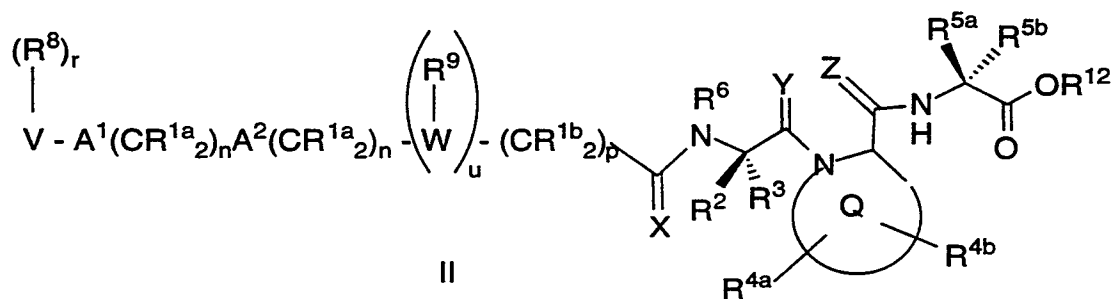
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- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 5 s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1;

or a pharmaceutically acceptable salt thereof.

10

2. A prodrug of a compound which inhibits farnesyl-protein transferase, the prodrug which is illustrated by the formula II:



15 wherein:

R^{1a} and R^{1b} are independently selected from:

- hydrogen,
- aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 20 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-;
- C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-,
 25 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-
 NR¹⁰-;

R² and R³ are independently selected from:

- a side chain of a naturally occurring amino acid.

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b) an oxidized form of a side chain of a naturally occurring amino acid which is:

- i) methionine sulfoxide, or
- ii) methionine sulfone, and

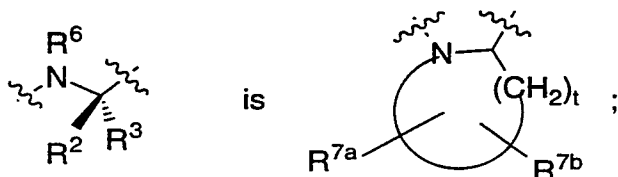
c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

15 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



20 R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

5 R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 10 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br, (R¹⁰)₂NC(O)-, NO₂, R¹⁰O-, R¹¹S(O)_m-,
 15 R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-
 20 C₁₀ cycloalkyl; or

R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

25

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- a) hydrogen,
 30 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

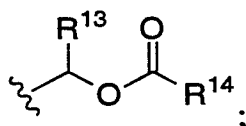
R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

R¹² is

- a) substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₅-C₈ cycloalkyl, or substituted or unsubstituted cyclic amine, wherein the substituted alkyl, cycloalkyl or cyclic amine is substituted with 1 or 2 substituents independently selected from:
- 1) C₁-C₆ alkyl,
 - 2) aryl,
 - 3) heterocycle,
 - 4) -N(R¹¹)₂,
 - 5) -OR¹⁰, or
- b)

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R^{13} is independently selected from hydrogen and C_1 - C_6 alkyl;

5 R^{14} is independently selected from C_1 - C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$,
 $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{10}-$, $-\text{NR}^{10}\text{C}(\text{O})-$, O , $-\text{N}(\text{R}^{10})-$,
 $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$, $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$, or $\text{S}(\text{O})_m$;

10

Q is a substituted or unsubstituted nitrogen-containing C_4 - C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C_5 - C_7 saturated ring;

15 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced
 20 with a heteroatom selected from O, S, and N, and
- e) C_2 - C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $\text{S}(\text{O})_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $\text{S}(\text{O})_m$;

25 W is a heterocycle;

X , Y and Z are independently H_2 or O ;

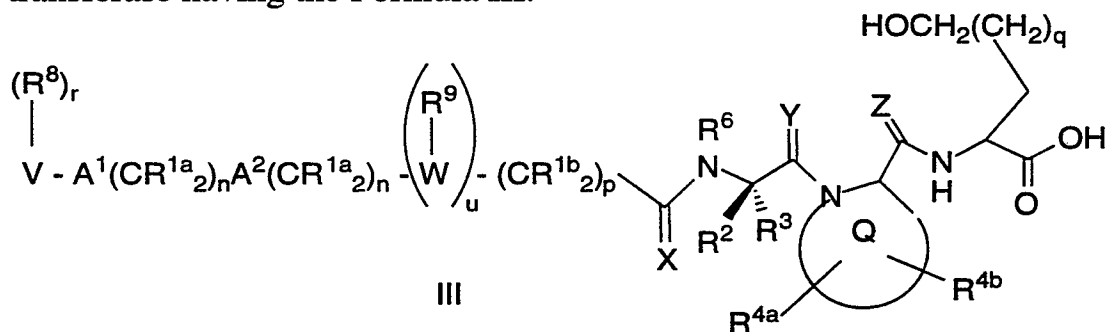
30 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;

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s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1;

5 or a pharmaceutically acceptable salt thereof.

3. A compound which inhibits farnesyl-protein transferase having the Formula III:



10

wherein:

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

25

R² and R³ are independently selected from:

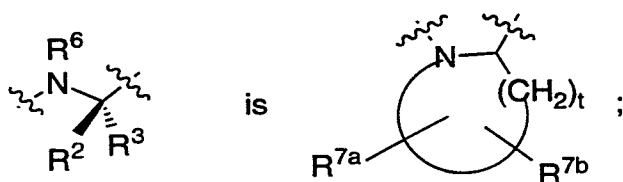
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or

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- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

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R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl,
 5 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F,
 10 Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-
 C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-
 (NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 20 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-;

- 25 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
 aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

- 30 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

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Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

5 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- 10 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

15 W is a heterocycle;

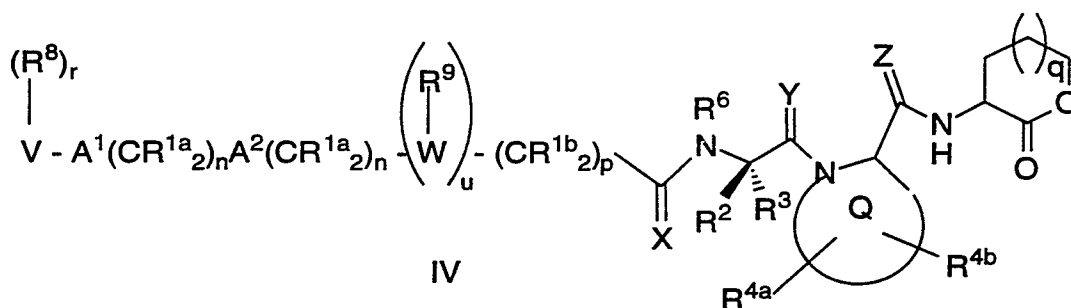
X, Y and Z are independently H₂ or O;

- m is 0, 1 or 2;
- 20 n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- q is 0, 1 or 2;
- r is 0 to 5, provided that r is 0 when V is hydrogen;
- s is 4 or 5;
- 25 t is 3, 4 or 5; and
- u is 0 or 1;

or a pharmaceutically acceptable salt thereof.

- 30 4. A prodrug of a compound which inhibits farnesyl-protein transferase, the prodrug which is illustrated by the formula IV:

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wherein:

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- 5 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;
- 15 R² and R³ are independently selected from:
 - a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - 20 ii) methionine sulfone, and
 - c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

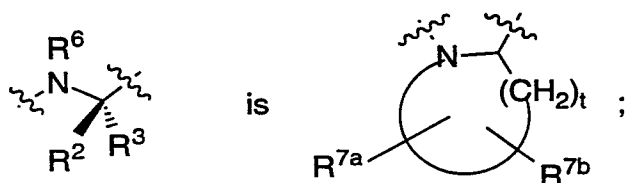
wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- 25

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- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



10

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

25

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 30

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- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be a C₅-C₇ saturated ring;

V is selected from:

- a) hydrogen,
 b) heterocycle,
 c) aryl,

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- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,
- provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

X, Y and Z are independently H₂ or O;

10

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2;

15 r is 0 to 5, provided that r is 0 when V is hydrogen;

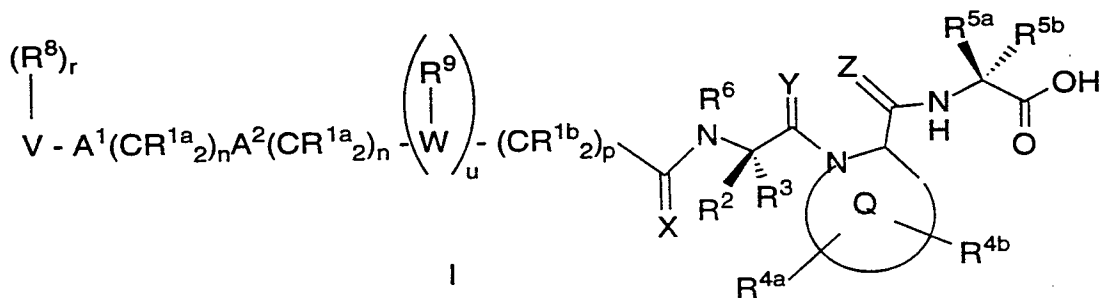
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

20 or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 of the formula I:



25 wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

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- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or alkenyl,
- c) C_1 - C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

5

R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 10 i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocyclic group,

wherein the substituent is selected from F, Cl, Br, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl, and
- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3 - C_{10} cycloalkyl; or

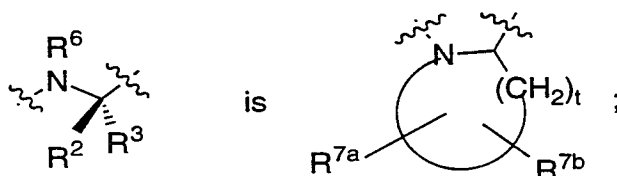
15

20

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that

25



R^4a and R^7a are independently selected from:

- a) hydrogen,

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- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 5 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;
- 10

R^{4b} and R^{7b} are hydrogen;

R^{5a} is selected from:

- 15 a) a side chain of a naturally occurring amino acid, wherein the amino acid is selected from methionine and glutamine,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 20 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
- wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- 25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;
- 30

R^{5b} is selected from:

- a) hydrogen, and
- b) C₁-C₃ alkyl;

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R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- 5 a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R⁹ is selected from:

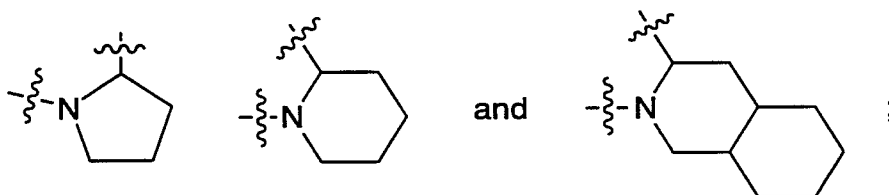
- 15 a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

- 25 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

- 30 Q is selected from:

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5 A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{10}-$, O, $-\text{N}(\text{R}^{10})-$, or $\text{S}(\text{O})_m$;

V is selected from:

- 10 a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
 c) aryl,
 d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 15 e) C_2 - C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $\text{S}(\text{O})_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $\text{S}(\text{O})_m$;

20 W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

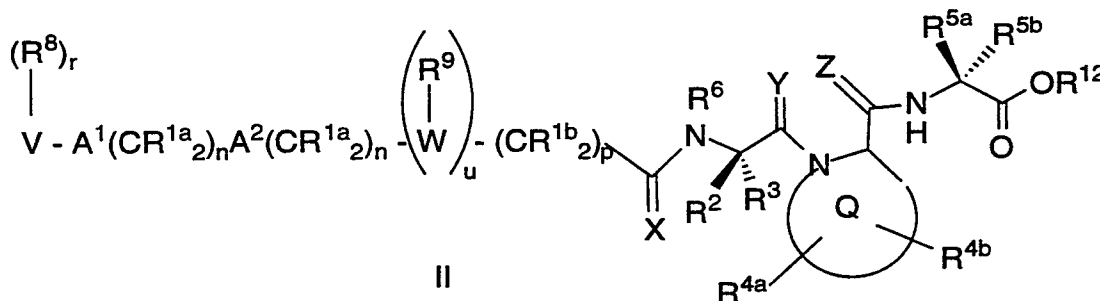
X, Y and Z are independently H_2 or O;

25 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 t is 3, 4 or 5; and
 30 u is 0 or 1;

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or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 2 of the formula II:



wherein:

R¹ᵃ is independently selected from: hydrogen or C₁-C₆ alkyl;

10 R¹ᵇ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or alkenyl,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

15

R² and R³ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

20

25

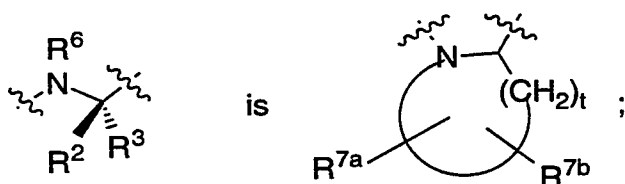
wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)ₘ-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

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- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



10

R^{4a} and R^{7a} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

R^{4b} and R^{7b} are hydrogen;

25

R^{5a} is selected from:

- a) a side chain of a naturally occurring amino acid, wherein the amino acid is selected from methionine and glutamine,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 30 i) methionine sulfoxide, or

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- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 - wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R^{5b} is selected from:

- a) hydrogen, and
- b) C₁-C₃ alkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

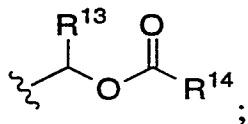
R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

R¹² is

- a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

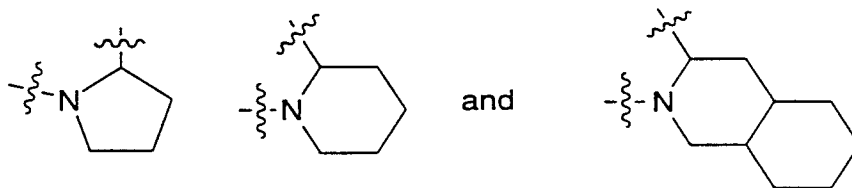
b)



R¹³ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹⁴ is independently selected from C₁-C₆ alkyl;

Q is selected from:



- 134 -

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

5 V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,
thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl,
isoquinolinyl, and thienyl,
- 10 c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced
with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl, and

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if

15 A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,
thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or
isoquinolinyl;

20

X, Y and Z are independently H₂ or O;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

25 p is 0, 1, 2, 3 or 4;

r is 0 to 5, provided that r is 0 when V is hydrogen;

t is 3, 4 or 5; and

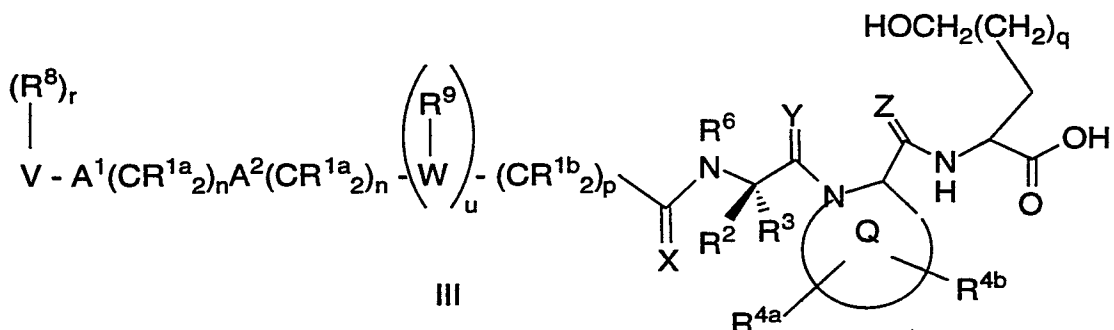
u is 0 or 1;

30 or the pharmaceutically acceptable salts thereof.

7. The compound according to Claim 3 of the formula

III:

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wherein:

5 R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

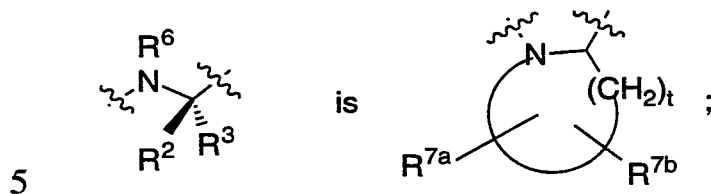
R² and R³ are independently selected from:

- 15 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
 20 C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 25 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

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R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a} and R^{7a} are independently selected from:

- 10
- a) hydrogen,
 - b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃- C₁₀ cycloalkyl;

20 R^{4b} and R^{7b} are hydrogen;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- 25
- a) hydrogen,
 - b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5 R⁹ is selected from:

- a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or
 10 R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

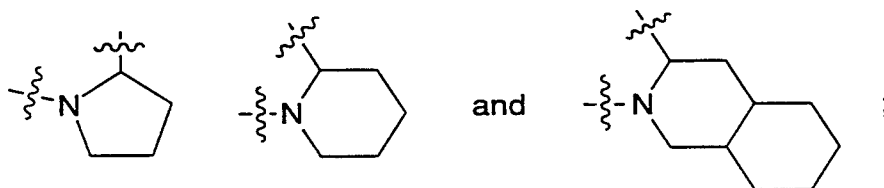
15

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

20

Q is selected from:



25

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

- a) hydrogen,

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b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

5 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C₂-C₂₀ alkenyl, and

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

10

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

15 X, Y and Z are independently H₂ or O;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

20 q is 0, 1 or 2;

r is 0 to 5, provided that r is 0 when V is hydrogen;

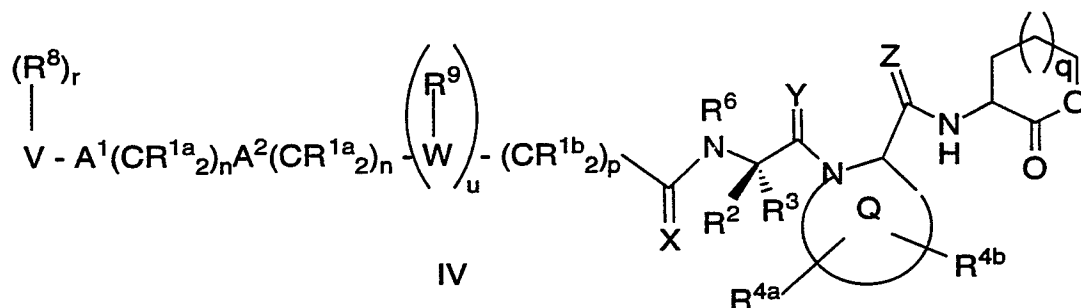
t is 3, 4 or 5; and

u is 0 or 1;

25 or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 4 of the formula
Formula IV:

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wherein:

5 R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 10 a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

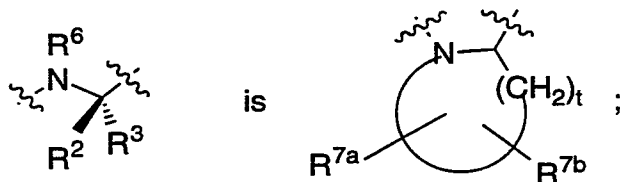
R² and R³ are independently selected from:

- 15 a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone,
c) substituted or unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
20 C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
wherein the substituent is selected from F, Cl, Br,
NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
-N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

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R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a} and R^{7a} are independently selected from:

- 10
- hydrogen,
 - C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - 15 aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - 20 C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

20 R^{4b} and R^{7b} are hydrogen;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- 25
- hydrogen,
 - C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5 R⁹ is selected from:

- a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or
 10 R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

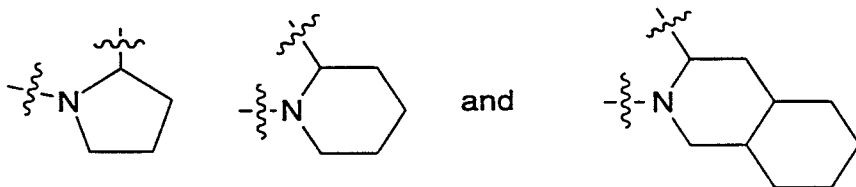
15

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

20

Q is selected from:



25

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

30

- a) hydrogen,

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- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
- c) aryl,
- 5 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl, and

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

10

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

15 X, Y and Z are independently H₂ or O;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

20 q is 0, 1 or 2;

r is 0 to 5, provided that r is 0 when V is hydrogen;

t is 3, 4 or 5; and

u is 0 or 1;

25 or a pharmaceutically acceptable salt thereof.

9. A compound which inhibits farnesyl-protein transferase which is:

30 N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine

35

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N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

5 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone isopropyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfoxide

10 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfoxide isopropyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine sulfone

15 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

20 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

25 N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

30 N-[1-Glycyl-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

35 N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

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N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

5 N-[1-[3-(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)propionyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester

10 N-[2(S)-(1H-Imidazol-4-ylacetyl-amino)-3(S)-methylpentyl]-prolyl-methionine

15 N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S-)ylmethyl]-prolyl-methionine methyl ester

N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S-)ylmethyl]-prolyl-methionine

20 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-prolyl-methionine

25 N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

30 N-[1-(1H-Imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

35 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

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N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester

5 N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

10 N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

N-[1-Glycyl-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

15 N-[1-[1-(4-Nitrobenzyl)-1H-imidazol-4-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

20 N-[1-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-(1-(1-Farnesyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine

25 N-[1-(1-(1-Geranyl)-1H-imidazol-5-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

N-[1-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

30 N-[1-[1-(2-Naphthylmethyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine or

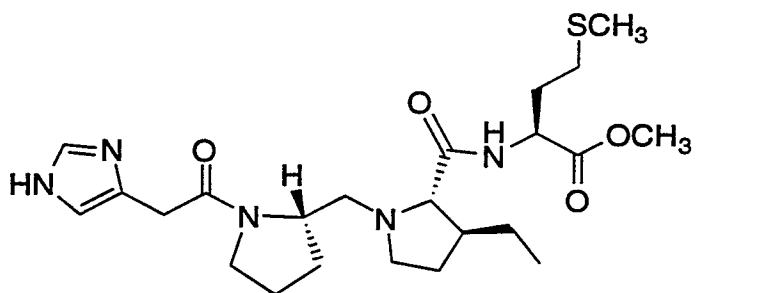
35 N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-(β -acetylamino)alanine

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or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9 which inhibits
5 farnesyl-protein transferase which is:

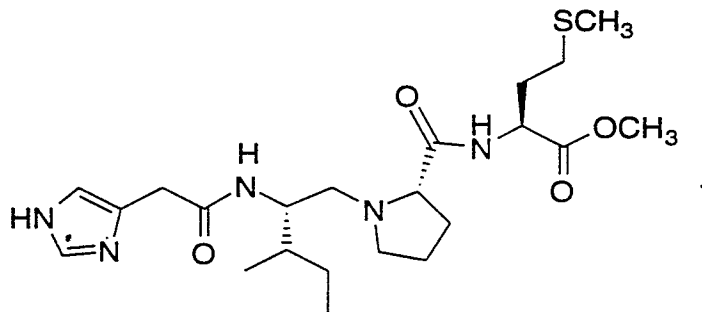
N-[1-(1H-Imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-
prolyl-methionine methyl ester



or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 9 which inhibits
15 farnesyl-protein transferase which is:

N-[(1H-Imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-
methionine methyl ester



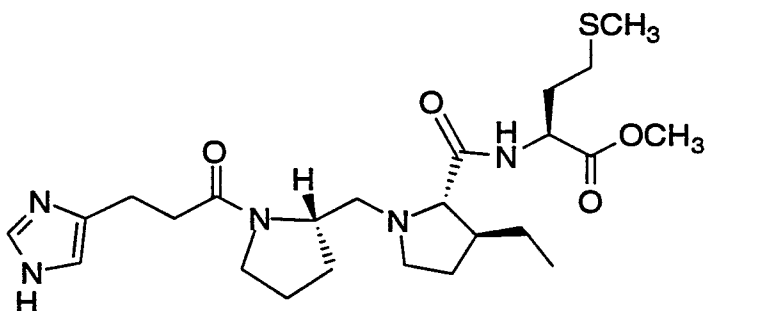
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or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 9 which inhibits farnesyl-protein transferase which is:

5

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester



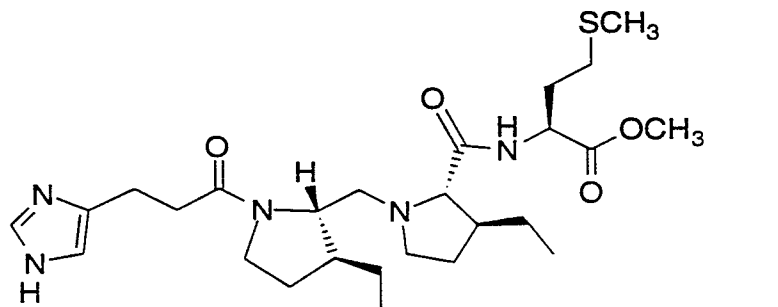
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or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 9 which inhibits farnesyl-protein transferase which is:

15

N-[1-(3-[1H-Imidazol-4-yl]propionyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester



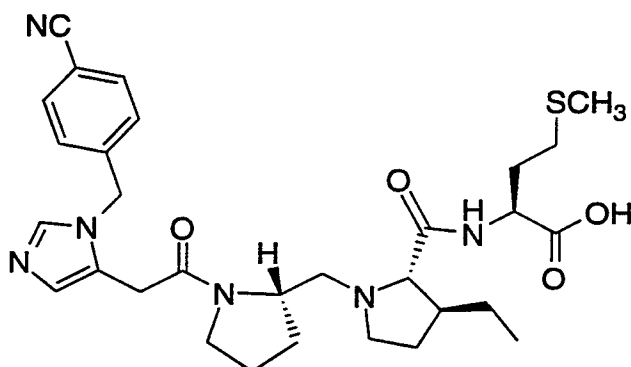
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or a pharmaceutically acceptable salt thereof.

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14. The compound according to Claim 9 which inhibits farnesyl-protein transferase which is:

- 5 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine

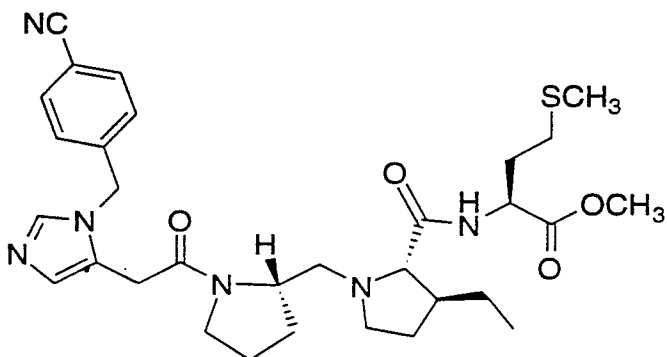


or a pharmaceutically acceptable salt thereof.

10

15. The compound according to Claim 9 which inhibits farnesyl-protein transferase which is:

- 15 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine methyl ester

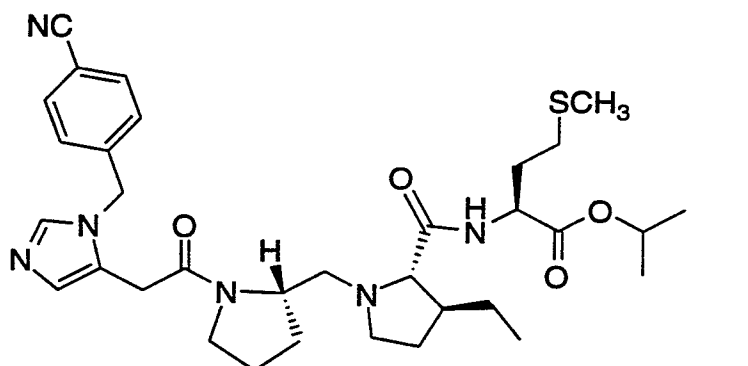


or a pharmaceutically acceptable salt thereof.

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16. The compound according to Claim 9 which inhibits farnesyl-protein transferase which is:

- 5 N-[1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl-methionine isopropyl ester



- 10 17. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

- 15 18. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 4.

- 20 19. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

- 25 20. A method for inhibiting farnesylation of Ras protein which comprises administering to a mammal in need thereof a therapeutically effective amount of the composition of Claim 17.

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21. A method for inhibiting farnesylation of Ras protein which comprises administering to a mammal in need thereof a therapeutically effective amount of the composition of Claim 18.

5 22. A method for inhibiting farnesylation of Ras protein which comprises administering to a mammal in need thereof a therapeutically effective amount of the composition of Claim 19.

10 23. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

15 24. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

20 25. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 19.

25 26. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

27. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

30 28. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

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29. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

5 30. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.