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(54) **INHIBITEURS DE FARNESYL-PROTEINE TRANSFERASE**

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

(57) L'invention concerne des composés qui inhibent la farnésylprotéine transférase (FTase) et la farnésylation de la protéine Ras oncogène. L'invention a en outre pour objet des compositions chimiothérapeutiques contenant les composés de cette invention et des procédés pour inhiber la farnésylprotéine transférase et la farnésylation de la protéine Ras oncogène.

(57) The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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(21) International Application Number: PCT/US97/04713 (22) International Filing Date: 27 March 1997 (27.03.97) (30) Priority Data: 60/014,793 3 April 1996 (03.04.96) US 9609667.2 9 May 1996 (09.05.96) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GRAHAM, Samuel, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WILLIAMS, Theresa, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WAI, John, S. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE (57) Abstract <p>The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.</p>		

- 1 -

TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

5 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
10 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.
15 Willumsen, *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
20 stimulatory 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
25 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
30 transferase, which 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 undergo post-translational farnesylation.

- 2 -

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
5 farnesylated. James, et al., have also 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
10 other aspects of their transformed phenotype. It has also been 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
15 inhibitor of farnesyl-protein transferase blocks the growth of *ras*-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 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
25 farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl 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
30 biosynthesis 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

- 3 -

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 farnesylation of proteins. It is a further object of this invention to

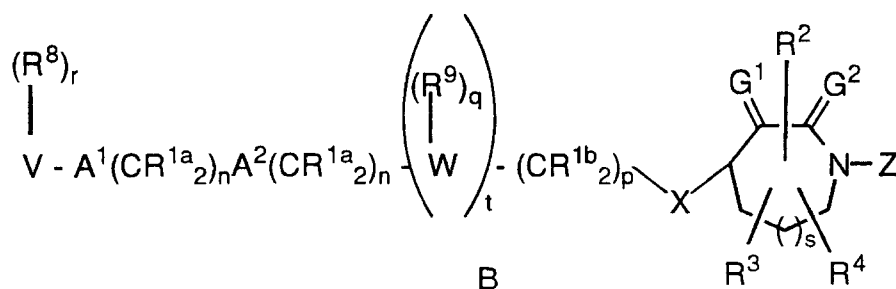
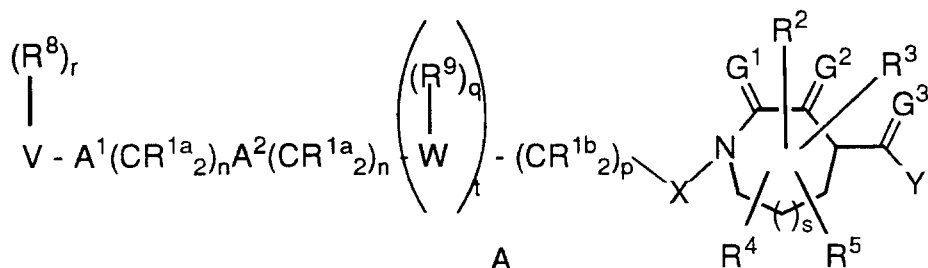
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develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

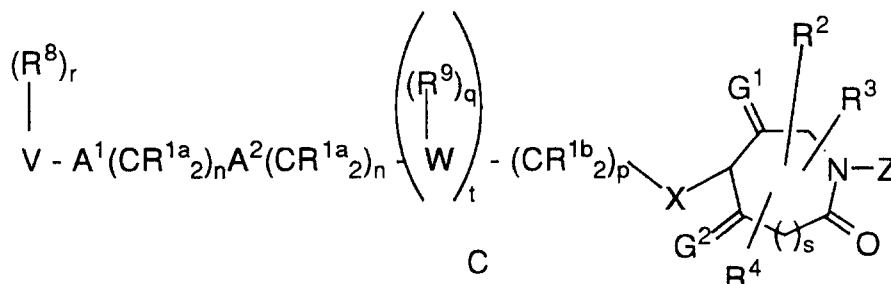
5 SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic piperidinone-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in
 10 animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

15 The compounds of this invention are illustrated by the formulae A, B and C:

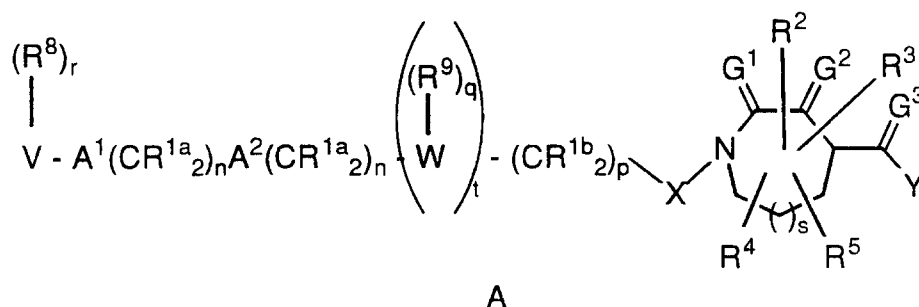


- 5 -



DETAILED DESCRIPTION OF THE INVENTION

- The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



wherein:

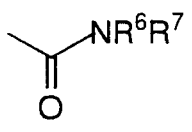
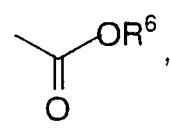
R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(O)-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(O)-, CN,

- 6 -

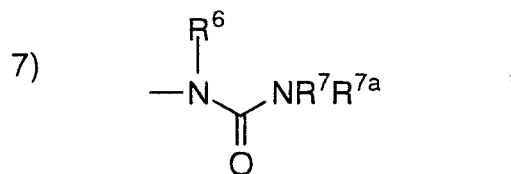
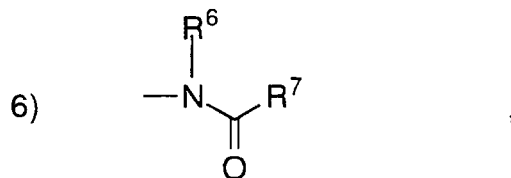
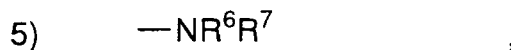
$(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, and $R^{11}OC(O)-NR^{10}-$;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C₁₋₈ alkyl, unsubstituted or substituted C₂₋₈ alkenyl, unsubstituted or substituted C₂₋₈ alkynyl, unsubstituted or substituted aryl,

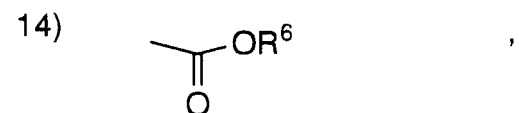
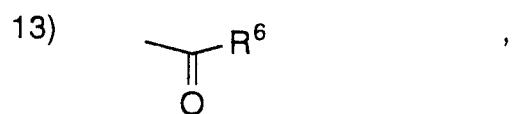
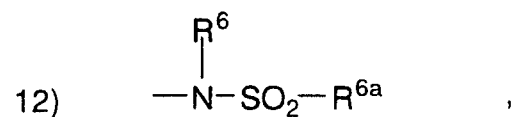
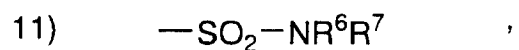
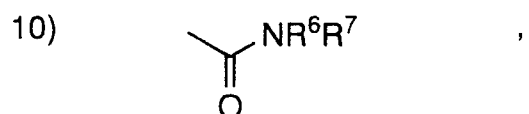
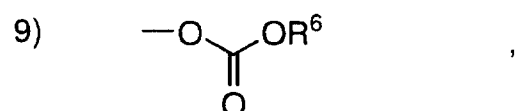
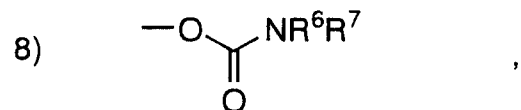
unsubstituted or substituted heterocycle,  and ,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁₋₄ alkyl,
 - b) $(CH_2)_pOR^6$,
 - c) $(CH_2)_pNR^6R^7$,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁₋₄ alkyl,
 - h) SR^{6a} , $S(O)R^{6a}$, SO_2R^{6a} ,
- 2) C₃₋₆ cycloalkyl,
- 3) OR^6 ,
- 4) SR^{6a} , $S(O)R^{6a}$, or SO_2R^{6a} ,



- 7 -



- 5 R² and R³ are attached to the same C atom and are combined to form - (CH₂)_u - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

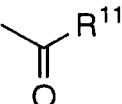
R⁴ and R⁵ are independently selected from H and CH₃;

10

and any two of R², R³, R⁴ and R⁵ are optionally attached to the same carbon atom;

- 8 -

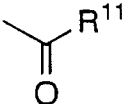
R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

- 5
- a) C₁₋₄ alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) ,
 - f) —SO₂R¹¹, or
 - g) N(R¹⁰)₂; or

10

R⁶ and R⁷ may be joined in a ring;
 R⁷ and R^{7a} may be joined in a ring;

15 R^{6a} is selected from: C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) ,
 - f) —SO₂R¹¹, or
 - g) N(R¹⁰)₂;
- 20

R⁸ is independently selected from:

- a) hydrogen,
- 25 b) aryl, heterocycle, C_{3-C10} cycloalkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,

- 9 -

- $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, NO_2 , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NH-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;
- 5 R^9 is selected from:
 a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, NO_2 , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;
- 20 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;
- R^{11} is independently selected from C₁-C₆ alkyl and aryl;
- 25 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ and $S(O)_m$;
- 30 G^1 and G^2 are independently oxygen or absent, provided that at least one of G^1 and G^2 is oxygen;
- G^3 is oxygen or H₂;

- 10 -

V is selected from:

- a) hydrogen,
- b) heterocycle,
- 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,

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;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

- 15 Y is unsubstituted or substituted aryl or unsubstituted or
substituted heterocycle, wherein the substituted aryl or
substituted heterocycle is substituted with one or
more of:

- 1) C₁-4 alkyl, unsubstituted or substituted with:
 - 20 a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - 25 f) -S(O)_mR^{6a}, or
 - g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR⁶,
- 30 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 9) -S(O)_mR^{6a},

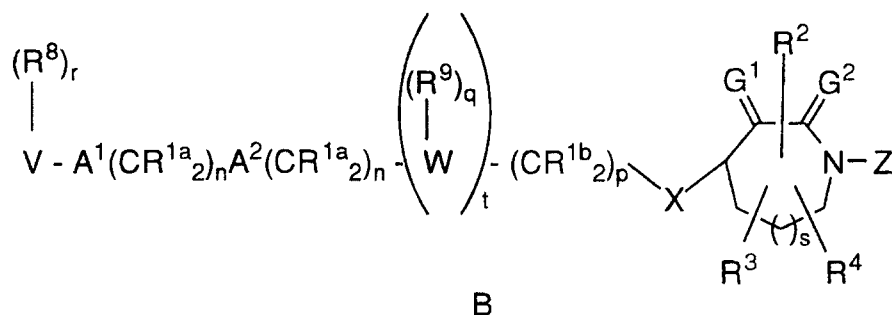
- 11 -

- 10) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 11) $\text{C}_3\text{-C}_6$ cycloalkyl;

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

or the pharmaceutically acceptable salts thereof.

- 15 In a second embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula B:



wherein:

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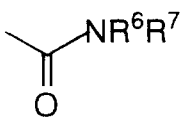
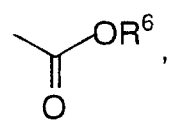
R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$,
 25 $\text{CN}(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN , NO_2 , $\text{R}^{10}\text{C}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
 c) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl wherein the substituent on the substituted $\text{C}_1\text{-C}_6$ alkyl is selected from

- 12 -

5 unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;

R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

10 unsubstituted or substituted heterocycle,  and ,
 wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - 15 c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁-4 alkyl,
 - 20 h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},

- 13 -

- 5) $\text{—NR}^6\text{R}^7$,
- 6) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—R}^7 \end{array}$,
- 7) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—NR}^7\text{R}^{7a} \end{array}$,
- 8) $\begin{array}{c} \text{—O—C(=O)—NR}^6\text{R}^7 \end{array}$,
- 9) $\begin{array}{c} \text{—O—C(=O)—OR}^6 \end{array}$,
- 10) $\begin{array}{c} \text{—C(=O)—NR}^6\text{R}^7 \end{array}$,
- 11) $\text{—SO}_2\text{—NR}^6\text{R}^7$,
- 12) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—SO}_2\text{—R}^{6a} \end{array}$,
- 13) $\begin{array}{c} \text{—C(=O)—R}^6 \end{array}$,
- 14) $\begin{array}{c} \text{—C(=O)—OR}^6 \end{array}$,
- 15) N_3 ,
- 16) F , or
- 17) perfluoro- C_{1-4} -alkyl; or

- 14 -

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

5

R^4 is selected from H and CH_3 ;

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

10

R^6 , R^7 and R^{7a} are independently selected from: H; C_1 -4 alkyl, C_3 -6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

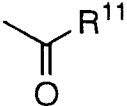
15

a) C_1 -4 alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f) $-\text{SO}_2R^{11}$, or

g) $N(R^{10})_2$; or

20

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

25

R^{6a} is selected from: C_1 -4 alkyl, C_3 -6 cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

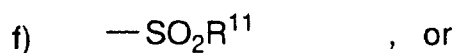
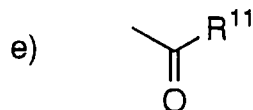
a) C_1 -4 alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

- 15 -



R^8 is independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN, NO₂, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NH}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or
- 15 $\text{R}^{10}\text{OC}(\text{O})\text{NH}-$;

R^9 is selected from:

- a) hydrogen,
- 20 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN, NO₂, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$;
- 25

R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

30

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

- 16 -

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 , $-\text{N}(\text{R}^{10})-$,
 $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$, $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$ and $\text{S}(\text{O})_m$;

5

G^1 and G^2 are independently oxygen or absent provided that at least one
of G^1 and G^2 is oxygen;

V is selected from:

10

- a) hydrogen,
- b) heterocycle,
- 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,

15

- 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 $\text{S}(\text{O})_m$;

20

W is a heterocycle;

X is a bond, $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})_m-$;

Z is selected from:

25

- 1) a unsubstituted or substituted group selected from aryl,
heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and
heteroarylsulfonyl, wherein the substituted group is substituted
with one or more of the following:

30

- a) C_1 -4 alkyl, unsubstituted or substituted with:
 C_1 -4 alkoxy, NR^6R^7 , C_3 -6 cycloalkyl, aryl,
heterocycle, HO , $-\text{S}(\text{O})_m\text{R}^{6a}$, or $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
- b) aryl or heterocycle,
- c) halogen,
- d) OR^6 ,

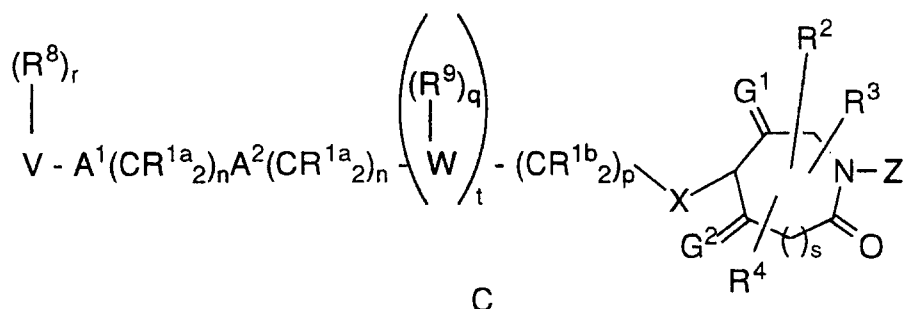
- 17 -

- 5 e) NR^6R^7 ,
 f) CN ,
 g) NO_2 ,
 h) CF_3 ;
 i) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 j) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 k) C3-C6 cycloalkyl; and
 2) unsubstituted C1-C6 alkyl, substituted C1-C6 alkyl,
 10 unsubstituted C3-C6 cycloalkyl or substituted C3-C6
 cycloalkyl, wherein the substituted C1-C6 alkyl and substituted
 C3-C6 cycloalkyl is substituted with one or two of the
 following:
 a) C1-4 alkoxy,
 b) NR^6R^7 ,
 15 c) C3-6 cycloalkyl,
 d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
 e) HO ,
 f) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 g) halogen, or
 20 h) perfluoroalkyl;

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

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

- 18 -



wherein:

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

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;
- 15

- R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl,
- 20 unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycle, $\begin{array}{c} \text{NR}^6\text{R}^7 \\ | \\ \text{O} \end{array}$ and $\begin{array}{c} \text{OR}^6 \\ | \\ \text{O} \end{array}$,

wherein the substituted group is substituted with one or more of:

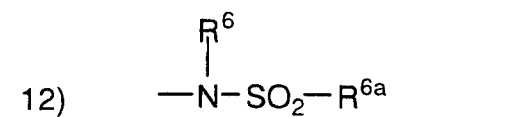
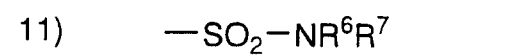
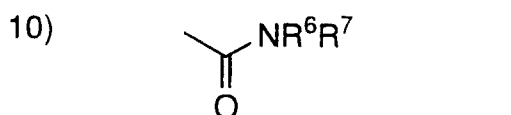
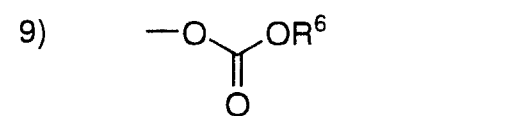
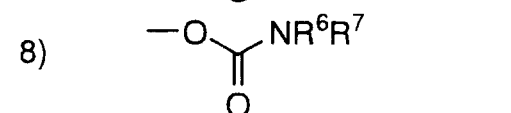
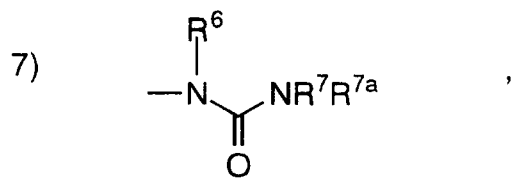
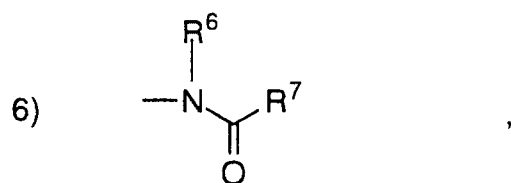
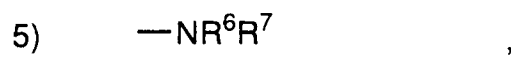
- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - 25 b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,

- 19 -

5

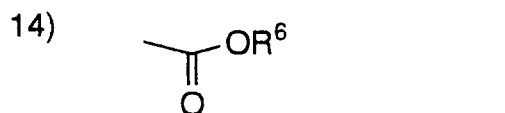
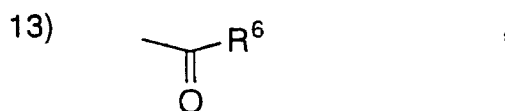
- e) CN,
 f) aryl or heteroaryl,
 g) perfluoro-C₁₋₄ alkyl,
 h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},

- 2) C₃₋₆ cycloalkyl,
 3) OR⁶,
 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



10

- 20 -



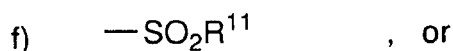
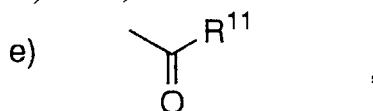
R^2 and R^3 are attached to the same C atom and are combined to form -
 (CH₂)_u - wherein one of the carbon atoms is optionally replaced by a
 5 moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R^4 is selected from H and CH₃;

10 and any two of R^2 , R^3 and R^4 are optionally attached to the same
 carbon atom;

R^6 , R^7 and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆
 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and
 heteroarylsulfonyl, unsubstituted or substituted with:

- 15 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,

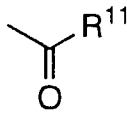


R^6 and R^7 may be joined in a ring;

- 21 -

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

- 5 a) C₁-4 alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) ,
 f) $-\text{SO}_2\text{R}^{11}$, or
 10 g) $\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-
 15 C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$,
 $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN,
 NO₂, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆
 20 alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$,
 $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NH}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$, $\text{R}^{10}_2\text{N}-$
 $\text{C}(\text{NR}^{10})-$, CN, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or
 $\text{R}^{10}\text{OC}(\text{O})\text{NH}-$;

25 R^9 is selected from:

- a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br,
 $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})-$,
 $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, CN, NO₂, $\text{R}^{10}\text{C}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or
 30 $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and

- 22 -

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(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- and S(O)_m;

- 15 G¹ and G² are independently oxygen or absent, provided that if G¹ is oxygen then G² is absent and if s=0, G¹ is oxygen;

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;

30

W is a heterocycle;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

Z is selected from:

- 23 -

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
- 5 a) C₁-4 alkyl, unsubstituted or substituted with:
C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
- b) aryl or heterocycle,
- c) halogen,
- 10 d) OR⁶,
- e) NR⁶R⁷,
- f) CN,
- g) NO₂,
- h) CF₃;
- 15 i) -S(O)_mR^{6a},
- j) -C(O)NR⁶R⁷, or
- k) C₃-C₆ cycloalkyl; and
- 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:
- 20 a) C₁-4 alkoxy,
- b) NR⁶R⁷,
- 25 c) C₃-6 cycloalkyl,
- d) -NR⁶C(O)R⁷,
- e) HO,
- f) -S(O)_mR^{6a},
- g) halogen, or
- 30 h) perfluoroalkyl;
- m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;

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

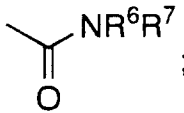
In a preferred embodiment of this invention, the inhibitors
10 of farnesyl-protein transferase are illustrated by the formula B:

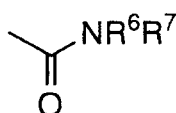
20

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and
- c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$ and $-N(R^{10})_2$;

25 R³ and R⁴ are independently selected from H and CH₃;

- 25 -

R² is H; ; or C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 5 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5) ;

and any two of R², R³, and R⁴ are optionally attached to the same carbon atom;

10

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- 15 b) halogen, or
- c) aryl or heterocycle;

R^{6a} is selected from:

C₁-4 alkyl and C₃-6 cycloalkyl, unsubstituted or substituted with:

- 20 a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

25 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)-, -N(R¹⁰)₂, or
- 30 R¹¹OC(O)NR¹⁰-, and

- 26 -

- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(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)-, -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)-, -N(R¹⁰)₂, or
 15 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;

20

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

V is selected from:

25

- a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
 c) aryl,
 30 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

- 27 -

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

5 G^1 is absent;
 G^2 is oxygen;

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

10

X is $-CH_2-$ or $-C(=O)-$;

Z is selected from:

- 15 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
- 20 a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^6R^7 , C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^{6a}$, or $-C(O)NR^6R^7$,
- b) aryl or heterocycle,
- c) halogen,
- d) OR^6 ,
- e) NR^6R^7 ,
- 25 f) CN,
- g) NO_2 ,
- h) CF_3 ;
- i) $-S(O)_mR^{6a}$,
- j) $-C(O)NR^6R^7$, or
- 30 k) C_3-C_6 cycloalkyl; and
- 2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl, wherein the substituted C_1-C_6 alkyl and substituted

- 28 -

C3-C6 cycloalkyl is substituted with one or two of the following:

- a) C₁-4 alkoxy,
- b) NR⁶R⁷,
- 5 c) C₃-6 cycloalkyl,
- d) -NR⁶C(O)R⁷,
- e) HO,
- f) -S(O)_mR^{6a},
- g) halogen, or
- 10 h) perfluoroalkyl;

m is 0, 1 or 2;

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

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

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

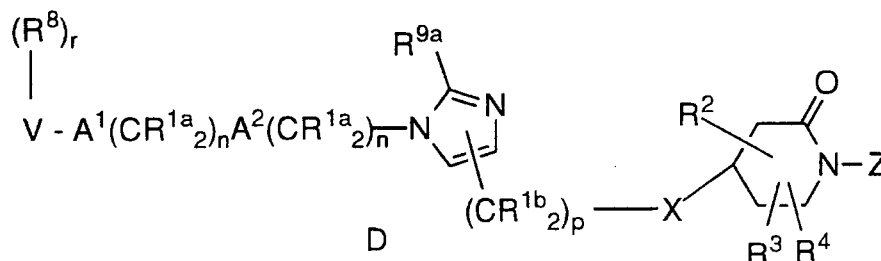
s is 0 or 1;

t is 0 or 1; and

u is 4 or 5;

20 or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula D:



25 wherein:

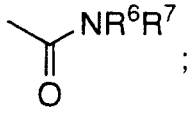
R^{1a} is selected from: hydrogen and C₁-C₆ alkyl;

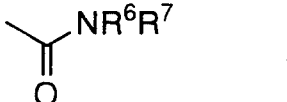
- 29 -

R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl, and
- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

R³ and R⁴ independently selected from H and CH₃;

10 R² is selected from H; ; and C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5) ;

15 and R², R³ and R⁴ are optionally attached to the same carbon atom;

20 R⁶ and R⁷ are independently selected from:
H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- 25 c) aryl or heterocycle;

25 R^{6a} is selected from:

- C₁-4 alkyl and C₃-6 cycloalkyl, unsubstituted or substituted with:
- a) C₁-4 alkoxy,
- 30 b) halogen, or
- c) aryl or heterocycle;

- 30 -

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)-, -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)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{9a} is hydrogen or methyl;

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-, O, -N(R¹⁰)- and 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,
- 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;

- 31 -

X is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$;

Z is selected from:

- 5 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
 - 10 a) C_1 -4 alkyl, unsubstituted or substituted with: C_1 -4 alkoxy, NR^6R^7 , C_3 -6 cycloalkyl, aryl, heterocycle, HO , $-\text{S}(\text{O})_m\text{R}^{6a}$, or $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) OR^6 ,
 - e) NR^6R^7 ,
 - 15 f) CN ,
 - g) NO_2 ,
 - h) CF_3 ;
 - i) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 - j) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 - 20 k) C_3 - C_6 cycloalkyl; and
- 2) unsubstituted C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, unsubstituted C_3 - C_6 cycloalkyl or substituted C_3 - C_6 cycloalkyl, wherein the substituted C_1 - C_6 alkyl and substituted C_3 - C_6 cycloalkyl is substituted with one or two of the
 - 25 following:
 - a) C_1 -4 alkoxy,
 - b) NR^6R^7 ,
 - c) C_3 -6 cycloalkyl,
 - d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
 - 30 e) HO ,
 - f) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 - g) halogen, or
 - h) perfluoroalkyl;

- 32 -

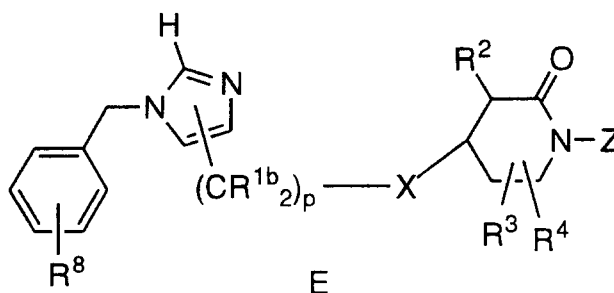
m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4; and
 r is 0 to 5, provided that r is 0 when V is hydrogen;

5

or the pharmaceutically acceptable salts thereof.

In another preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula

10 E:



wherein:

15 R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl, and
- c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

20

R^3 and R^4 independently selected from H and CH_3 ;

R^2 is selected from H; $\begin{array}{c} \text{NR}^6\text{R}^7 \\ \parallel \\ \text{O} \end{array}$; and C_1-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

25

- 1) aryl,
- 2) heterocycle,

- 33 -

- 3) OR^6 ,
 4) SR^{6a} , SO_2R^{6a} , or
 5) NR^6R^7
 $\text{C}(=\text{O})$;

and R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_1 -4 alkyl, C_3 -6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C_1 -4 alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

R^{6a} is selected from:

C_1 -4 alkyl and C_3 -6 cycloalkyl, unsubstituted or substituted with:

- a) C_1 -4 alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

R^8 is independently selected from:

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

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

- 34 -

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

X is -CH₂- or -C(=O)-;

5 Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

- 10 a) C₁-4 alkyl, unsubstituted or substituted with:
C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl,
heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
b) aryl or heterocycle,
c) halogen,
15 d) OR⁶,
e) NR⁶R⁷,
f) CN,
g) NO₂,
h) CF₃;
20 i) -S(O)_mR^{6a},
j) -C(O)NR⁶R⁷, or
k) C₃-C₆ cycloalkyl; and

2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:

- 25 a) C₁-4 alkoxy,
b) NR⁶R⁷,
30 c) C₃-6 cycloalkyl,
d) -NR⁶C(O)R⁷,
e) HO,
f) -S(O)_mR^{6a},
g) halogen, or

- 35 -

h) perfluoroalkyl;

m is 0, 1 or 2; and

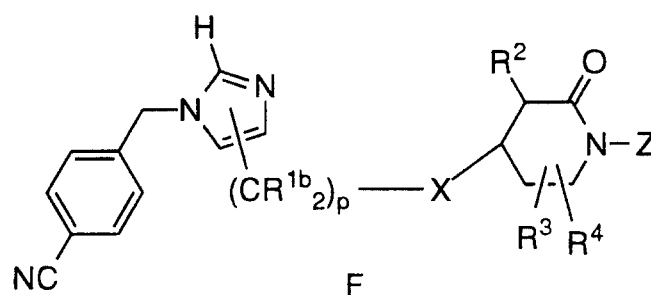
p is 0, 1, 2, 3 or 4;

5

or the pharmaceutically acceptable salts thereof.

In another preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula

10 F:



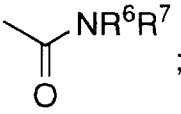
wherein:

15 R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,

20

heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;R³ and R⁴ independently selected from H and CH₃;

R² is selected from H; ; and C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

25

- 1) aryl,
- 2) heterocycle,

- 36 -

- 3) OR^6 ,
 4) SR^{6a} , SO_2R^{6a} , or
 5) NR^6R^7 ;
- $$\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \parallel \\ \text{O} \end{array}$$

and R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_1 -4 alkyl, C_3 -6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C_1 -4 alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

R^{6a} is selected from:

C_1 -4 alkyl and C_3 -6 cycloalkyl, unsubstituted or substituted with:

- a) C_1 -4 alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

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;

X is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$;

Z is selected from:

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

- a) C_1 -4 alkyl, unsubstituted or substituted with:

- C₁₋₄ alkoxy, NR⁶R⁷, C₃₋₆ cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
b) aryl or heterocycle,
c) halogen,
5 d) OR⁶,
e) NR⁶R⁷,
f) CN,
g) NO₂,
h) CF₃;
10 i) -S(O)_mR^{6a},
j) -C(O)NR⁶R⁷, or
k) C₃-C₆ cycloalkyl; and
2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:
a) C₁₋₄ alkoxy,
b) NR⁶R⁷,
20 c) C₃₋₆ cycloalkyl,
d) -NR⁶C(O)R⁷,
e) HO,
f) -S(O)_mR^{6a},
g) halogen, or
25 h) perfluoroalkyl;

m is 0, 1 or 2; and

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

30 or the pharmaceutically acceptable salts thereof.

Examples of the compounds of this invention are as follows:

- 38 -

4-[5-(4-Cyanobenzyl)imidazol-1-ylmethyl]-1-phenyl-2-piperidinone

4-[2-{5-(4-Cyanobenzyl)imidazol-1-yl}ethyl]-1-phenyl-2-piperidinone

5 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-1-phenyl-2-piperidinone

(±)*cis*- 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone

10 (±)*trans*- 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone

4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}carbonyl]-1-phenyl-2-piperidinone and

15

Ethyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate

or a pharmaceutically acceptable salt or optical isomer thereof.

20

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. When any variable (e.g. aryl, heterocycle, R¹, R² etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

25

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

30

- 39 -

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl,
5 phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four
10 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
15 include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny,
20 naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydroquinoliny, thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable
30 monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl,

- 40 -

benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl,
 benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny,
 dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl,
 dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indoliny, indolyl,
 5 isochromanyl, isoindoliny, isoquinoliny, isothiazolyl, naphthyridiny,
 oxadiazolyl, pyridyl, pyraziny, pyrazolyl, pyridaziny, pyrimidiny,
 pyrrolyl, quinazoliny, quinoliny, quinoxaliny,
 tetrahydroisoquinoliny, tetrahydroquinoliny, thiazolyl, thienofuryl,
 thienothienyl, and thienyl.

10 As used herein in the definition of R^2 and R^3 , the term "the substituted group" intended to mean a substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R^2 and R^3 are selected.

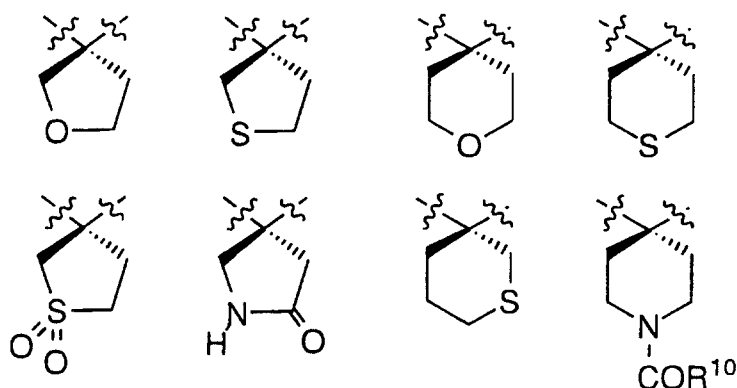
As used herein in the definition of R^6 , R^{6a} , R^7 and R^{7a} ,
 15 the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

20 As used herein in the definition of R^{1a} and R^{1b} , the term substituted aryl includes moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

Preferably, such substituents are selected from the group which includes but is not limited to F, Cl, Br, CF_3 , NH_2 , $N(C_1-C_6 \text{ alkyl})_2$,
 25 NO_2 , CN, $(C_1-C_6 \text{ alkyl})O-$, $-OH$, $(C_1-C_6 \text{ alkyl})S(O)_m-$, $(C_1-C_6 \text{ alkyl})C(O)NH-$, $H_2N-C(NH)-$, $(C_1-C_6 \text{ alkyl})C(O)-$, $(C_1-C_6 \text{ alkyl})OC(O)-$, N_3 , $(C_1-C_6 \text{ alkyl})OC(O)NH-$, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C_1-C_{20} alkyl.

30 When R^2 and R^3 are combined to form $-(CH_2)_u-$, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

5

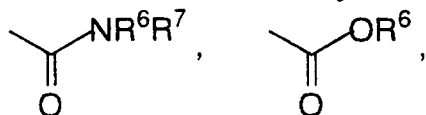


When substituents G¹ and/or G² are "absent," the ring carbons to which G¹ and/or G² are attached are understood to be substituted with two hydrogen atoms and are considered substitutable ring carbon atoms, and are therefore optionally substituted with a substituent selected from R², R³, R⁴ and R⁵.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, -N(R¹⁰)₂, R¹⁰C(O)NR¹⁰- or unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted phenyl, -N(R¹⁰)₂, R¹⁰O- and R¹⁰C(O)NR¹⁰-.

- 42 -

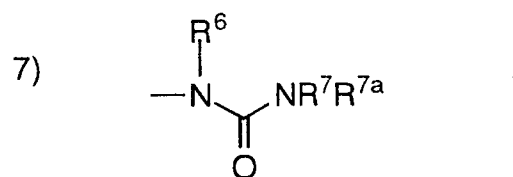
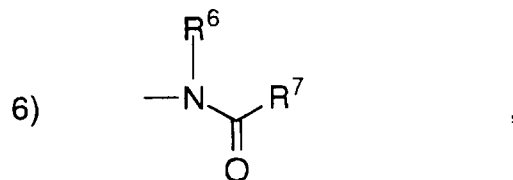
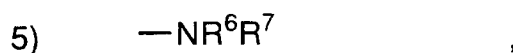
Preferably, R^2 is selected from: H,



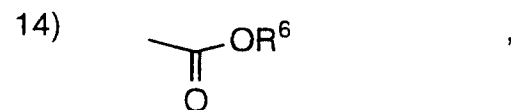
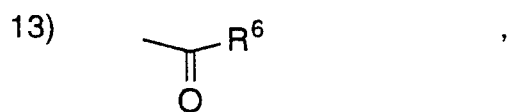
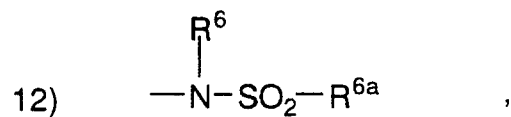
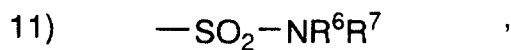
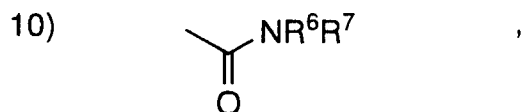
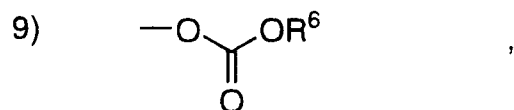
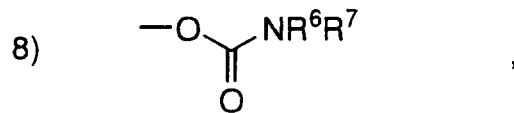
and an unsubstituted or substituted group, the group selected from C1-8 alkyl, C2-8 alkenyl and C2-8 alkynyl;

wherein the substituted group is substituted with one or more of:

- 5 1) aryl or heterocycle, unsubstituted or substituted with:
- a) C1-4 alkyl,
- b) $(\text{CH}_2)_p\text{OR}^6$,
- c) $(\text{CH}_2)_p\text{NR}^6\text{R}^7$,
- d) halogen,
- 10 2) C3-6 cycloalkyl,
- 3) OR^6 ,
- 4) SR^{6a} , S(O)R^{6a} , SO_2R^{6a} ,



- 43 -



5 Preferably, R^3 is selected from: hydrogen and $\text{C}_1\text{—C}_6$ alkyl.
Preferably, R^4 is hydrogen.

Preferably, R^6 , R^7 and R^{7a} is selected from: hydrogen, unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

10 Preferably, R^{6a} is unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^9 is hydrogen or methyl. Most preferably, R^a is hydrogen.

- 44 -

Preferably, R^{10} is selected from H, C_1 - C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, $-C(O)NR^{10}$ -, $-NR^{10}C(O)$ -, O, $-N(R^{10})$ -, $-S(O)_2N(R^{10})$ - and-
 5 $N(R^{10})S(O)_2$ -.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, Y is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or
 10 substituted pyridyl, unsubstituted or substituted furanyl and unsubstituted or substituted thienyl. More preferably, Y is unsubstituted or substituted phenyl.

Preferably, Z is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or
 15 substituted pyridyl, unsubstituted or substituted furanyl, unsubstituted or substituted thienyl, unsubstituted or substituted C_1 - C_6 alkyl and unsubstituted or substituted C_3 - C_6 cycloalkyl. More preferably, Z is unsubstituted or substituted phenyl.

Preferably, W is selected from imidazolyl, imidazolyl, oxazolyl, pyrazolyl, pyrrolidinyl, thiazolyl and pyridyl. More
 20 preferably, W is selected from imidazolyl and pyridyl.

Preferably, in compounds of the formula A, G^1 is oxygen and G^2 is absent.

Preferably, in compounds of the formula B, G^2 is oxygen
 25 and G^1 is absent.

Preferably, in compounds of the formula C, G^1 is oxygen and G^2 is absent.

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

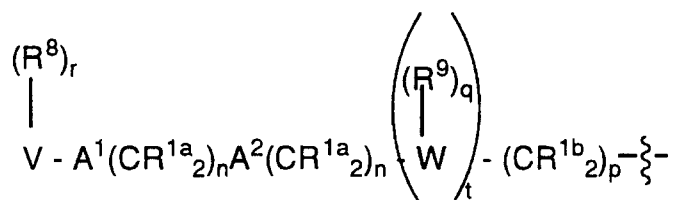
Preferably p is 1, 2 or 3.

30 Preferably s is 0.

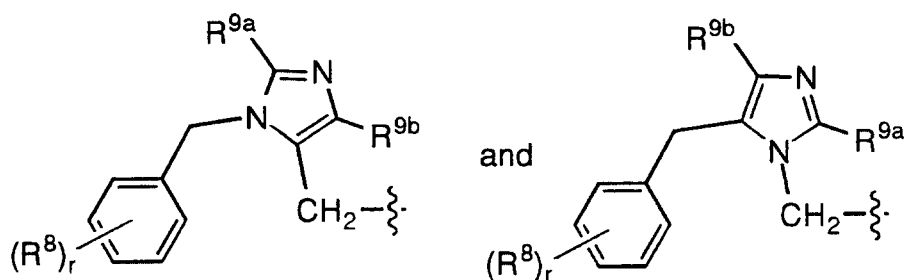
Preferably t is 1.

Preferably, the moiety

- 45 -



is selected from:



5

It is intended that the definition of any substituent or variable (e.g., R^{1a} , R^9 , n , etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, 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, from readily available starting materials.

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 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, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic,

20

- 46 -

fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods.

Generally, the salts are prepared either 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.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-14, 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. Substituents R and R^a, as shown in the Schemes, represent the substituents R², R³, R⁴, and R⁵; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

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 alkylation reactions described in the Schemes.

Synopsis of Schemes 1-14:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. A general synthesis of multiply substituted piperidinones is illustrated in Scheme 1. Thus, a suitably substituted bromoacetonitrile is treated with the sodium salt of diethylmalonate to provide the diester I. Intermediate I is itself deprotonated and alkylated to provide the triester II, which, upon catalytic hydrogenation spontaneously cyclizes to the lactam III. Acidic rearrangement provides the substituted piperidone IV.

As shown in Scheme 2, the piperidone nitrogen may be arylated by employing a triaryl bismuth - copper coupling. The

- 47 -

resulting diester Va can then be converted to the acid VIa and the aldehyde VIIa by procedures well known in the art. Scheme 3 illustrates the analogous preparation of the piperidone having an alkyl substituent on the ring nitrogen.

5 The aldehyde intermediates VII can undergo a Wittig coupling with a protected imidazole to provide compound IX, which can then be catalytically reduced to the intermediate X (Scheme 4). Intermediate X can be deprotected to provide the instant compound XI or it can be further alkylated to eventually provide the instant compound
10 XII.

 Synthesis of compounds of the invention that have an alternate connectivity of the piperidinon-4-ylethyl to the preferred imidazolyl moiety is illustrated in Scheme 4a. The Scheme illustrates use of a suitably substituted protected piperidine XIII, which is either
15 commercially available or may be prepared by techniques known in the art, as the precursor to the 2-piperidinone XV. The nitrogen of intermediate XV may then be functionalized and the suitably substituted imidazolyl moiety incorporated via nucleophilic displacement.

 Schemes 4b and 4c illustrate syntheses of suitably
20 substituted homologous 4-hydroxymethyl 2-piperidinones, that may be utilized in the reactions illustrated in Scheme 4a, starting with commercially available materials.

 Schemes 4d and 4e illustrate alternate syntheses of the homologous piperidinon-4-ylmethyl-1-imidazolyl compounds starting
25 with the previously described intermediate IV.

 The key intermediates whose syntheses are illustrated in Schemes 2, 3a, 3b and 3c may also be utilized in the subsequent reactions.

 Scheme 5 illustrates the preparation of the instant
30 compound wherein the linker between the piperidone and the heterocyclic substituent is a carbonyl. Thus the protected imidazolyl Grignard XVI is reacted with the key intermediate VII to provide the secondary alcohol, which can be oxidized and alkylated as illustrated above to provide the instant compound XVII. Scheme 6 illustrates the

- 48 -

analogous synthesis of the instant compound XVIII wherein the heterocyclic moiety is linked to the piperidone carbon by an acetyl linker.

The carboxylic acid VI can be converted to the
5 phosphonium salt XIX which can then be coupled to a variety of aldehydes, such as XX, as shown in Scheme 7. 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), from the appropriate amino acid. The coupling reaction provides
10 the unsaturated intermediate, which is catalytically reduced to the bisprotected diamine XXI. The product XXI can be deprotected to give the instant compound XXII with trifluoroacetic acid in methylene chloride. The final product XXII is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among
15 others. The product diamine XXII can further be selectively protected to obtain XXIII, which can subsequently be reductively alkylated with a second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XXV can be accomplished by literature procedures.

20 If the phosphonium XIX is coupled with with an aldehyde which also has a protected hydroxyl group, such as XXVI in Scheme 8, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 8, 9). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a
25 variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 9), or tertiary amines.

30 The Boc protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperidones such as XXXII (Scheme 10). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXXII. The aziridine reacted in the presence of

- 49 -

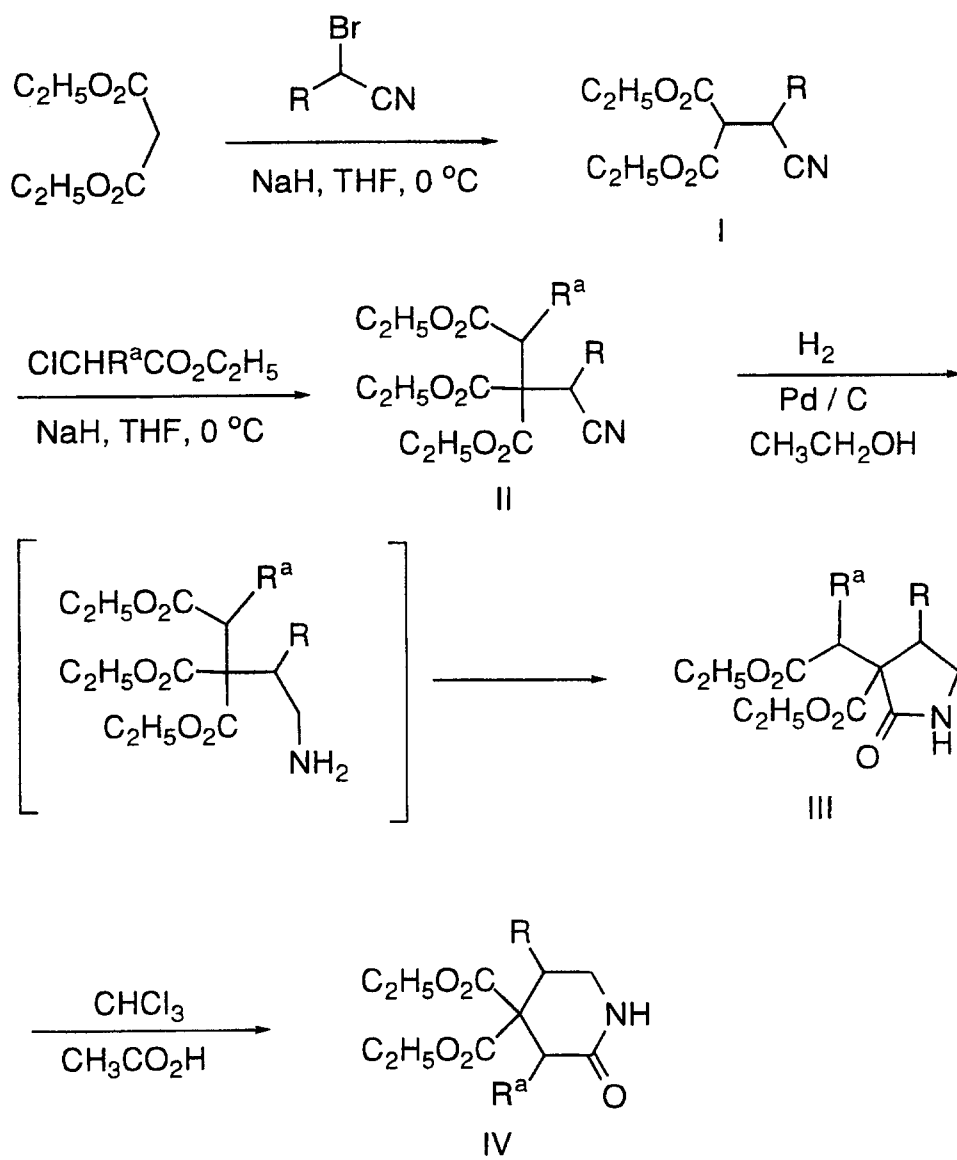
a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

In addition, as illustrated in Scheme 11, the phosphonium XVIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXIII. When R' is an aryl group, catalytic hydrogenation of XXXIII also unmasks the phenol, and the amine group is then deprotected with acid to produce XXXV. Alternatively, when R' is not an aryl group, XXXV is an O-alkylated phenolic amines.

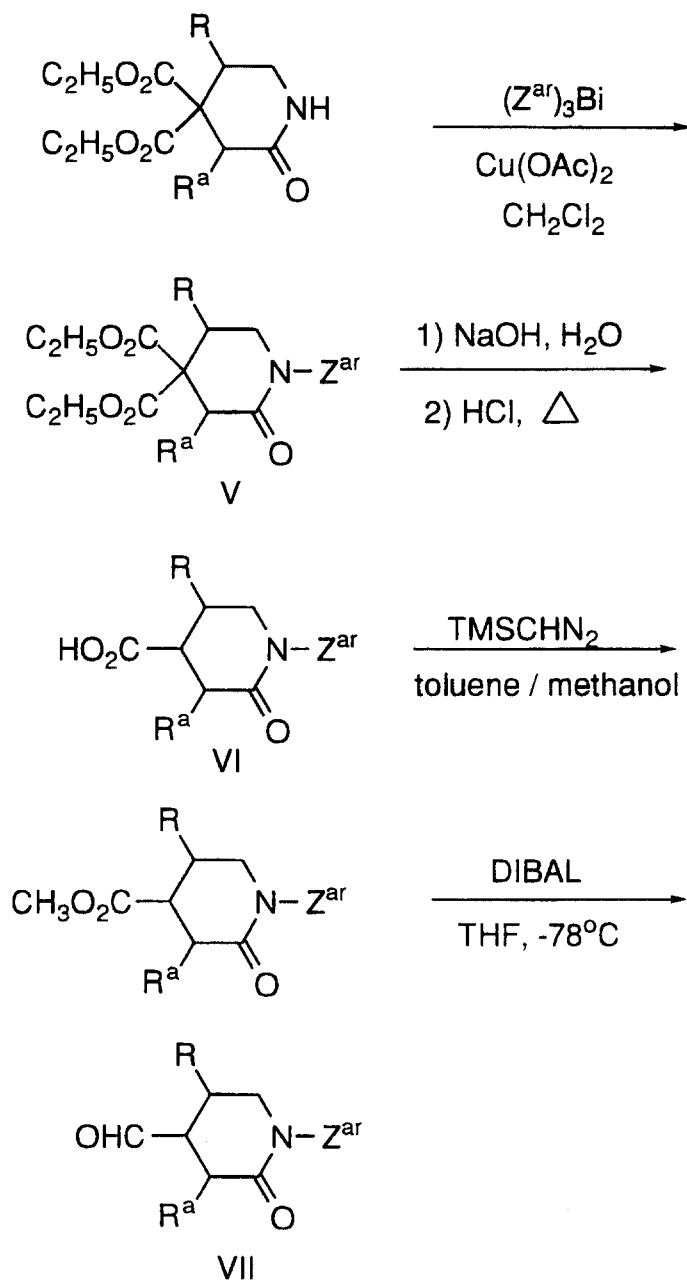
Schemes 12-15 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

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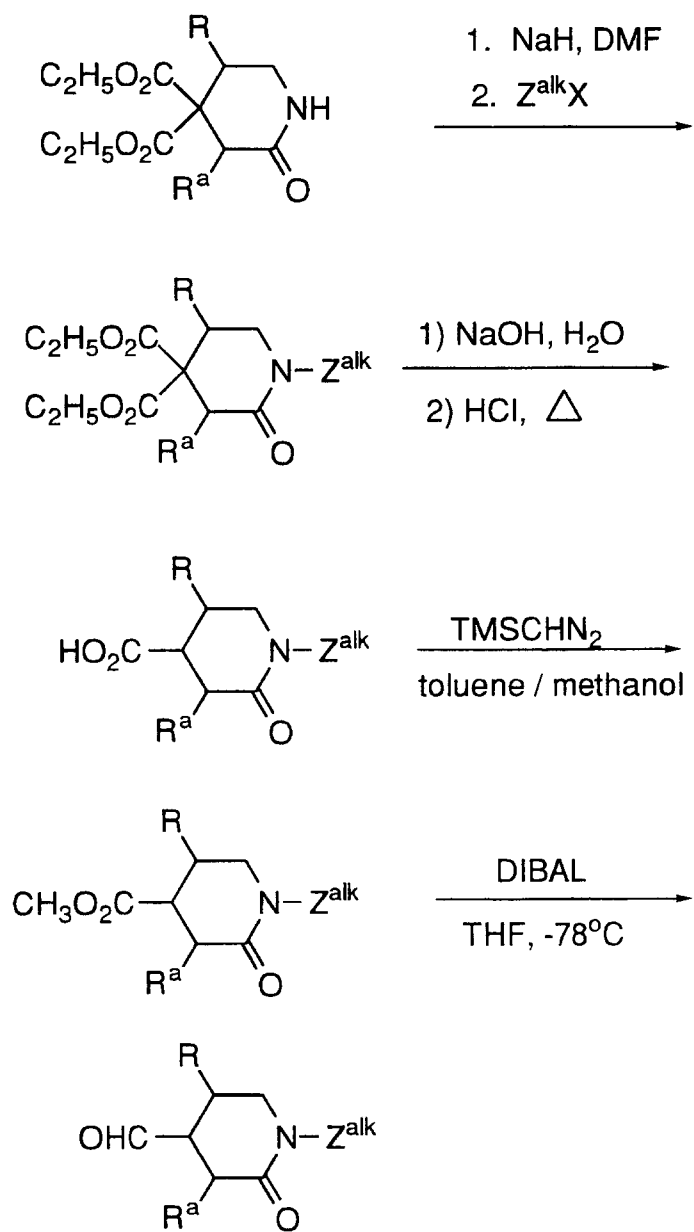
- 50 -

SCHEME 1

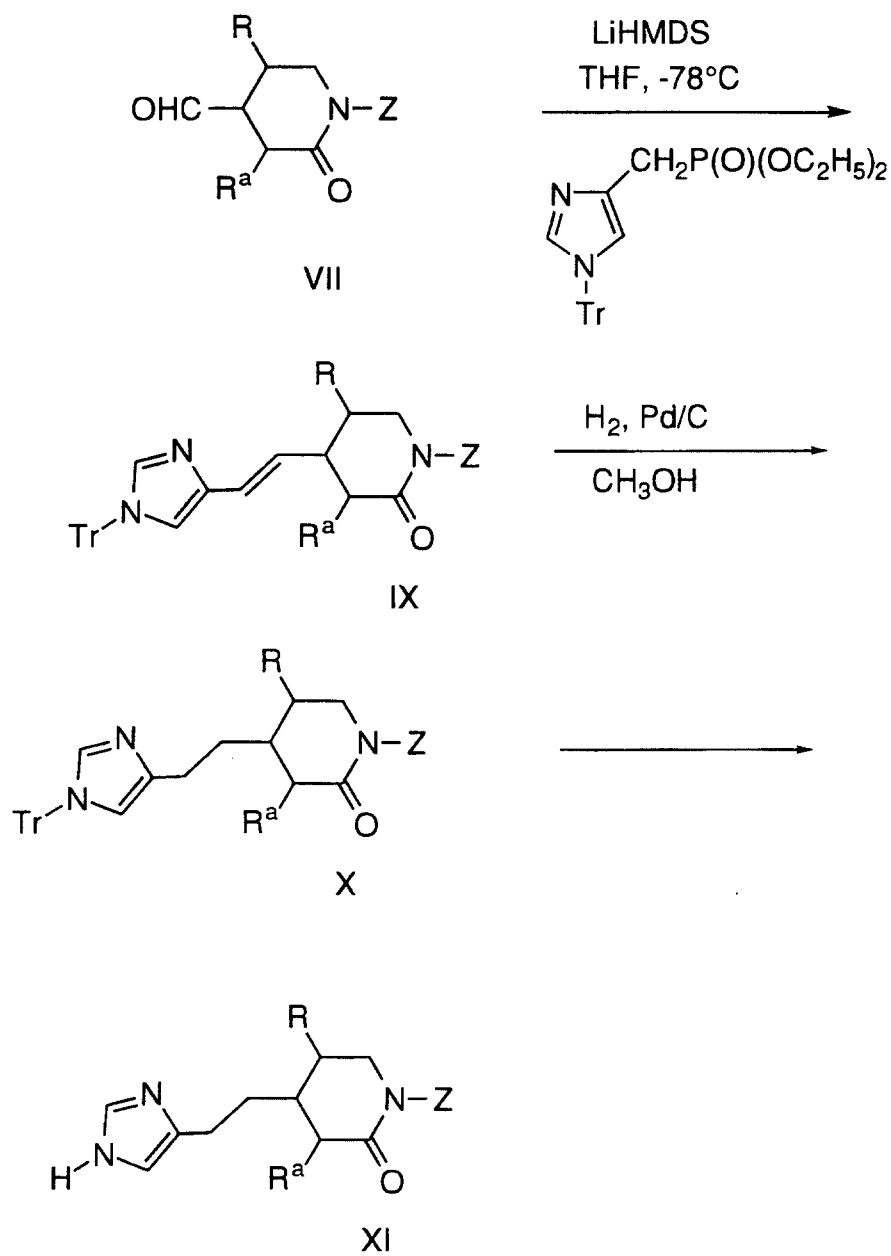
- 51 -

SCHEME 2

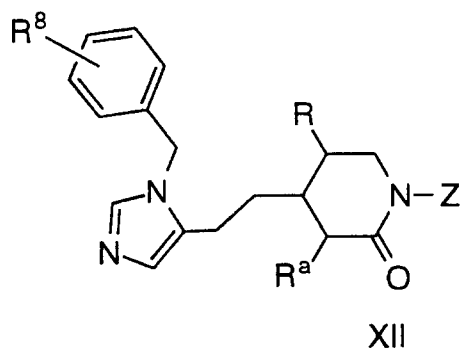
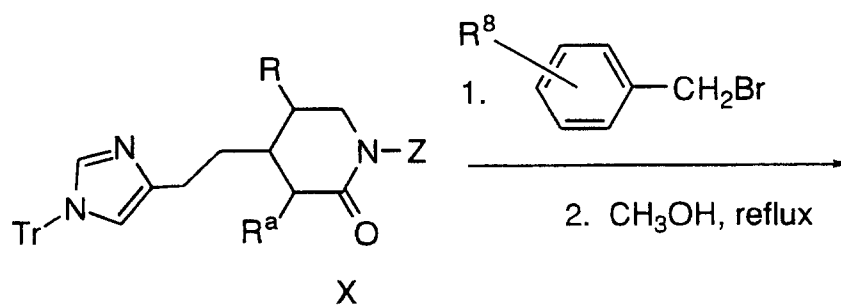
- 52 -

SCHEME 3

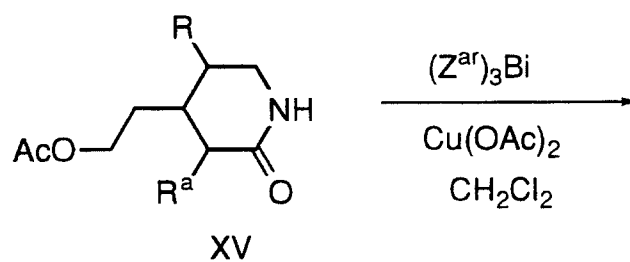
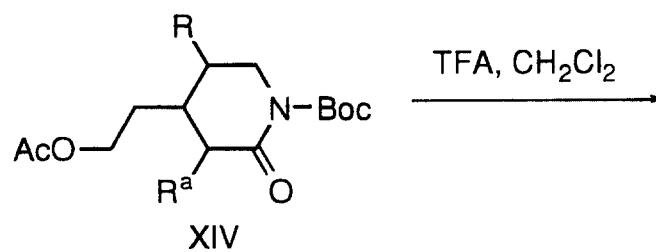
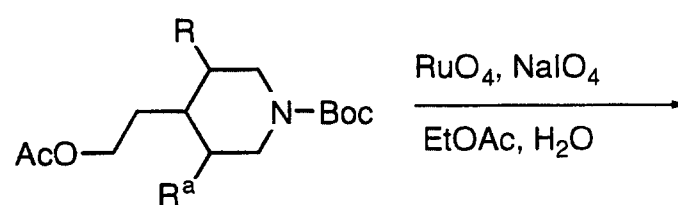
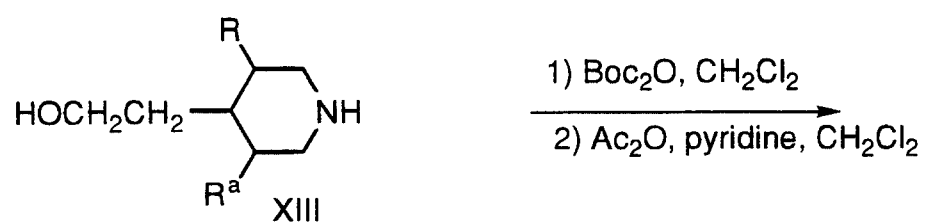
- 53 -

SCHEME 4

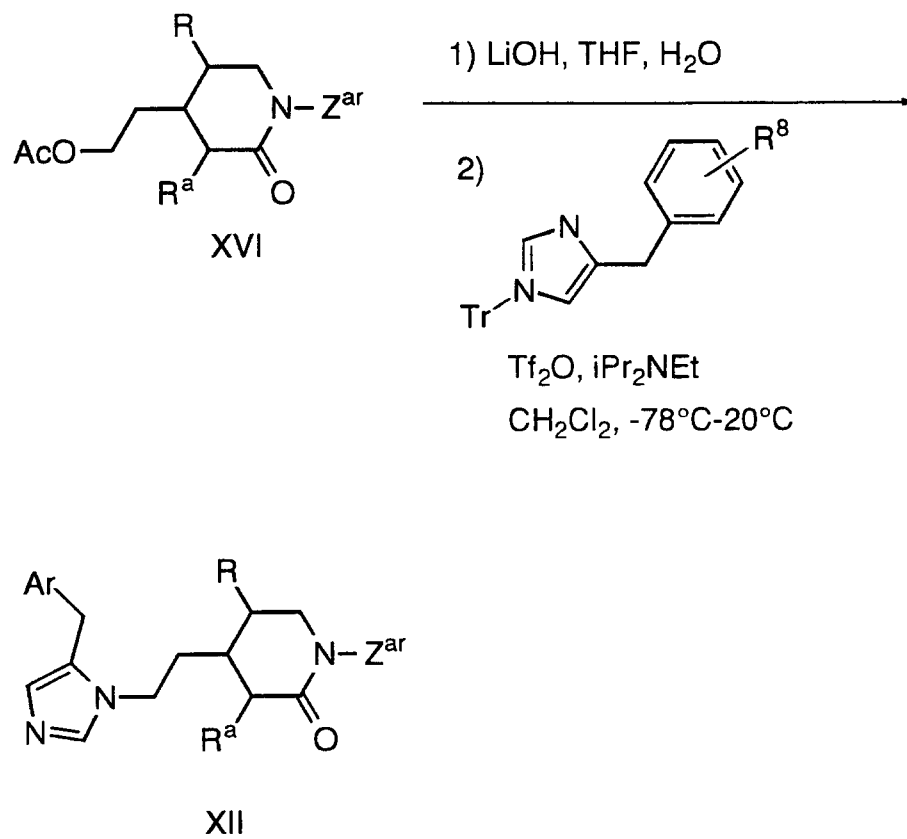
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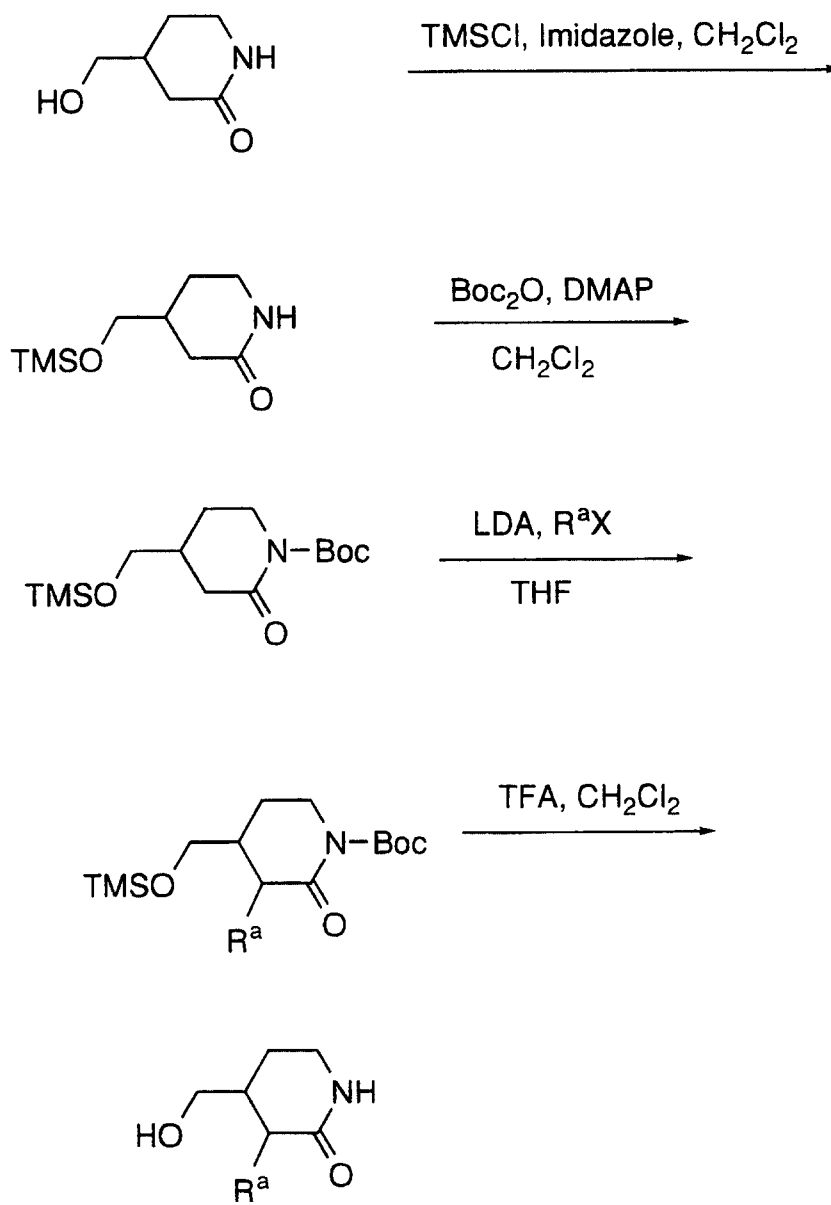
SCHEME 4 (continued)

- 55 -

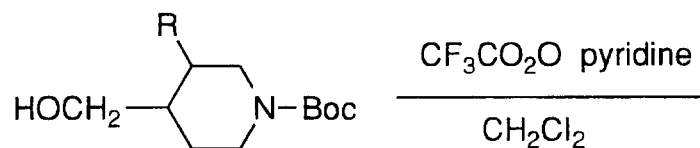
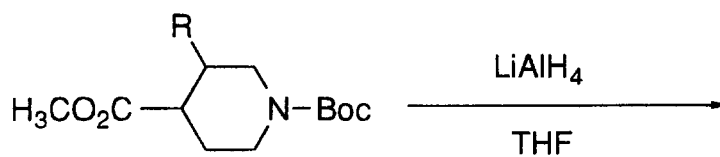
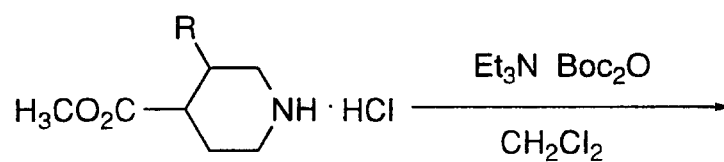
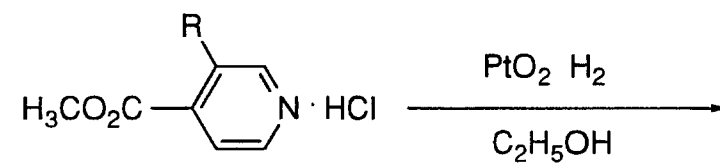
SCHEME 4a

- 56 -

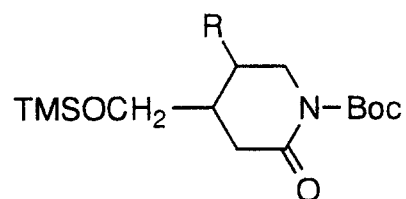
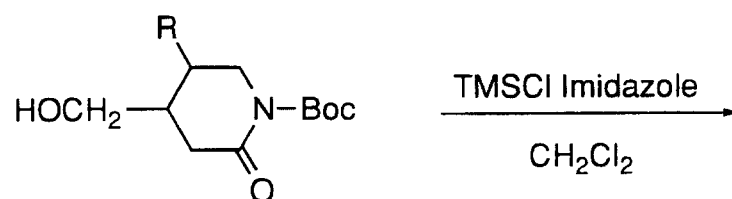
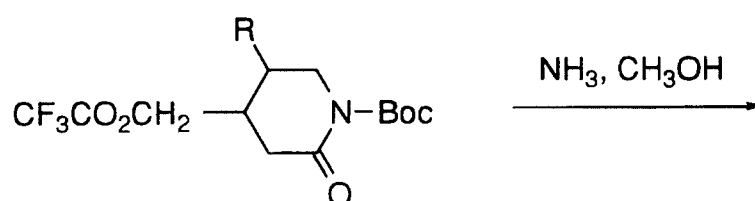
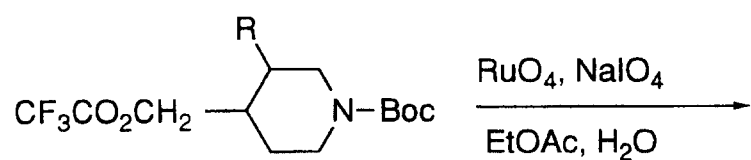
SCHEME 4a (continued)



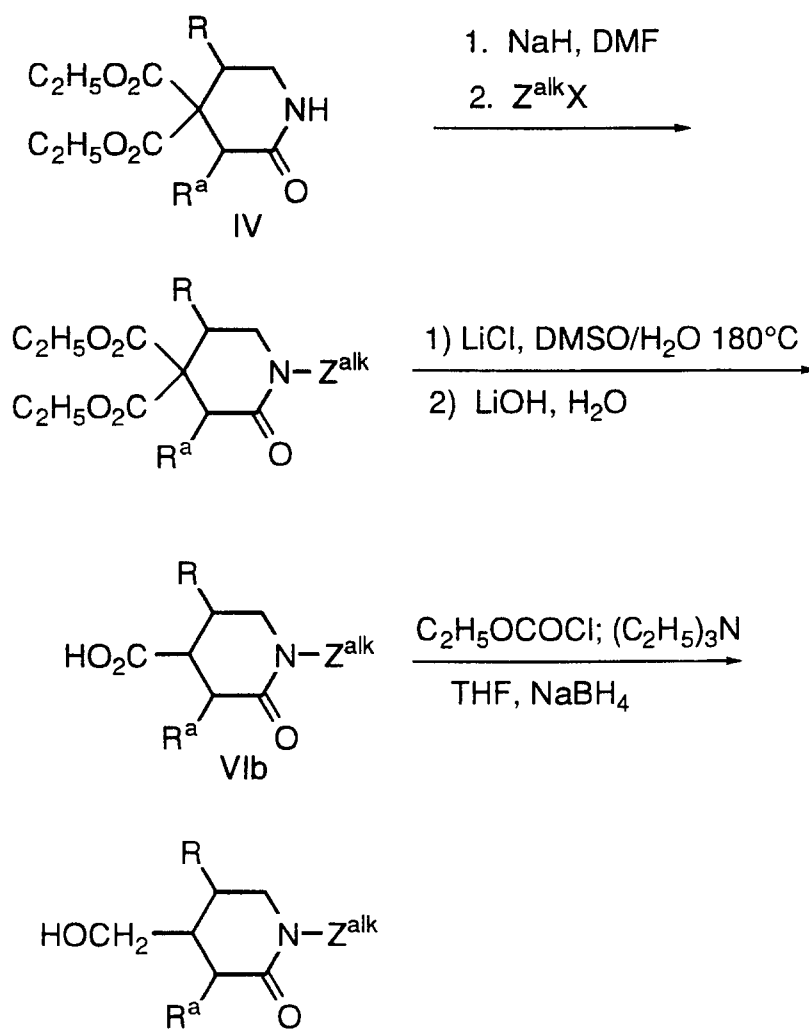
- 58 -

SCHEME 4c

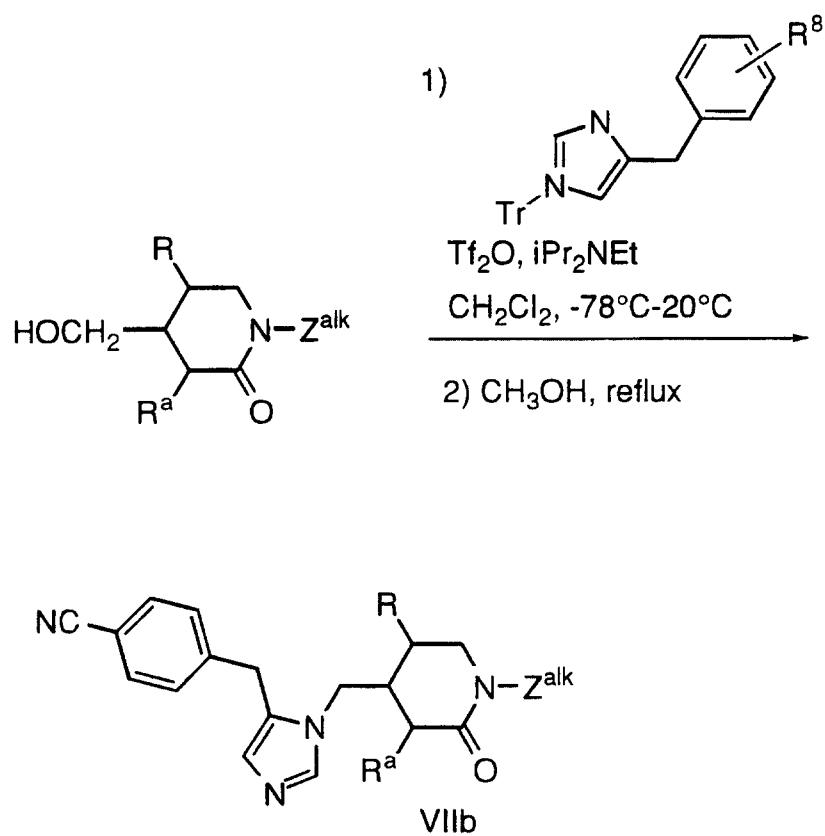
- 59 -

SCHEME 4c (continued)

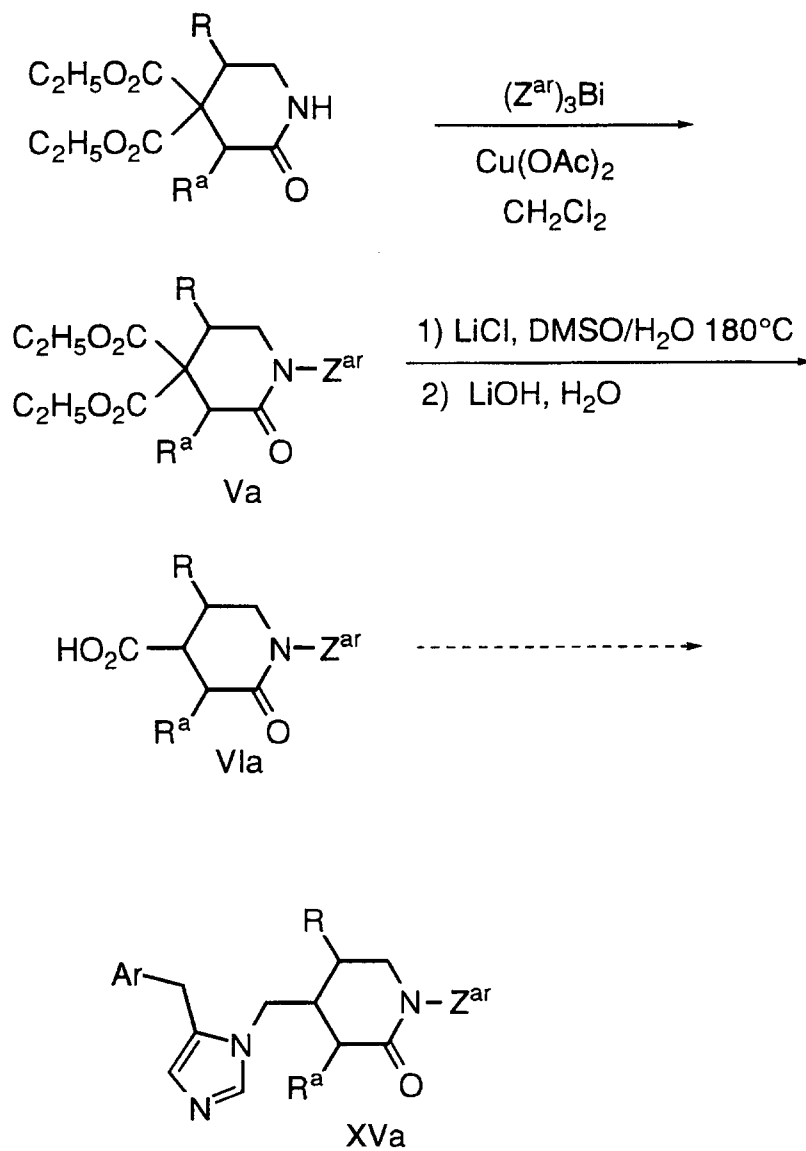
- 60 -

SCHEME 4d

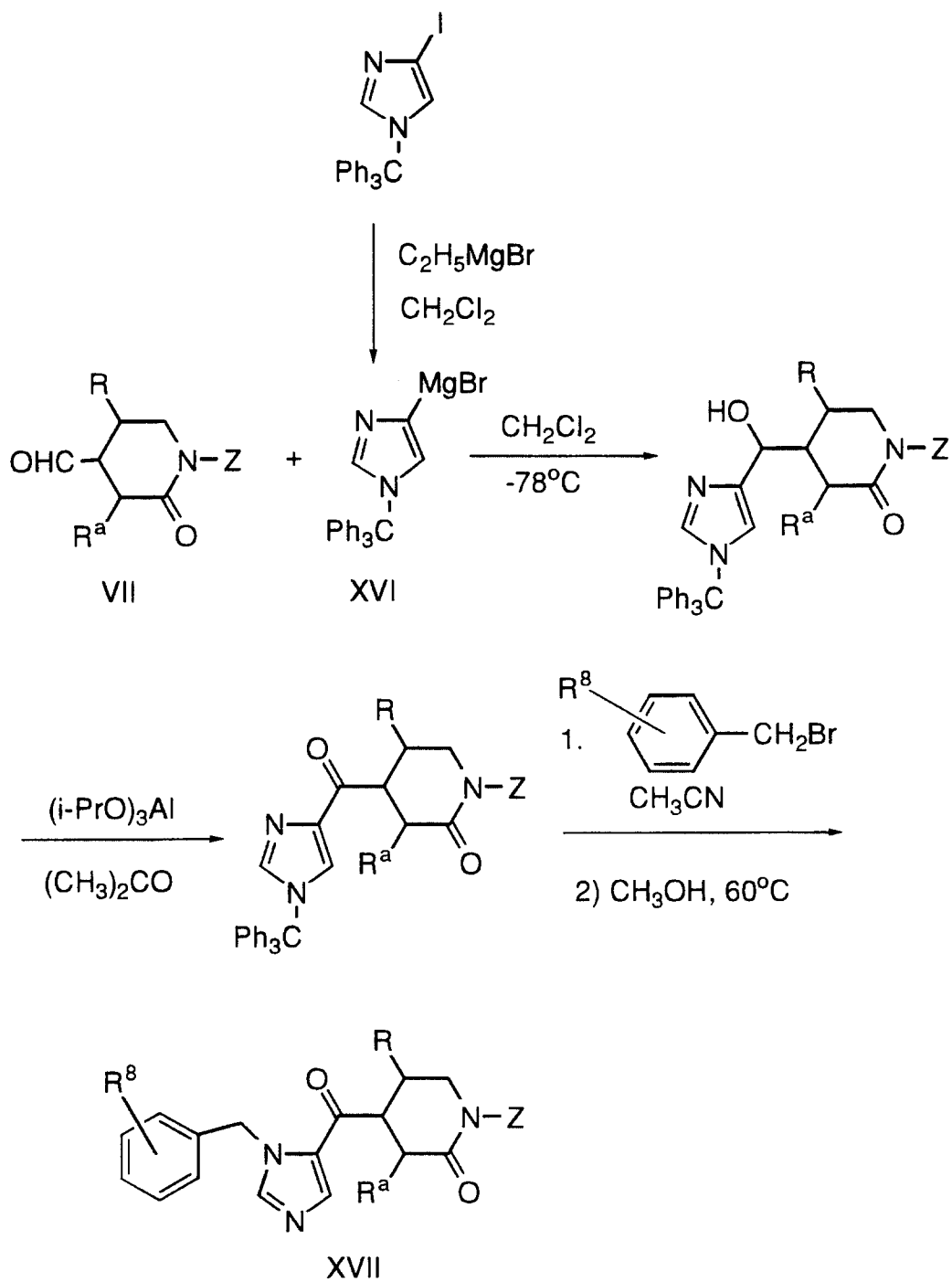
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SCHEME 4d (continued)

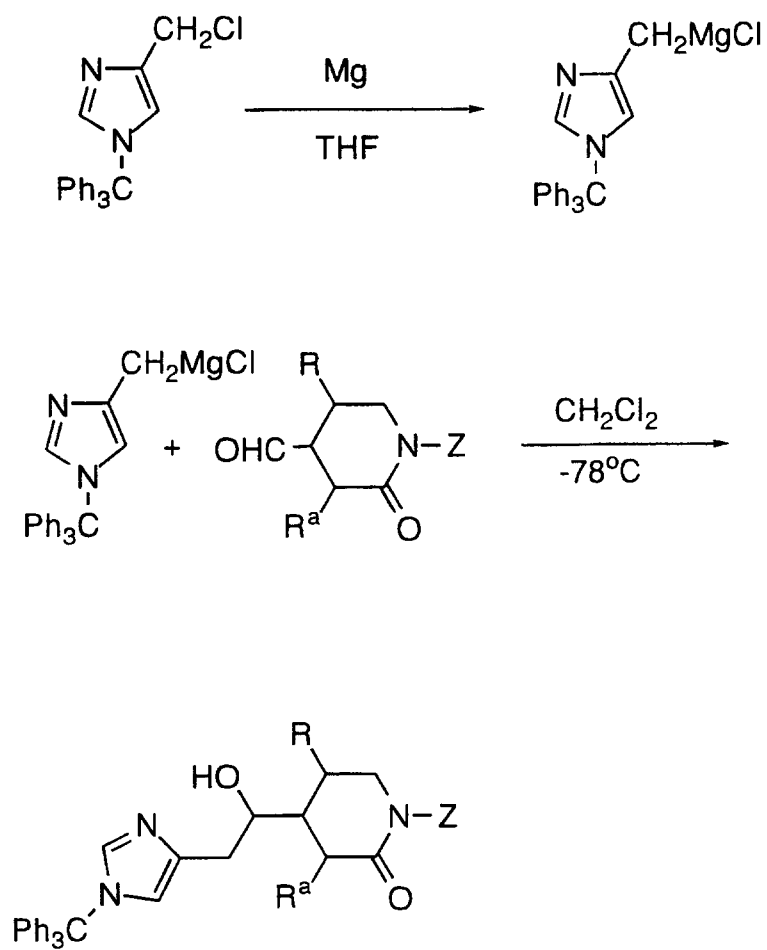
- 62 -

SCHEME 4e

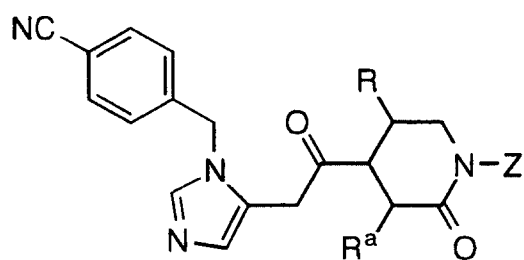
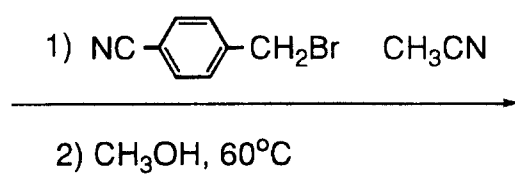
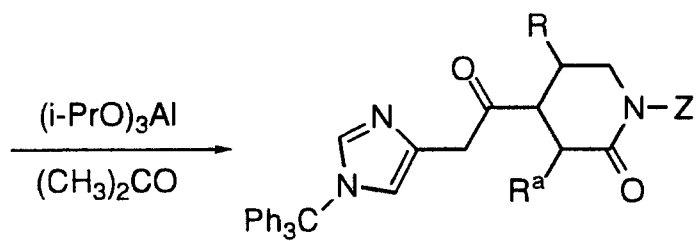
- 63 -

SCHEME 5

- 64 -

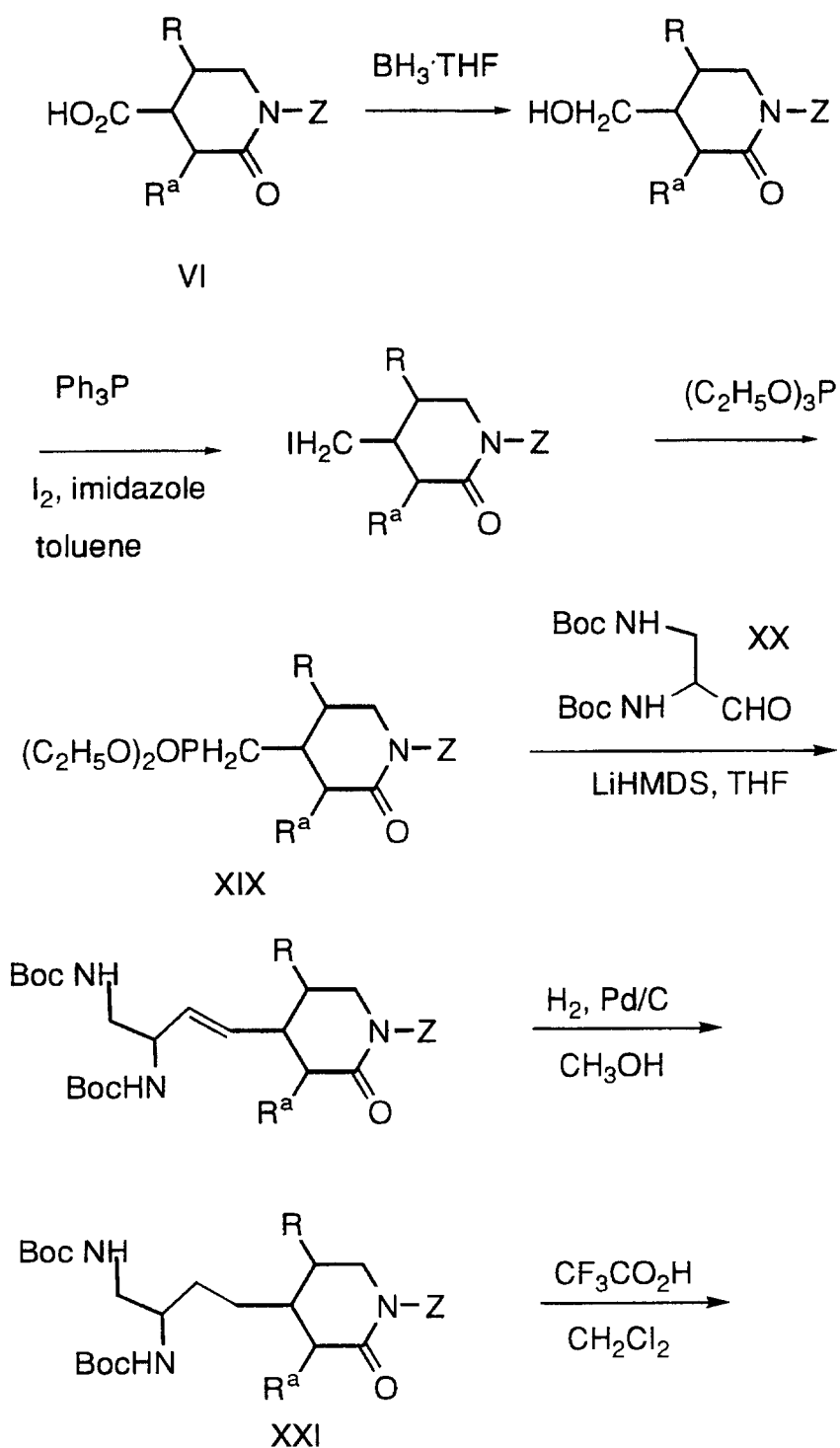
SCHEME 6

- 65 -

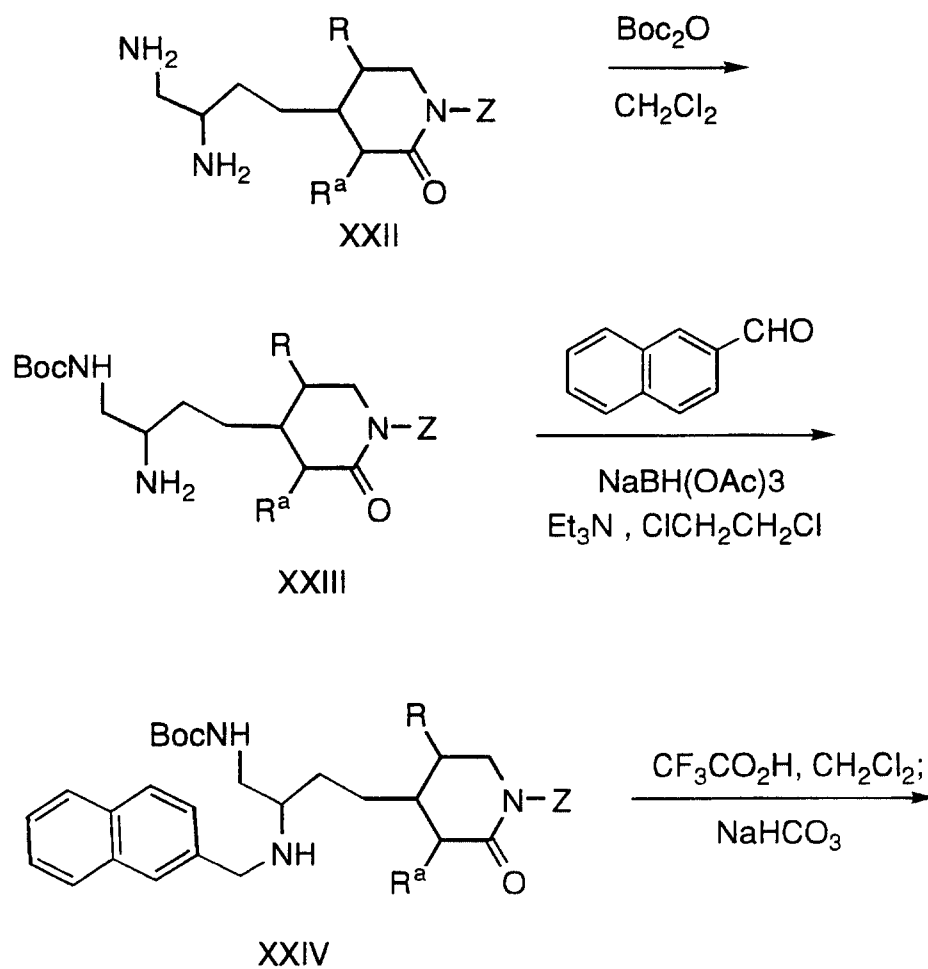
SCHEME 6 (continued)

XVIII

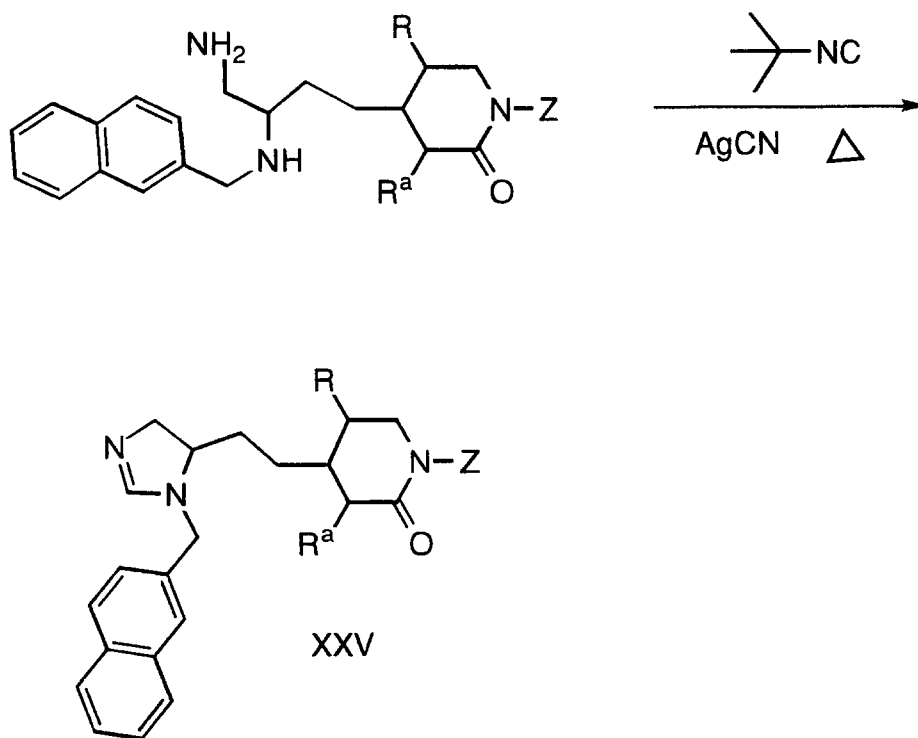
- 66 -

SCHEME 7

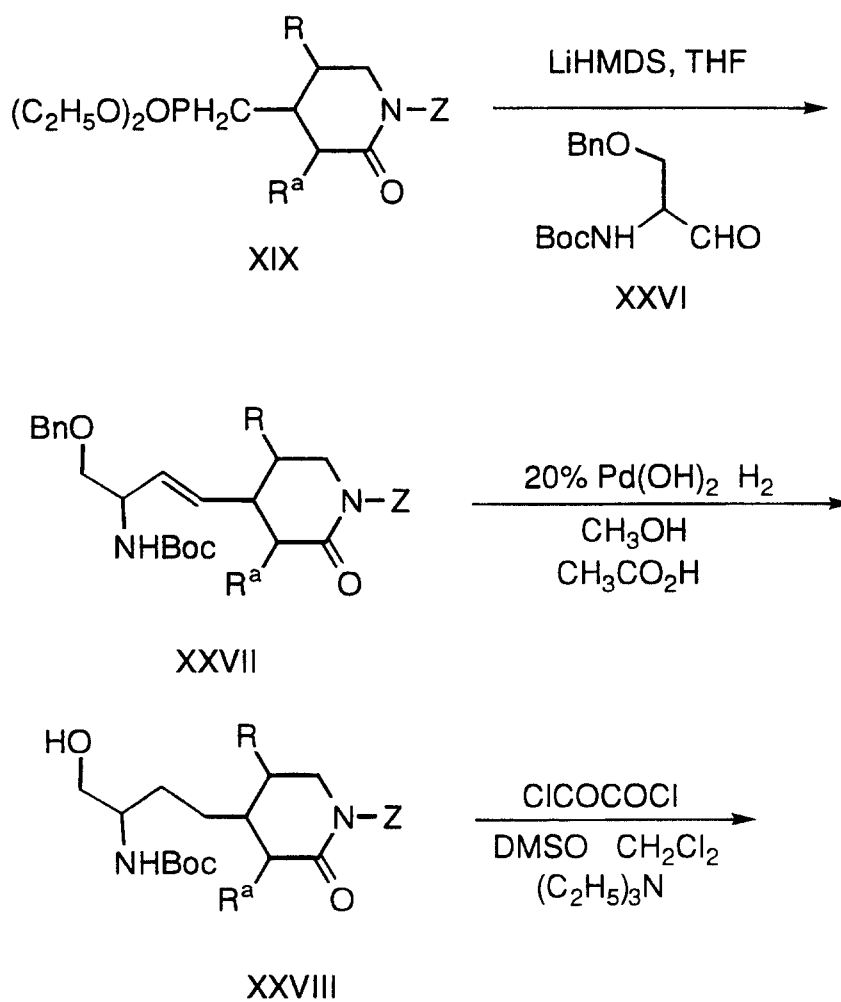
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SCHEME 7 (continued)

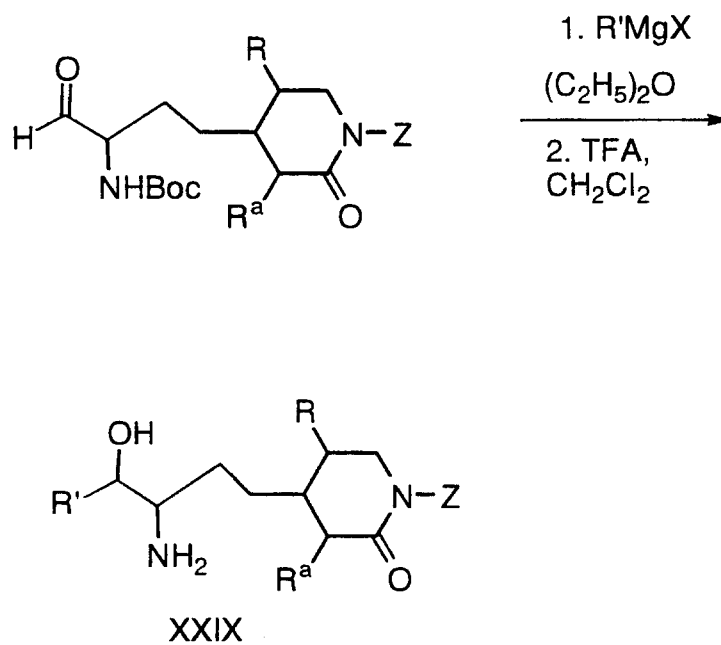
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SCHEME 7 (continued)

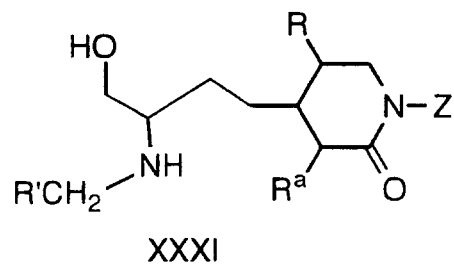
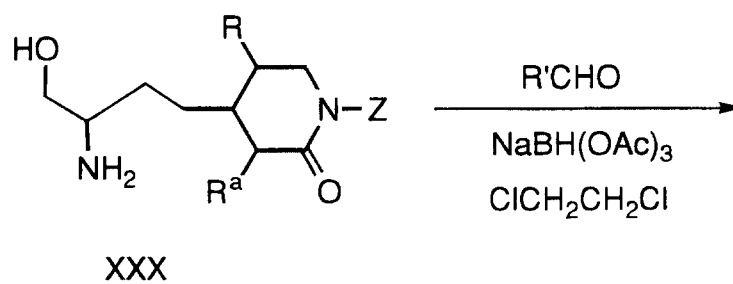
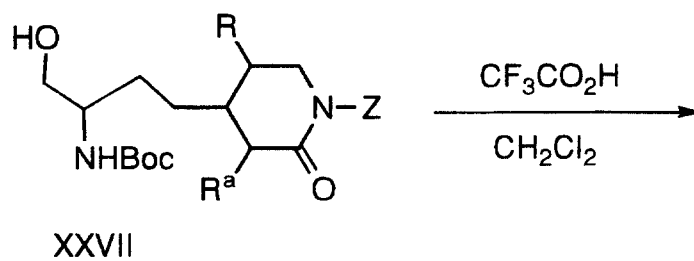
- 69 -

SCHEME 8

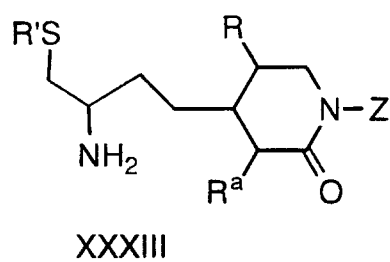
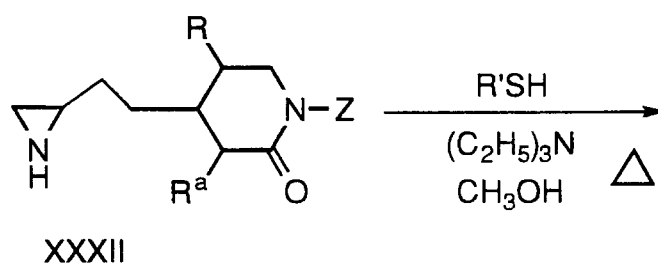
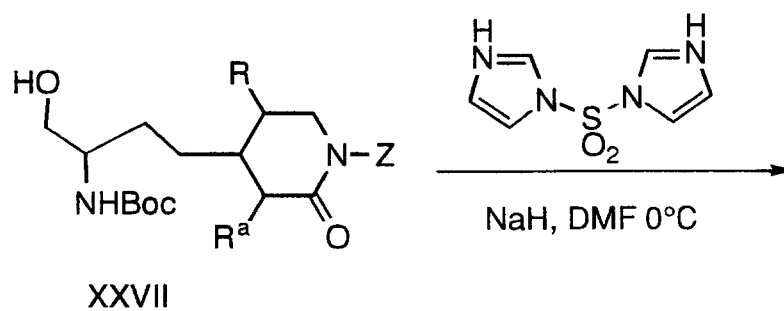
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SCHEME 8 (continued)

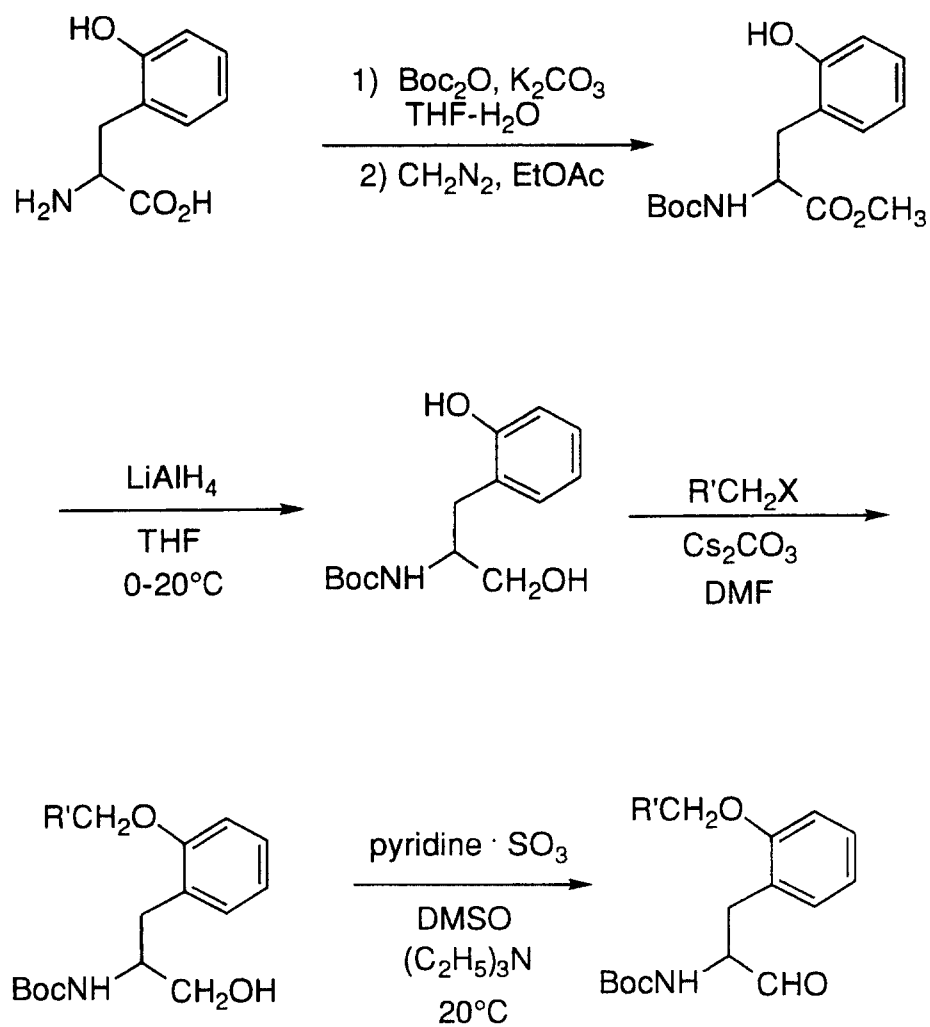
- 71 -

SCHEME 9

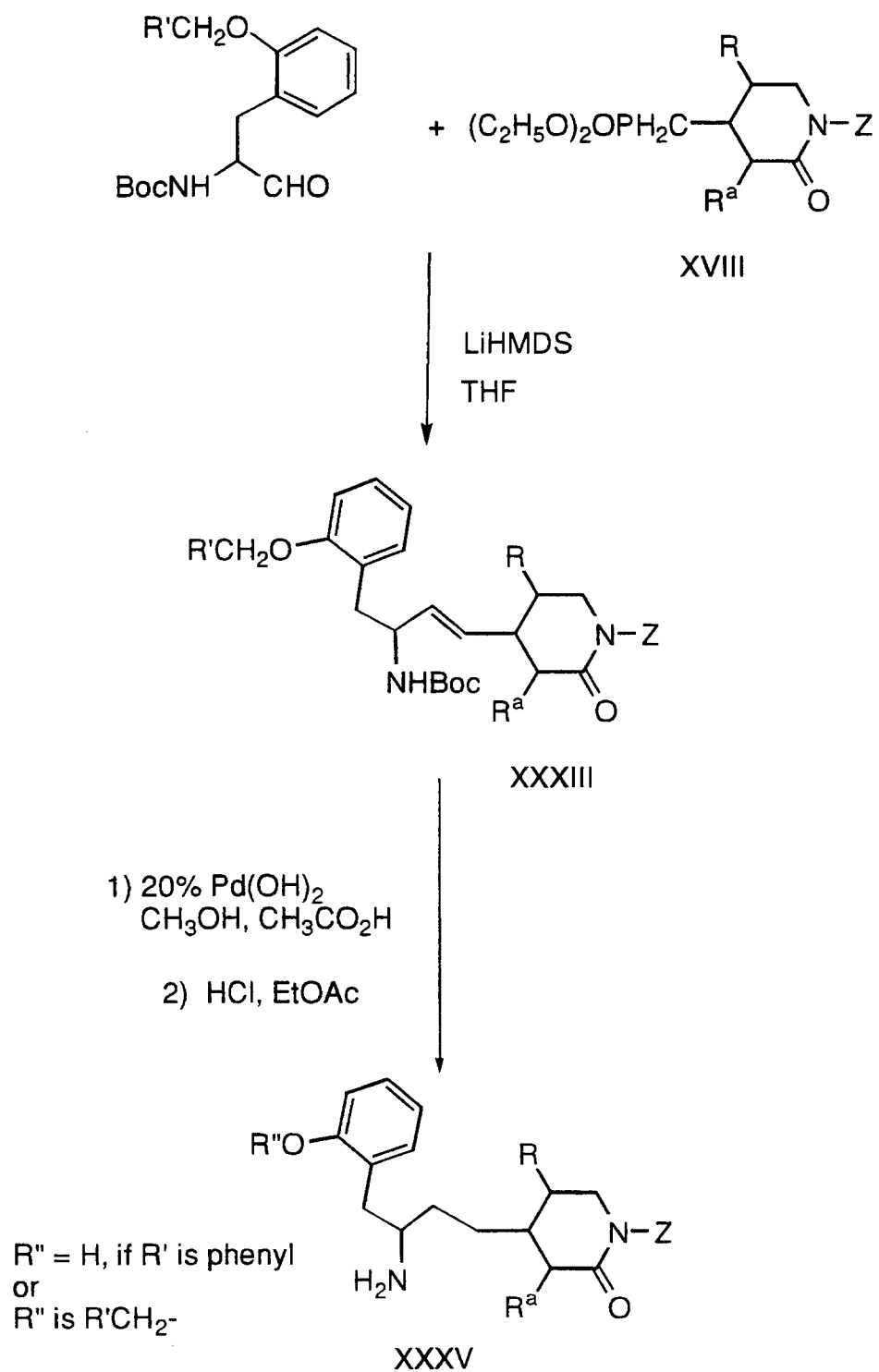
- 72 -

SCHEME 10

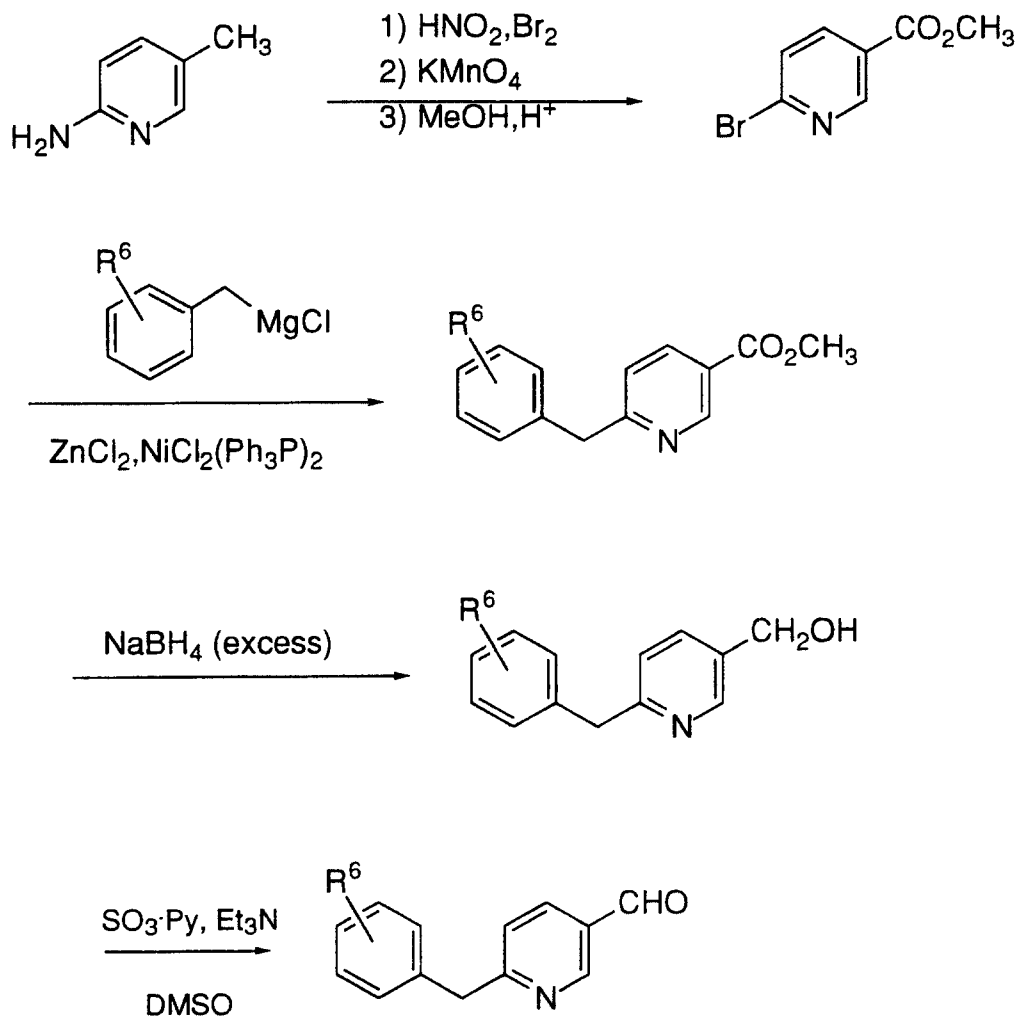
- 73 -

SCHEME 11

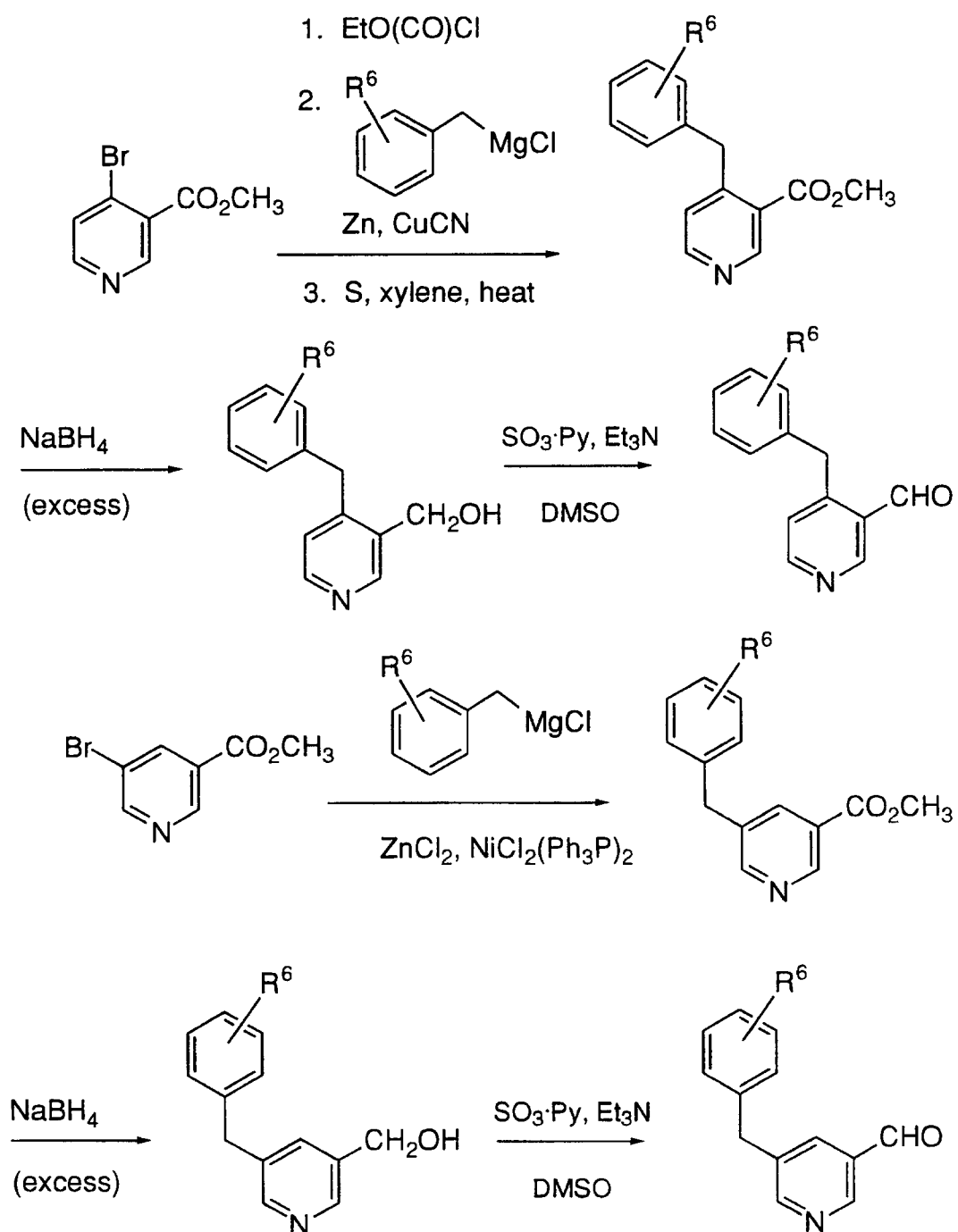
- 74 -

SCHEME 11 (continued)

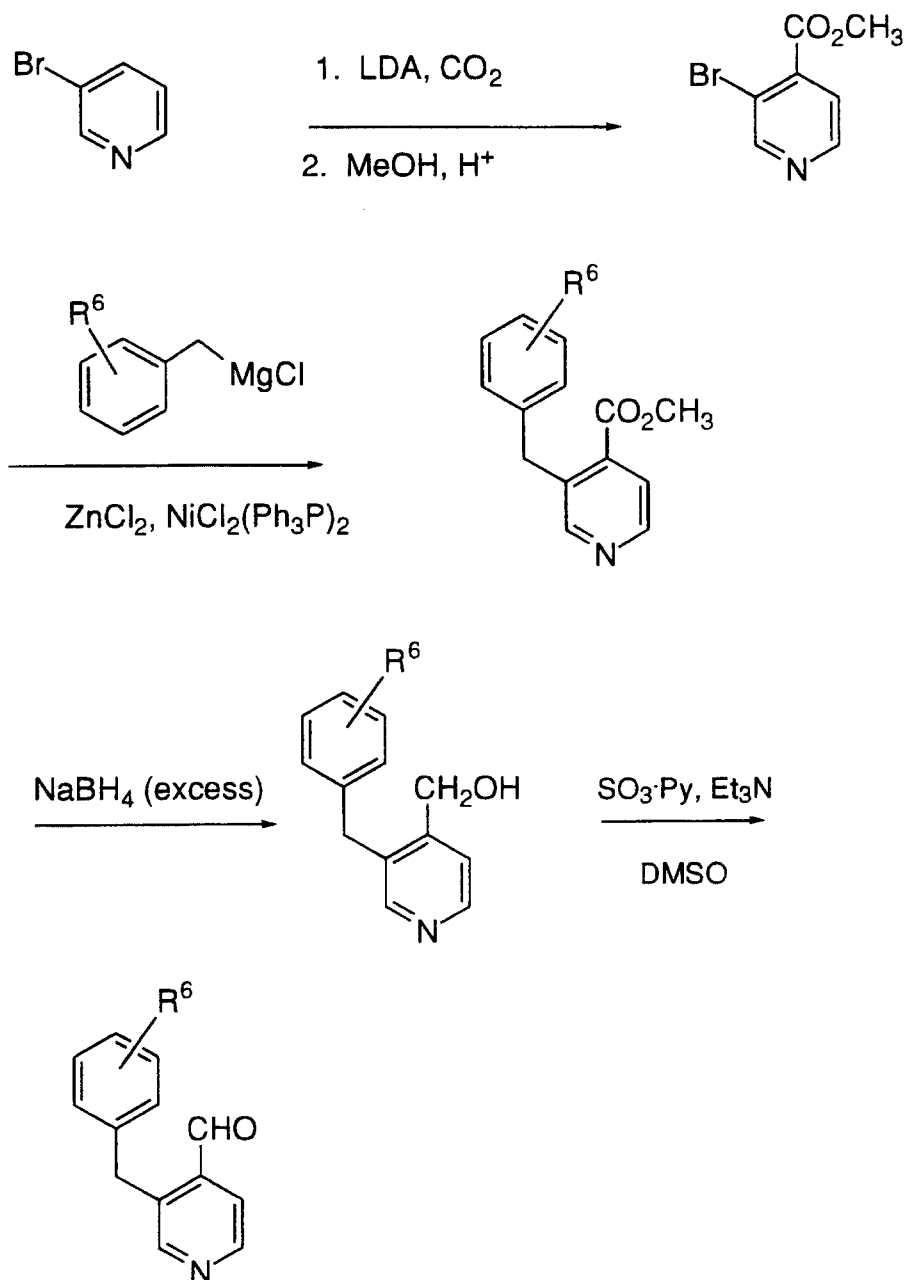
- 75 -

REACTION SCHEME 12

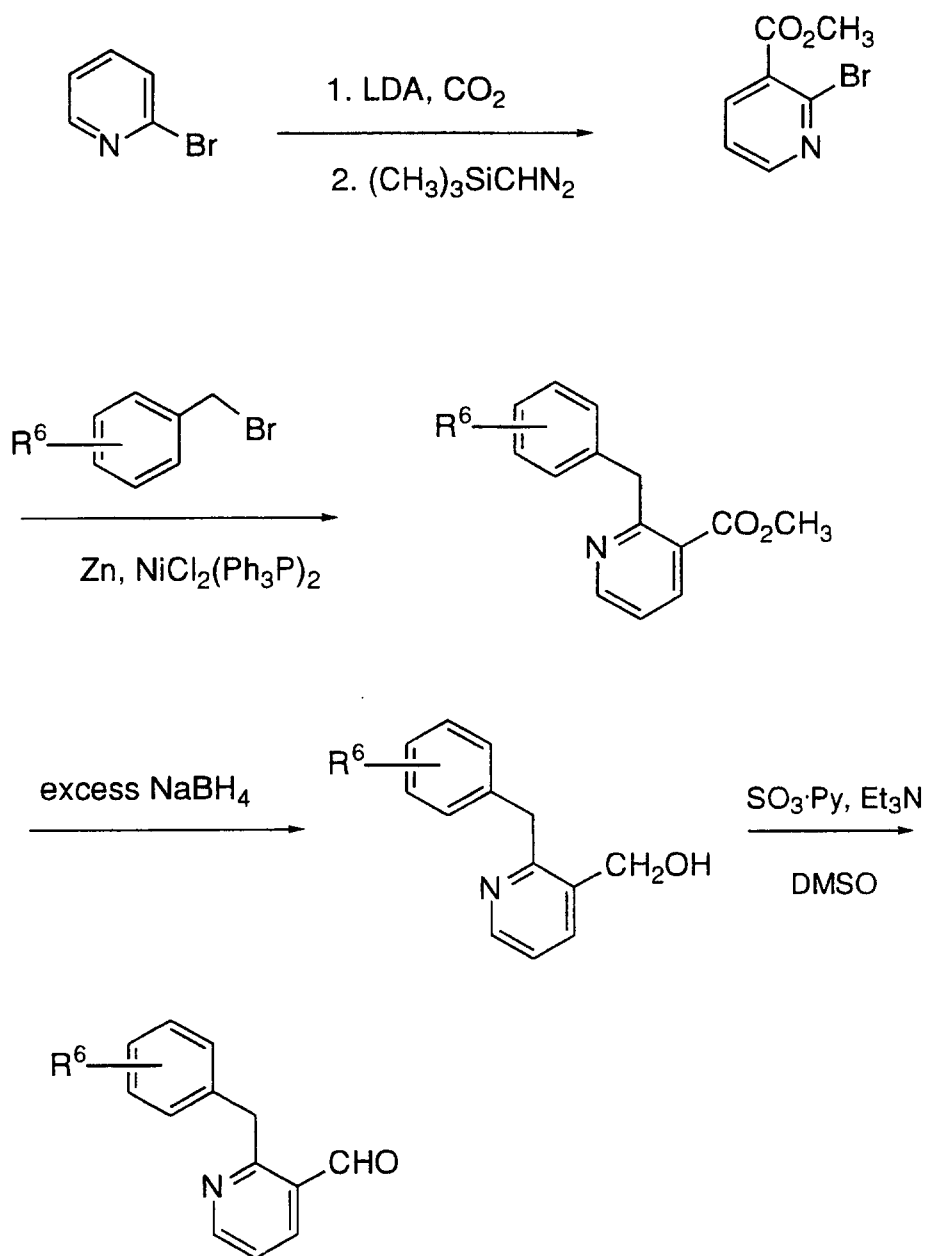
- 76 -

REACTION SCHEME 13

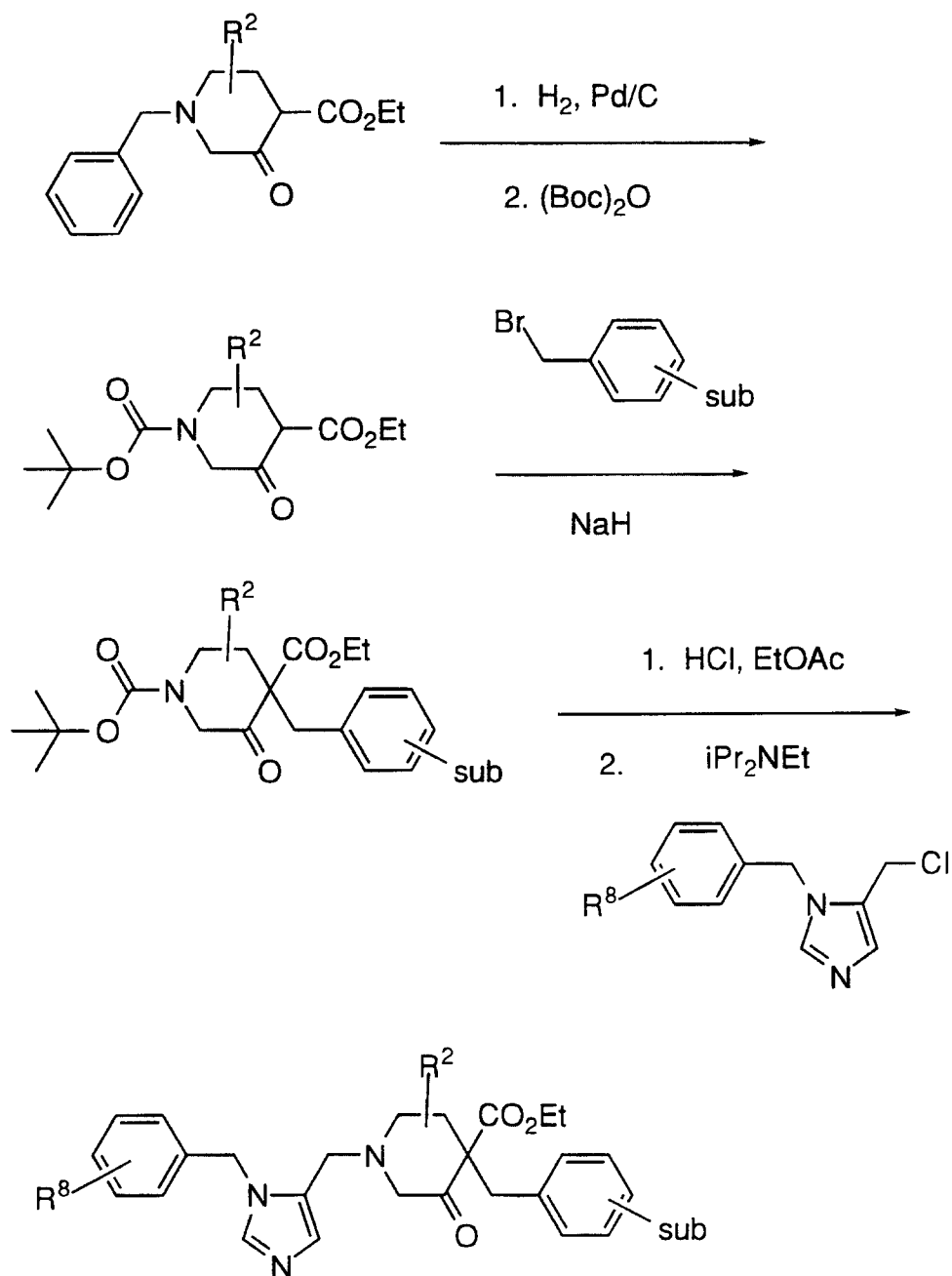
- 77 -

REACTION SCHEME 14

- 78 -

REACTION SCHEME 15

- 79 -

REACTION SCHEME 16

- 80 -

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 activity (i.e., neurofibromin (NF-1), neu, scr, abl, 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.

- 81 -

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

The instant compounds may also be useful for the treatment of fungal infections.

5 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The
10 compounds can be administered orally or parenterally, including the intravenous, 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
15 example, in the form of tablets or capsules, or as an aqueous solution or 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
20 corn starch. When aqueous suspensions are required for oral use, the 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
25 of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

 The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected
30 for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restinosis, polycystic kidney

- 82 -

disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its
5 approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical
10 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 diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacolo-
15 gically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific
20 amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

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
25 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
30 of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 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

- 83 -

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-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.

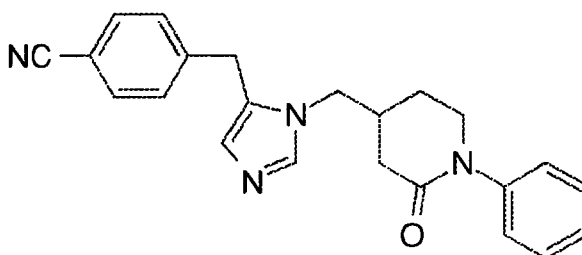
- 84 -

EXAMPLES

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

EXAMPLE 1

10 4-[5-(4-Cyanobenzyl)imidazol-1-ylmethyl]-1-phenyl-2-piperidinone
hydrochloride



15

Step A: 1-Phenyl-2-piperidinone-4,4-dicarboxylic acid diethyl
ester

2-Piperidinone-4,4-dicarboxylic acid diethyl ester,
20 prepared as described in US 4,870,173, is dissolved in methylene
chloride and treated with triphenylbismuth (1.5 equivalents),
copper(II)acetate (1.5 equivalents) and triethylamine (1.5 equivalents)
and stirred for 17 h at 20°C in dichloromethane (60 mL). The reaction
mixture was adsorbed onto silica gel and chromatographed to provide
25 the title compound.

Step B: 1-Phenyl-2-piperidinone-4-carboxylic acid ethyl ester

The product from Step A (4.78 g, 14.98 mmol) was
dissolved in DMSO (90 mL) containing water (0.27 mL, 14.98 mmol)
30 and lithium chloride (1.27 g, 29.96 mmol). The reaction was heated at

- 85 -

180°C under argon for 3.5 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated brine, and dried over magnesium sulfate. The title compound was isolated as a white solid following chromatography on silica gel with 50% ethyl acetate in hexane.

Step C: 1-Phenyl-2-piperidinone-4-carboxylic acid

The product from Step B (2.60 g, 10.52 mmol) was dissolved in THF (60 mL) and lithium hydroxide hydrate (2.15 g, 51 mmol) and water (10 mL) were added. The reaction was stirred for 4 h at room temperature, at which time 6N aqueous hydrogen chloride solution was added to adjust the pH to 1, and the product extracted with ethyl acetate. The organic phase was dried with magnesium sulfate, filtered and evaporated to reveal the title compound.

Step D: 4-Hydroxymethyl-1-phenyl-2-piperidinone

The product from Step C (1.57 g, 7.16 mmol) was dissolved in THF (30 mL) and triethylamine (1.20 mL, 8.59 mmol) was added. The reaction was cooled to 0°C under argon, and ethyl chloroformate added (0.82 mL, 8.59 mmol). The reaction was stirred for 1 h at 0°C, and then sodium borohydride was added (0.81 g, 21.5 mmol). After 3 h, the reaction was quenched by the addition of saturated sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with 2% aqueous potassium hydrogen sulfate and saturated brine. After drying over magnesium sulfate, the crude product was chromatographed on silica gel with 5% methanol in chloroform. The title compound was obtained as a white solid.

Step E: 1-Trityl-4-(4-cyanobenzyl)-imidazole.

To a suspension of activated zinc dust (3.57 g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon at 20°C. The suspension was cooled to 0°C and α -bromo-p-tolunitrile (9.33 g, 47.6 mmol) in THF

- 86 -

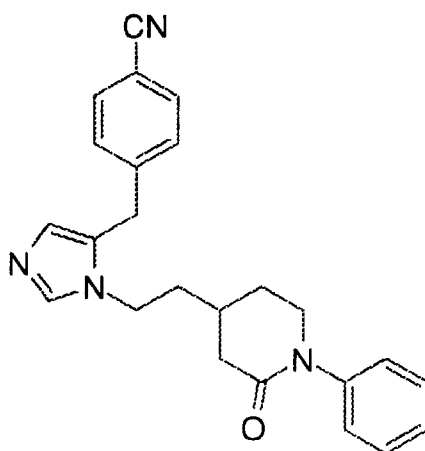
(100 mL) was added dropwise over a period of 10 min. The reaction was then allowed to stir at 20°C for 6 h and bis(triphenylphosphine)Nickel II chloride (2.4 g, 3.64 mmol) and 4-iodotriptyl imidazole (15.95 g, 36.6 mmol) were added in one portion. The resulting mixture was stirred 16 h at 20°C and then quenched by addition of saturated ammonium chloride solution (100 mL) and the mixture stirred for 2 h. Saturated sodium bicarbonate solution was added to give a pH of 8 and the solution was extracted with ethyl acetate (2 x 250 mL), dried with magnesium sulfate, and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel with 0-20% ethyl acetate in methylene chloride to afford the title compound as a white solid.

¹H NMR δ CDCl₃ (7.54 (2H,d, J=7.9Hz), 7.38(1H,s), 7.36-7.29 (11H,m), 7.15-7.09(6H,m), 6.58(1H,s), and 3.93(2H,s)ppm.

Step F: 4-[5-(4-Cyanobenzyl)imidazol-1-ylmethyl]-1-phenyl-2-piperidinone hydrochloride

The product from Step D (0.205 g, 1.00 mmol) and the product from Step E (0.425 g, 1.00 mmol) were dissolved in methylene chloride (2 mL) containing diisopropylethylamine (0.191 mL, 1.10 mmol) and cooled to -78°C under argon. Trifluoromethane sulfonic anhydride was added (0.173 mL, 1.03 mmol) and the reaction stirred at -78°C for 1 h, followed by warming to room temperature over 2 h. The solvent was evaporated, and the residue dissolved in methanol. After refluxing for 30 min, the methanol was evaporated, and the residue is partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. The free base product was chromatographed on silica gel with 3% methanol in methylene chloride followed by 7% 9:1 methanol:ammonium hydroxide in methylene chloride. The title compound was obtained after conversion to the hydrochloride salt. FAB ms: 371 (M+1). Anal. Calc for C₂₃H₂₂N₄O · HCl · H₂O, C, 65.01; H, 5.93; N, 13.19. Found: C, 64.77; H, 5.89; N, 13.11.

- 87 -

EXAMPLE 25 4-[2-{5-(4-Cyanobenzyl)imidazol-1-yl}ethyl]-1-phenylpiperidin-2-one
hydrochloride

10

Step A: 1-tert-Butoxycarbonyl-4-hydroxyethylpiperidine

4-(2-Hydroxyethyl)piperidine (4.91 g, 38.06 mmol) was dissolved in methylene chloride (80 mL) and di-*tert*-butyl dicarbonate (8.71 g, 39.96 mmol) was added. After stirring at room temperature overnight, saturated sodium bicarbonate was added, and the layers separated. The organic phase was washed with 2% potassium hydrogen sulfate, saturated sodium carbonate and saturated brine, then dried over magnesium sulfate. The title compound was obtained as a yellow oil.

20 Step B: 4-(2-Acetoxyethyl)-1-tert-butoxycarbonylpiperidine

The product from Step A (6.62 g, 28.90 mmol) was dissolved in methylene chloride (50 mL) containing pyridine (5.8 mL, 72.27 mmol). The reaction was cooled to 0°C under argon, and acetic anhydride added (3.3 mL, 34.68 mmol). The reaction was stirred overnight at room temperature. Saturated sodium bicarbonate solution was added, and the layers separated. The organic phase was washed

- 88 -

with 10% aqueous hydrogen chloride, saturated sodium bicarbonate solution, and saturated brine. The organic phase was dried over magnesium sulfate. The title compound was obtained as an oil.

5 **Step C:** 4-(2-Acetoxyethyl)-1-*tert*-butoxycarbonylpiperidin-2-one

The product from Step B (0.275 g, 1.01 mmol) was dissolved in ethyl acetate (5 mL). A solution of sodium periodate in water (0.5 g in 5 mL) and ruthenium tetroxide (13 mg, 0.10 mmol) was added, and the heterogeneous reaction stirred vigorously overnight at
10 room temperature. An additional portion of sodium periodate in water was added (0.5 g in 5 mL) and the reaction stirred overnight. The reaction was quenched with 10% sodium thiosulfate, and filtered through celite. The phases were separated, and the organic phase dried over magnesium sulfate. Filtration and evaporation gave the title
15 compound.

Step D: 4-(2-Acetoxyethyl)piperidin-2-one

The product from Step C is dissolved in 2:1 methylene
20 chloride and trifluoroacetic acid. The reaction is stirred for 1 h, and evaporated, giving the title compound.

Step E: 4-(2-Acetoxyethyl)-1-phenylpiperidin-2-one

25 The product from Step D is dissolved in methylene chloride and treated with triphenylbismuth (1.5 equivalents), copper(II)acetate (1.5 equivalents) and triethylamine (1.5 equivalents) and stirred for 17 h at 20°C in dichloromethane (60 mL). The reaction mixture is adsorbed onto silica gel and chromatographed to provide the title compound.

30

Step F: 4-(2-Hydroxyethyl)-1-phenylpiperidin-2-one

The product from Step E is hydrolyzed according to the procedure described in Example 1, Step C, giving the title compound.

- 89 -

Step G: 4-[2-{5-(4-Cyanobenzyl)imidazol-1-yl}ethyl]-1-phenylpiperidin-2-one hydrochloride

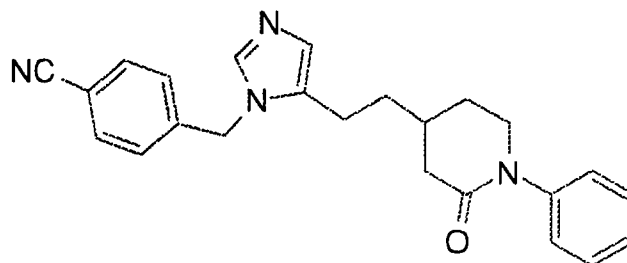
- 5 The product from Step F (1 eq) and the product from Example 1, Step E (1 eq) were dissolved in methylene chloride containing diisopropylethylamine, cooled to -78°C under argon and treated with trifluoromethane sulfonic anhydride as described in Example 1, Step F. After methanolysis, the title compound was isolated by chromatography on silica gel.

10

EXAMPLE 3

4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-1-phenyl-2-piperidinone hydrochloride

15



- 20 Step A: 1-Phenyl-2-piperidinone-4,4-dicarboxylic acid diethyl ester
ester
2-Piperidinone-4,4-dicarboxylic acid diethyl ester, prepared as described in US 4,870,173, is dissolved in methylene chloride and treated with triphenylbismuth (1.5 equivalents),
25 copper(II)acetate (1.5 equivalents) and triethylamine (1.5 equivalents) and stirred for 17 h at 20°C in dichloromethane (60 mL). The reaction mixture is adsorbed onto silica gel and chromatographed to provide the title compound.

30 Step B: 1-Phenyl-2-piperidinone-4,4-dicarboxylic acid

- 90 -

The product from Step A is dissolved in methanol and 5% aqueous sodium hydroxide added. When the hydrolysis is complete, 6 N aqueous hydrochloric acid is added to obtain pH 1, and the solution extracted with ethyl acetate. The organic phase is washed with saturated brine, dried over magnesium sulfate, filtered and concentrated to provide the title compound.

Step C: 1-Phenyl-2-piperidinone-4-carboxylic acid

The product from step B is dissolved in toluene and refluxed for 6 h. The reaction is cooled and concentrated to provide the title compound.

Step D: 1-Phenyl-2-piperidinone-4-carboxylic acid methyl ester

The product from Step C is dissolved in 10 % methanol in toluene, and trimethylsilyldiazomethane added. The reaction is quenched with acetic acid and concentrated. The residue is partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with saturated brine, dried over magnesium sulfate, filtered and concentrated to provide the title compound.

Step E: 4-Formyl-1-phenyl-2-piperidinone

The product from Step D is dissolved in THF and cooled to -78°C under nitrogen. A solution of diisobutylaluminum hydride (1 eq.) in toluene is added dropwise. After 30 min, the reaction is quenched with saturated sodium potassium tartrate solution. The mixture is extracted with ethyl acetate, and the organic phase washed with saturated brine, and dried over MgSO₄. Filtration and concentration provides the title compound

Step F: 4-Hydroxymethyl-1-triphenylmethylimidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature is added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g,

- 91 -

273 mmol) in 500 mL of DMF is added dropwise. The reaction mixture is stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product is slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid
5 which is sufficiently pure for use in the next step.

Step G: 4-Chloromethyl-1-triphenylmethyylimidazole

The product from Step F is dissolved in chloroform and cooled to 0°C under nitrogen. Thionyl chloride (molar equivalent) is
10 added slowly *via* syringe. The reaction is stirred for 30 min, and extracted with sodium bicarbonate solution. The organic phase is dried over magnesium sulfate, filtered and concentrated to provide the title compound.

15 Step H: 4-Diethylphosphonomethyl-1-triphenylmethyylimidazole

The product from Step G is dissolved in acetonitrile and cooled to 0°C. Triethyl phosphite (1 equivalent) and sodium iodide (1
equivalent) were added, and the reaction stirred at room temperature overnight. The reaction is quenched with ammonium chloride, and
20 extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and concentrated to provide the title compound.

25 Step I: 4-[2-{1-(Triphenylmethyl)-4-imidazolyl}ethenyl]-1-phenyl-2-piperidinone

The product from Step H is dissolved in THF and cooled to -78°C under nitrogen. A solution of LDA in THF is added dropwise. The reaction is stirred at -78°C for 1 h, then a solution of 4-formyl-1-phenyl-2-piperidinone from Step E is added, and the reaction warmed to
30 room temperature overnight. The reaction is quenched with ammonium chloride solution, and extracted with ethyl acetate. The title compound is obtained after chromatography on silica gel

- 92 -

Step J: 4-[2-{1-(Triphenylmethyl)-4-imidazolyl}ethyl]-1-phenyl-2-piperidinone

The product from Step I is dissolved in methanol and hydrogenated at 60 psi hydrogen with 10% palladium on carbon. When reaction is complete, the catalyst is filtered and the title compound obtained after evaporation of solvent.

Step K: 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-1-phenyl-2-piperidinone hydrochloride

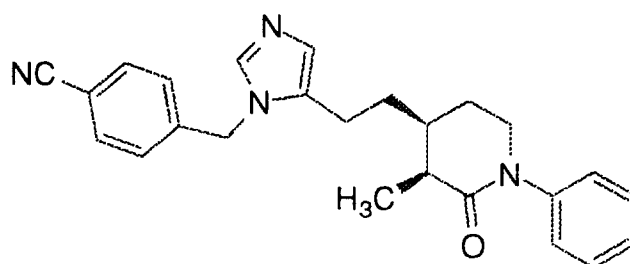
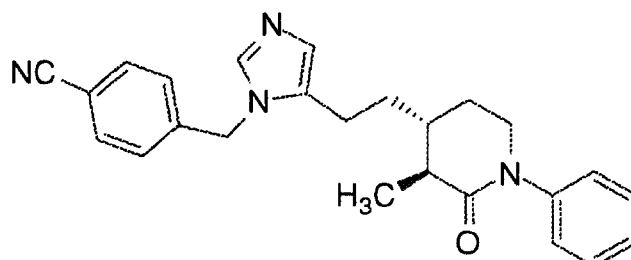
The product from Step J is dissolved in acetonitrile and reacted with 4-cyanobenzylbromide (1 equivalent) at room temperature overnight. The reaction is concentrated *in vacuo*, and the residue dissolved in methanol. The methanol solution is refluxed for 3 h and then concentrated. The residue is partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. The title compound is obtained after purification by silica gel chromatography, and conversion to the hydrochloride salt.

20

EXAMPLE 4

(±)*cis*- and (±)*trans*- 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone hydrochloride

- 93 -



Step A: (±)cis- and (±)trans-3-Methyl-1-phenyl-4-[2-{1-(triphenylmethyl)-4-imidazolyl}ethyl]-2-piperidinone

5 4-[2-{1-(Triphenylmethyl)-4-imidazolyl}ethyl]-1-phenyl-2-piperidinone in THF is added to a solution of 1 eq lithium hexamethyldisilylazide in THF at -78°C, under argon. The reaction is stirred for 30 min, and 1 eq methyl iodide is added. The reaction is warmed to room temperature, quenched with saturated ammonium sulfate solution, and extracted with ethyl acetate. The organic phase is washed with saturated brine and dried over magnesium sulfate. The crude products are purified by column chromatography and provide the title compounds.

15 **Step B:** (±)cis- and (±)trans-4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone hydrochloride

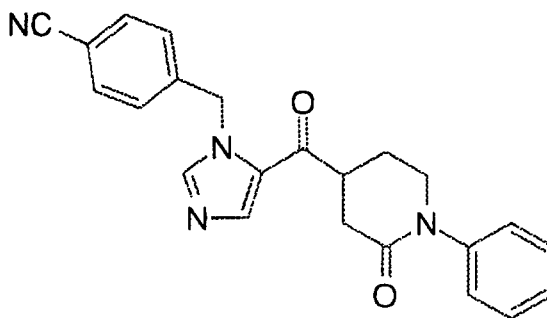
20 The title compound is prepared according to the procedure described in Example 3, Step K, except using the product from Step A in place of 4-[2-{1-(triphenylmethyl)-4-imidazolyl}ethyl]-1-phenyl-2-piperidinone. The title compound is obtained after purification by silica gel chromatography, and conversion to the hydrochloride salt.

- 94 -

EXAMPLE 5

4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}carbonyl]-1-phenyl-2-piperidinone hydrochloride

5



Step A: N-Methyl N-methoxy 1-phenyl-2-piperidinone-4-carboxamide

10

1-Phenyl-2-piperidinone-4-carboxylic acid is stirred with 1 eq N,O-dimethylhydroxylamine hydrochloride, 1.1 eq EDC · HCl, 1 eq hydroxybenzotriazole in DMF at pH 7 overnight. The reaction is poured into water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and concentrated, and provides the title compound.

15

Step B: 1-Phenyl-4-[1-triphenylmethyl-4-imidazolyl}carbonyl]-2-piperidinone hydrochloride

20

1-Triphenylmethylimidazole-4-magnesium iodide in methylene chloride is prepared as described by R.M. Turner, S.D. Lindell and S.V. Ley in J. Org. Chem., **1991**, 56, 5739-5740, and is added to 1 eq of N-methyl N-methoxy 1-phenyl-2-piperidinone-4-carboxamide in dichloromethane under argon at -78°C. The reaction is warmed to room temperature and quenched with saturated ammonium chloride solution. The reaction is extracted with ethyl acetate and the organic phase dried over magnesium sulfate, filtered and concentrated, providing the title compound.

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- 95 -

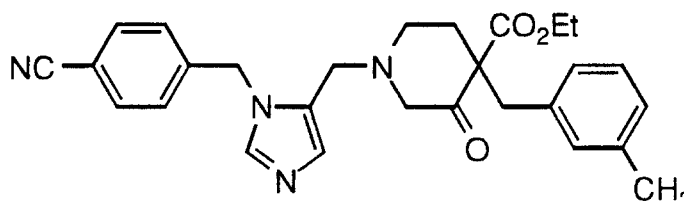
Step C: 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}carbonyl]-1-phenyl-2-piperidinone hydrochloride

The title compound is prepared according to the procedure described in Example 3, Step K, except using the product from Step B in place of 4-[2-{1-(triphenylmethyl)-4-imidazolyl}ethyl]-1-phenyl-2-piperidinone. The title compound is obtained after purification by silica gel chromatography, and conversion to the hydrochloride salt.

EXAMPLE 6

10

Preparation of Ethyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate trifluoroacetate salt



Step A: Preparation of Ethyl N-tert-butoxycarbonyl-3-oxo-piperidine-4-carboxylate

15

A mixture of ethyl N-benzyl-3-oxo-piperidine-4-carboxylate hydrochloride salt (3.5 g, 11.7 mmol; purified) and 10% palladium on charcoal (0.35 g) in a mixture of ethanol (100 mL) and water (100 mL) was hydrogenated at room temp. at 60 psi overnight. The resultant mixture was filtered through a plug of Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in mixture of triethylamine (5 mL), dioxane (20 mL) and water (19 mL), and treated with di-tert-butyl dicarbonate (3.2 g). The reaction mixture was stirred at room temp. overnight. The product mixture was concentrated and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 20% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title

- 96 -

compound as clear colorless oil, which was stored under argon at -10 °C.

Step B: Preparation of Ethyl N-tert-butoxycarbonyl-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate

To a cold (0 °C) slurry of sodium hydride (0.29 g, 12 mmol) in anhydrous dimethylformamide (50 mL), a solution of ethyl N-tert-butoxycarbonyl-3-oxo-piperidine-4-carboxylate (2.73 g, 10 mmol) in DMF (10 mL) was added. The mixture was stirred at 0 °C for 30 min., and at room temp. for 30 min. The resultant solution was cooled back to 0 °C and treated with 3-methylbenzyl bromide (1.63 mL, 12 mmol). The reaction mixture was stirred at room temp. overnight and concentrated under vacuum. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 17.5% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title compound.

Step C: Preparation of Ethyl 3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate hydrochloride salt

To a cold (0 °C) solution of ethyl N-tert-butoxycarbonyl-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate (1.55 g, 4.13 mmol) in ethyl acetate (75 mL), a stream of anhydrous hydrogen chloride gas was bubbled for 20 min. The resultant mixture was stirred at 0 °C for 1 h, purged with argon for 10 min., and concentrated under vacuum to provide the title compound as white solid.

Step D: Preparation of Ethyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate trifluoroacetate salt

A solution of ethyl 3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate hydrochloride salt (4.13 mmol), 1-(4-cyanobenzyl)-5-chloromethylimidazole hydrochloride salt (1.11 g, 4.13 mmol), and

- 97 -

diisopropylethylamine (1.58 mL, 9.1 mmol) in anhydrous acetonitrile (10 mL) was heated under reflux overnight. The resultant mixture was concentrated under vacuum, and the residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic
5 extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 1:1 mixture of chloroform and chloroform saturated with ammonia gas. After collection and concentration of appropriate fractions, the residue further
10 purified by subjecting to high pressure liquid column chromatography on C-18 reverse phase stationary phase. Collection and lyophilization of appropriate fractions provided the title compound as white solid. Anal. Calcd for $C_{28}H_{30}N_4O_3 \cdot 1.6 \text{ TFA} \cdot 0.1 \text{ H}_2\text{O}$: C, 57.23; H, 4.90; N, 8.56. Found: C, 57.21; H, 4.85; N, 8.53.

15

EXAMPLE 7

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified
20 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-(2-
25 hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl_2 , 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.
30 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
35 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the

- 98 -

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.

5 Human FPTase was prepared as described by Omer et al., 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.,
10 stopped with 100 μ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples are tested for inhibitory activity against human FPTase by the assay described above. The compound of the instant invention
15 described in Examples 1 and 6 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC₅₀ of ≤ 10 μ M.

EXAMPLE 8

20

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
25 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
30 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 aprotinen/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

- 99 -

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. *Virology* 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a
5 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
10 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.

15 EXAMPLE 9

In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the
20 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* may be included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

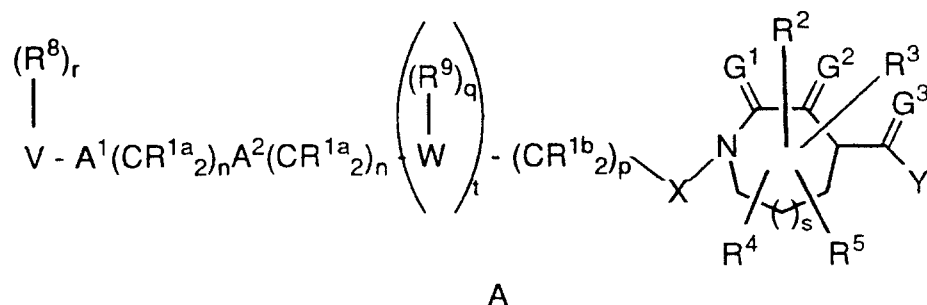
Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos*
25 are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in
30 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 days after the cultures are seeded and comparisons are made.

- 100 -

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



wherein:

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

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(O)-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(O)-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;

R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycle, $\text{C}(=\text{O})\text{NR}^6\text{R}^7$ and $\text{C}(=\text{O})\text{OR}^6$,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:

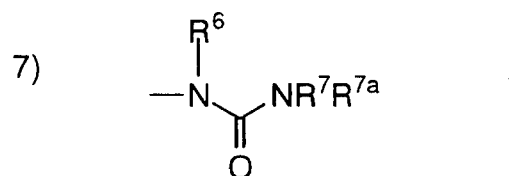
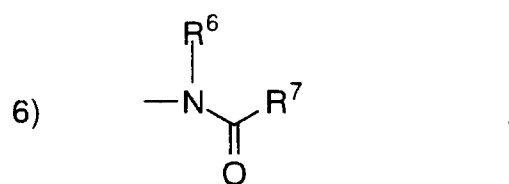
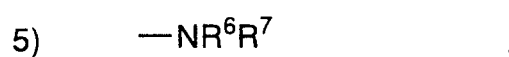
- 101 -

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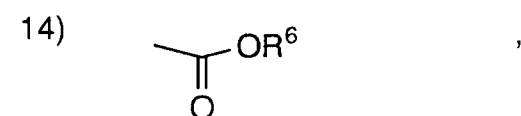
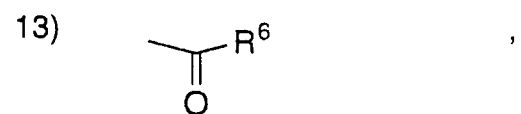
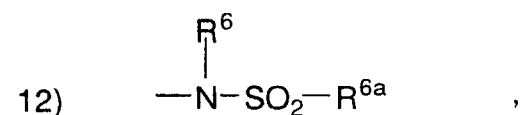
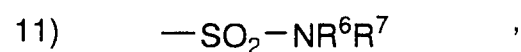
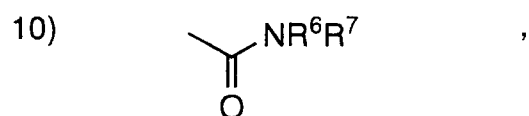
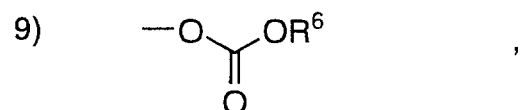
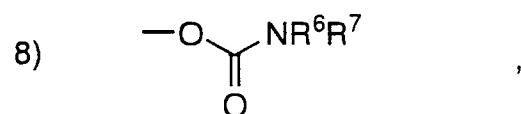
10

- a) C₁₋₄ alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- e) CN,
- f) aryl or heteroaryl,
- g) perfluoro-C₁₋₄ alkyl,
- h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},

- 2) C₃₋₆ cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



- 102 -



- 5 R^2 and R^3 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

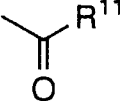
R^4 and R^5 are independently selected from H and CH_3 ;

10

and any two of R^2 , R^3 , R^4 and R^5 are optionally attached to the same carbon atom;

- 103 -

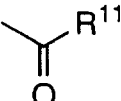
R⁶, R⁷ and R^{7a} are independently selected from: H; C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

- 5
- a) C₁-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) ,
 - f) —SO₂R¹¹, or
 - g) N(R¹⁰)₂; or

10

R⁶ and R⁷ may be joined in a ring;
 R⁷ and R^{7a} may be joined in a ring;

15 R^{6a} is selected from: C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) ,
 - f) —SO₂R¹¹, or
 - g) N(R¹⁰)₂;
- 20

R⁸ is independently selected from:

- a) hydrogen,
- 25 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,

- 104 -

- $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, NO₂, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NH-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;
- 10 R^9 is selected from:
- a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, NO₂, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;
- 20 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;
- R^{11} is independently selected from C₁-C₆ alkyl and aryl;
- 25 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ and $S(O)_m$;
- 30 G^1 and G^2 are independently oxygen or absent, provided that at least one of G^1 and G^2 is oxygen;
- G^3 is oxygen or H₂;

- 105 -

V is selected from:

- a) hydrogen,
- b) heterocycle,
- 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,

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;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

- 15 Y is unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted aryl or substituted heterocycle is substituted with one or more of:

- 1) C₁-4 alkyl, unsubstituted or substituted with:
 - 20 a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - 25 f) -S(O)_mR^{6a}, or
 - g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR⁶,
- 30 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 9) -S(O)_mR^{6a},

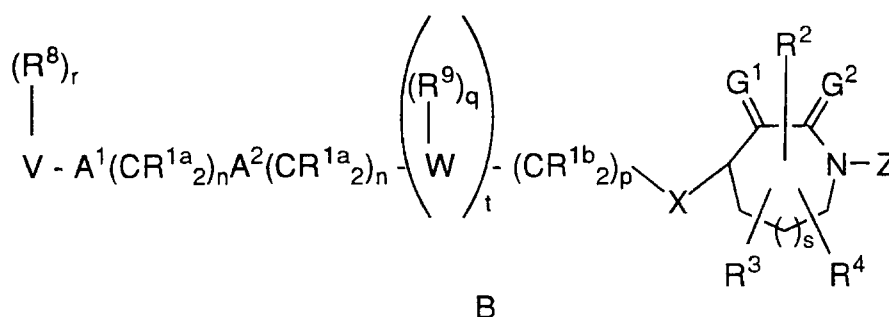
- 106 -

- 10) $-C(O)NR^6R^7$, or
 11) C₃-C₆ cycloalkyl;

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

or an optical isomer or pharmaceutically acceptable salt thereof.

- 15 2. A compound which inhibits farnesyl-protein transferase of the formula B:



wherein:

20

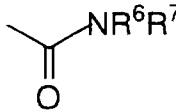
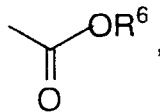
R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 25 CN(R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂,
 R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from

- 107 -

5 unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;

R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

10 unsubstituted or substituted heterocycle,  and ,
 wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - 15 c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁-4 alkyl,
 - 20 h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},

- 108 -

- 5) $\text{—NR}^6\text{R}^7$,
- 6) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—R}^7 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 7) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—NR}^7\text{R}^{7a} \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 8) $\begin{array}{c} \text{—O—C(=O)—NR}^6\text{R}^7 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 9) $\begin{array}{c} \text{—O—C(=O)—OR}^6 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 10) $\begin{array}{c} \text{—C(=O)—NR}^6\text{R}^7 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 11) $\text{—SO}_2\text{—NR}^6\text{R}^7$,
- 12) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—SO}_2\text{—R}^{6a} \end{array}$,
- 13) $\begin{array}{c} \text{—C(=O)—R}^6 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 14) $\begin{array}{c} \text{—C(=O)—OR}^6 \\ \quad \quad \quad | \\ \quad \quad \quad \text{O} \end{array}$,
- 15) N_3 ,
- 16) F, or
- 17) perfluoro- C_{1-4} -alkyl; or

- 109 -

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

5

R^4 is selected from H and CH_3 ;

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

10

R^6 , R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and heteroarylsulfonyl, unsubstituted or substituted with:

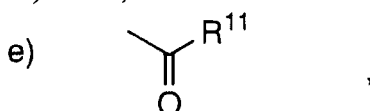
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a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,



f) $-\text{SO}_2R^{11}$, or

g) $N(R^{10})_2$; or

20

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

25

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

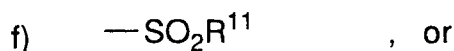
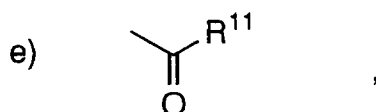
a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

- 110 -



R^8 is independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
- 15 R¹⁰OC(O)NH-;

R^9 is selected from:

- a) hydrogen,
- 20 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(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-,
- 25 (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

30

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

- 111 -

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 , $-\text{N}(\text{R}^{10})-$,
 $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$, $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$ and $\text{S}(\text{O})_m$;

5

G^1 and G^2 are independently oxygen or absent provided that at least one
of G^1 and G^2 is oxygen;

V is selected from:

10

- a) hydrogen,
- b) heterocycle,
- 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,

15

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 $\text{S}(\text{O})_m$;

20

W is a heterocycle;

X is a bond, $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})_m-$;

Z is selected from:

25

- 1) a unsubstituted or substituted group selected from aryl,
heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and
heteroarylsulfonyl, wherein the substituted group is substituted
with one or more of the following:

30

- a) C_1 -4 alkyl, unsubstituted or substituted with:
 C_1 -4 alkoxy, NR^6R^7 , C_3 -6 cycloalkyl, aryl,
heterocycle, HO , $-\text{S}(\text{O})_m\text{R}^{6a}$, or $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
- b) aryl or heterocycle,
- c) halogen,
- d) OR^6 ,

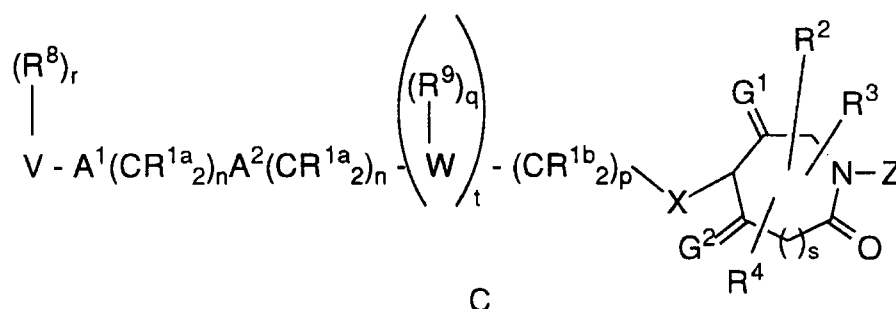
- 112 -

- e) NR^6R^7 ,
 f) CN ,
 g) NO_2 ,
 h) CF_3 ;
 5 i) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 j) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 k) $\text{C}_3\text{-C}_6$ cycloalkyl; and
 2) unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_1\text{-C}_6$ alkyl,
 unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl or substituted $\text{C}_3\text{-C}_6$
 10 cycloalkyl, wherein the substituted $\text{C}_1\text{-C}_6$ alkyl and substituted
 $\text{C}_3\text{-C}_6$ cycloalkyl is substituted with one or two of the
 following:
 a) $\text{C}_1\text{-4}$ alkoxy,
 b) NR^6R^7 ,
 15 c) $\text{C}_3\text{-6}$ cycloalkyl,
 d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
 e) HO ,
 f) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 g) halogen, or
 20 h) perfluoroalkyl;
- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 25 q is 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0 or 1;
 t is 0 or 1; and
 u is 4 or 5;
 30

or a pharmaceutically acceptable salt thereof.

3. A compound which inhibits farnesyl-protein transferase of the formula C:

- 113 -

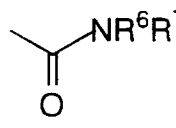
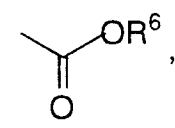


wherein:

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

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;
- 15

R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycle,  and ,

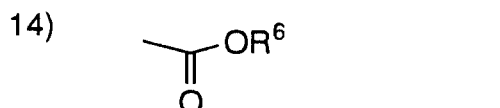
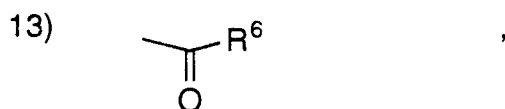
wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - 25 a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,

- 114 -

- 5
- e) CN,
 f) aryl or heteroaryl,
 g) perfluoro-C₁₋₄ alkyl,
 h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃₋₆ cycloalkyl,
 3) OR⁶,
 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},
- 5) —NR⁶R⁷ ,
- 6) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C—R}^7 \\ || \\ \text{O} \end{array}$,
- 7) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C—NR}^7\text{R}^{7a} \\ || \\ \text{O} \end{array}$,
- 8) $\begin{array}{c} \text{—O—C—NR}^6\text{R}^7 \\ || \\ \text{O} \end{array}$,
- 9) $\begin{array}{c} \text{—O—C—OR}^6 \\ || \\ \text{O} \end{array}$,
- 10) $\begin{array}{c} \text{—C—NR}^6\text{R}^7 \\ || \\ \text{O} \end{array}$,
- 11) —SO₂—NR⁶R⁷ ,
- 12) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—SO}_2\text{—R}^{6a} \end{array}$,
- 10

- 115 -



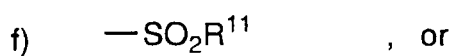
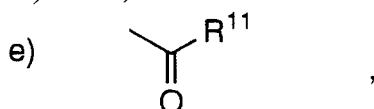
R^2 and R^3 are attached to the same C atom and are combined to form -
 (CH₂)_u - wherein one of the carbon atoms is optionally replaced by a
 5 moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R^4 is selected from H and CH₃;

10 and any two of R^2 , R^3 and R^4 are optionally attached to the same
 carbon atom;

R^6 , R^7 and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆
 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl and
 heteroarylsulfonyl, unsubstituted or substituted with:

- 15 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



R^6 and R^7 may be joined in a ring;

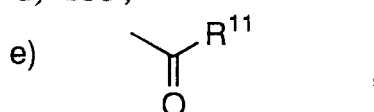
- 116 -

R⁷ and R^{7a} may be joined in a ring;

R^{6a} is selected from: C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle and aryl, unsubstituted or substituted with:

5

- a) C₁₋₄ alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,



10

- f) $\text{—SO}_2\text{R}^{11}$, or
- g) N(R¹⁰)₂;

R⁸ is independently selected from:

15

- a) hydrogen,
- b) aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁₋₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

20

25 R⁹ is selected from:

- a) hydrogen,
- b) C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

30

- 117 -

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(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- and S(O)_m;

- 15 G¹ and G² are independently oxygen or absent, provided that if G¹ is oxygen then G² is absent and if s=0, G¹ is oxygen;

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;

30

W is a heterocycle;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

Z is selected from:

- 118 -

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
- 5 a) C₁₋₄ alkyl, unsubstituted or substituted with:
C₁₋₄ alkoxy, NR⁶R⁷, C₃₋₆ cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
- b) aryl or heterocycle,
- c) halogen,
- 10 d) OR⁶,
- e) NR⁶R⁷,
- f) CN,
- g) NO₂,
- h) CF₃;
- 15 i) -S(O)_mR^{6a},
- j) -C(O)NR⁶R⁷, or
- k) C₃₋₆ cycloalkyl; and
- 2) unsubstituted C₁₋₆ alkyl, substituted C₁₋₆ alkyl, unsubstituted C₃₋₆ cycloalkyl or substituted C₃₋₆ cycloalkyl, wherein the substituted C₁₋₆ alkyl and substituted C₃₋₆ cycloalkyl is substituted with one or two of the following:
- 20 a) C₁₋₄ alkoxy,
- b) NR⁶R⁷,
- 25 c) C₃₋₆ cycloalkyl,
- d) -NR⁶C(O)R⁷,
- e) HO,
- f) -S(O)_mR^{6a},
- g) halogen, or
- 30 h) perfluoroalkyl;

m is 0, 1 or 2;

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

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

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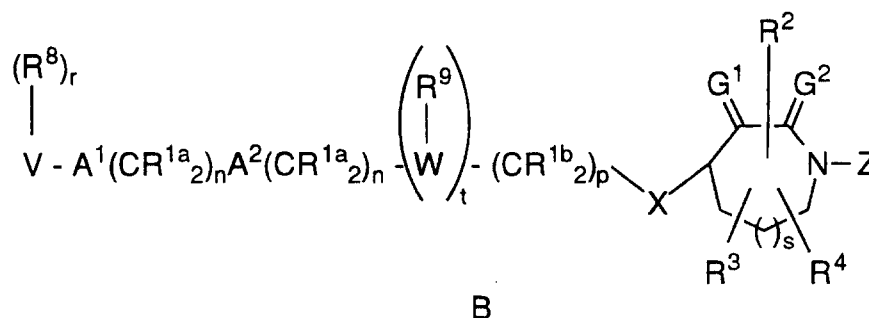
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- 119 -

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

or a pharmaceutically acceptable salt thereof.

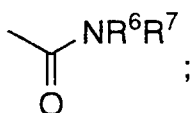
4. The compound according to Claim 2 of the formula
 10 B:

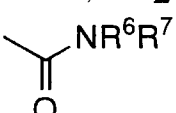


wherein:

- R^{1a} is independently selected from: hydrogen and C₁-C₆ alkyl;
 15 R^{1b} is independently selected from:
 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆
 alkenyl, and
 20 c) unsubstituted or substituted C₁-C₆ alkyl wherein the
 substituent on the substituted C₁-C₆ alkyl is selected from
 unsubstituted or substituted aryl, heterocycle, cycloalkyl,
 alkenyl, R¹⁰O- and -N(R¹⁰)₂;
 25 R³ and R⁴ are independently selected from H and CH₃;

- 120 -

R² is H; ; or C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5) ;

and any two of R², R³, and R⁴ are optionally attached to the same carbon atom;

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

R^{6a} is selected from:

C₁-4 alkyl and C₃-6 cycloalkyl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

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)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

- 121 -

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

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

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

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

25 V is selected from:

- a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
 c) aryl,
 30 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

- 122 -

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

5 G^1 is absent;
 G^2 is oxygen;

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

10

X is $-CH_2-$ or $-C(=O)-$;

Z is selected from:

- 15 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
- 20 a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^6R^7 , C_{3-6} cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^{6a}$, or $-C(O)NR^6R^7$,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) OR^6 ,
 - 25 e) NR^6R^7 ,
 - f) CN,
 - g) NO_2 ,
 - h) CF_3 ;
 - i) $-S(O)_mR^{6a}$,
 - j) $-C(O)NR^6R^7$, or
 - 30 k) C_{3-6} cycloalkyl; and
- 2) unsubstituted C_{1-6} alkyl, substituted C_{1-6} alkyl, unsubstituted C_{3-6} cycloalkyl or substituted C_{3-6} cycloalkyl, wherein the substituted C_{1-6} alkyl and substituted

- 123 -

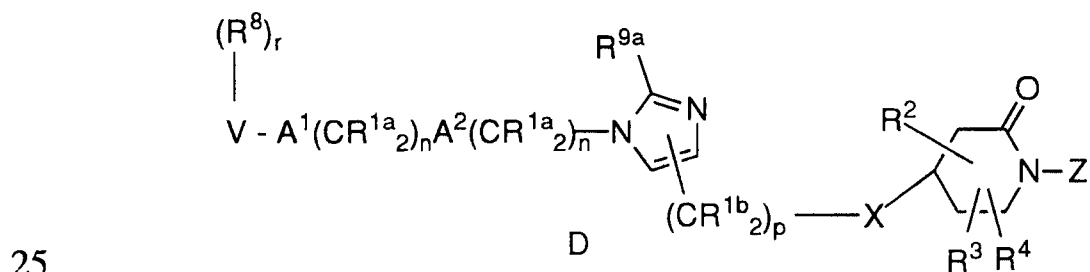
C3-C6 cycloalkyl is substituted with one or two of the following:

- a) C1-4 alkoxy,
- b) NR^6R^7 ,
- 5 c) C3-6 cycloalkyl,
- d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
- e) HO,
- f) $-\text{S}(\text{O})_m\text{R}^{6a}$,
- g) halogen, or
- 10 h) perfluoroalkyl;

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

20 or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 2 of the formula D:



wherein:

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

- 124 -

R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C₂-C₆ alkenyl, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

R^3 and R^4 independently selected from H and CH₃;

10 R^2 is selected from H; $\begin{array}{c} \text{NR}^6\text{R}^7 \\ \diagup \\ \text{C} \\ \parallel \\ \text{O} \end{array}$; and C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR^6 ,
- 4) SR^{6a} , SO_2R^{6a} , or
- 15 5) $\begin{array}{c} \text{NR}^6\text{R}^7 \\ \diagup \\ \text{C} \\ \parallel \\ \text{O} \end{array}$;

and R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

20 R^6 and R^7 are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- 25 c) aryl or heterocycle;

R^{6a} is selected from:

C₁-4 alkyl and C₃-6 cycloalkyl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- 30 b) halogen, or
- c) aryl or heterocycle;

- 125 -

R^8 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)-, -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)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, and 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,
- 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 A^1 is S(O)_m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)_m;

- 126 -

X is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$;

Z is selected from:

- 5 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
 - 10 a) C₁₋₄ alkyl, unsubstituted or substituted with: C₁₋₄ alkoxy, NR^6R^7 , C₃₋₆ cycloalkyl, aryl, heterocycle, HO, $-\text{S}(\text{O})_m\text{R}^{6a}$, or $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) OR^6 ,
 - e) NR^6R^7 ,
 - 15 f) CN,
 - g) NO_2 ,
 - h) CF_3 ;
 - i) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 - j) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 - 20 k) C₃₋₆ cycloalkyl; and
- 2) unsubstituted C₁₋₆ alkyl, substituted C₁₋₆ alkyl, unsubstituted C₃₋₆ cycloalkyl or substituted C₃₋₆ cycloalkyl, wherein the substituted C₁₋₆ alkyl and substituted C₃₋₆ cycloalkyl is substituted with one or two of the
 - 25 following:
 - a) C₁₋₄ alkoxy,
 - b) NR^6R^7 ,
 - c) C₃₋₆ cycloalkyl,
 - d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
 - 30 e) HO,
 - f) $-\text{S}(\text{O})_m\text{R}^{6a}$,
 - g) halogen, or
 - h) perfluoroalkyl;

- 127 -

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

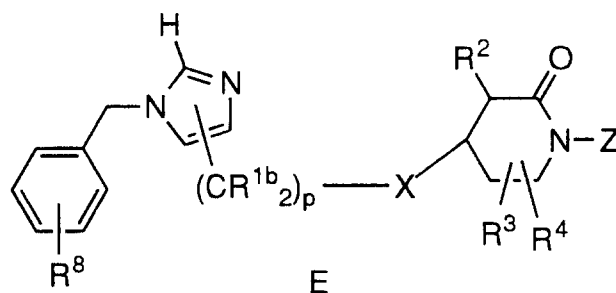
5

or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 2 of the formula

E:

10



wherein:

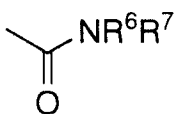
R^{1b} is independently selected from:

15

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C₂-C₆ alkenyl, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

20

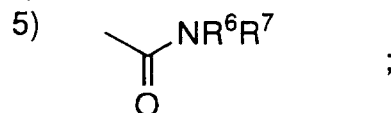
R^3 and R^4 independently selected from H and CH₃;

R^2 is selected from H; ; and C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

25

- 1) aryl,
- 2) heterocycle,
- 3) OR^6 ,

- 128 -

4) SR^{6a} , SO_2R^{6a} , or

and R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

5

R^6 and R^7 are independently selected from:

H; C_1 -4 alkyl, C_3 -6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- 10 a) C_1 -4 alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:

C_1 -4 alkyl and C_3 -6 cycloalkyl, unsubstituted or substituted with:

- 15 a) C_1 -4 alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

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

30 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;

- 129 -

X is -CH₂- or -C(=O)-;

Z is selected from:

- 5 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
 - 10 a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) OR⁶,
 - e) NR⁶R⁷,
 - 15 f) CN,
 - g) NO₂,
 - h) CF₃;
 - i) -S(O)_mR^{6a},
 - j) -C(O)NR⁶R⁷, or
 - 20 k) C₃-C₆ cycloalkyl; and
- 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the
 - 25 following:
 - a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) -NR⁶C(O)R⁷,
 - 30 e) HO,
 - f) -S(O)_mR^{6a},
 - g) halogen, or
 - h) perfluoroalkyl;

- 130 -

m is 0, 1 or 2; and

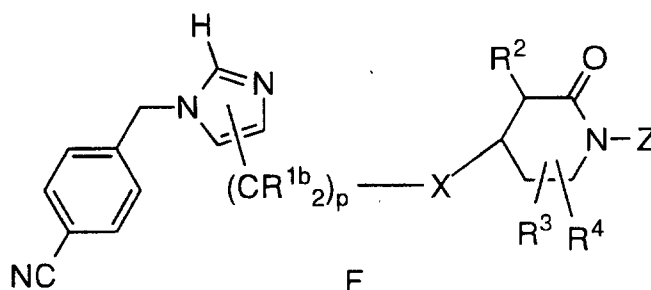
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

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7. The compound according to Claim 2 of the formula

F:



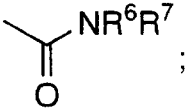
10 wherein:

R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

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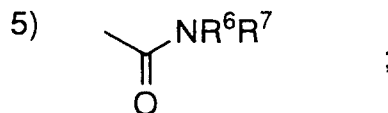
R³ and R⁴ independently selected from H and CH₃;

20 R² is selected from H; ; and C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or

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- 131 -



and R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

5 R^6 and R^7 are independently selected from:

H; C_1 -4 alkyl, C_3 -6 cycloalkyl, aryl and heterocycle, unsubstituted or substituted with:

- 10 a) C_1 -4 alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:

C_1 -4 alkyl and C_3 -6 cycloalkyl, unsubstituted or substituted with:

- 15 a) C_1 -4 alkoxy,
b) halogen, or
c) aryl or heterocycle;

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

20

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

X is $-CH_2-$ or $-C(=O)-$;

25 Z is selected from:

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl and heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

- 30 a) C_1 -4 alkyl, unsubstituted or substituted with:
 C_1 -4 alkoxy, NR^6R^7 , C_3 -6 cycloalkyl, aryl, heterocycle, HO, $-S(O)_mR^{6a}$, or $-C(O)NR^6R^7$,
b) aryl or heterocycle,

- 132 -

- 5 c) halogen,
 d) OR^6 ,
 e) NR^6R^7 ,
 f) CN,
 g) NO_2 ,
 h) CF_3 ;
 i) $-S(O)_mR^{6a}$,
 j) $-C(O)NR^6R^7$, or
 k) C3-C6 cycloalkyl; and
 10 2) unsubstituted C1-C6 alkyl, substituted C1-C6 alkyl,
 unsubstituted C3-C6 cycloalkyl or substituted C3-C6
 cycloalkyl, wherein the substituted C1-C6 alkyl and substituted
 C3-C6 cycloalkyl is substituted with one or two of the
 following:
 15 a) C1-4 alkoxy,
 b) NR^6R^7 ,
 c) C3-6 cycloalkyl,
 d) $-NR^6C(O)R^7$,
 e) HO,
 20 f) $-S(O)_mR^{6a}$,
 g) halogen, or
 h) perfluoroalkyl;
 m is 0, 1 or 2; and
 25 p is 0, 1, 2, 3 or 4;

or pharmaceutically acceptable salt thereof.

8. A compound which inhibits farnesyl-protein
 30 transferase which is:

4-[5-(4-Cyanobenzyl)imidazol-1-ylmethyl]-1-phenyl-2-piperidinone

4-[2-{5-(4-Cyanobenzyl)imidazol-1-yl}ethyl]-1-phenyl-2-piperidinone

- 133 -

4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-1-phenyl-2-piperidinone

(±)*cis*- 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone

(±)*trans*- 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-3-methyl-1-phenyl-2-piperidinone

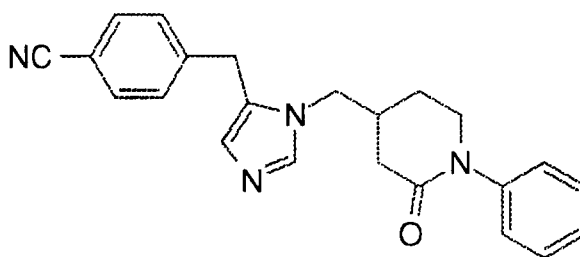
10 4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}carbonyl]-1-phenyl-2-piperidinone or

Ethyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-3-oxo-4-(3-methylbenzyl)piperidine-4-carboxylate

15 or a pharmaceutically acceptable salt or optical isomer thereof.

9. The compound according to Claim 8 which is:

20 4-[5-(4-Cyanobenzyl)imidazol-1-ylmethyl]-1-phenyl-2-piperidinone



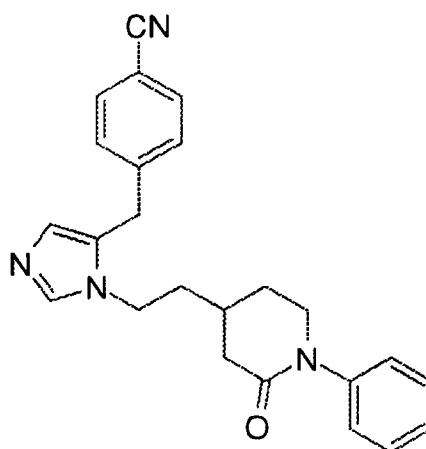
or a pharmaceutically acceptable salt or optical isomer thereof.

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10. The compound according to Claim 8 which is:

4-[2-{5-(4-Cyanobenzyl)imidazol-1-yl}ethyl]-1-phenyl-2-piperidinone

- 134 -



or a pharmaceutically acceptable salt or optical isomer thereof.

- 5 11. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 1.
- 10 12. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 2.
- 15 13. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 3.
- 20 14. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 8.
15. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 11.

- 135 -

16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.
- 5 17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.
- 10 18. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.
- 15 19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.
- 20 20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.
21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.
- 25 22. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.
- 30 23. 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 12.

- 136 -

24. 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 12.

5 25. 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 12.

10 26. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

15 27. 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 12.

28. A pharmaceutical composition made by combining the compound of Claim 2 and a pharmaceutically acceptable carrier.

20 29. A process for making a pharmaceutical composition comprising combining a compound of Claim 2 and a pharmaceutically acceptable carrier.