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(54) **INHIBITEURS DE FARNESYL-PROTEINE TRANSFERASE**
(54) **INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE**

(57) Composés qui inhibent la farnésyl-protéine transférase (Ttase) et la farnésylation de la protéine oncogène Ras. La présente invention concerne en outre des compositions chimiothérapeutiques contenant lesdits composés et des procédés permettant d'inhiber la farnésyl-protéine transférase et la farnésylation de la protéine oncogène Ras.

(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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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

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.

TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

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 growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory 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 contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} 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.

Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-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 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 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

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 thereapy 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).

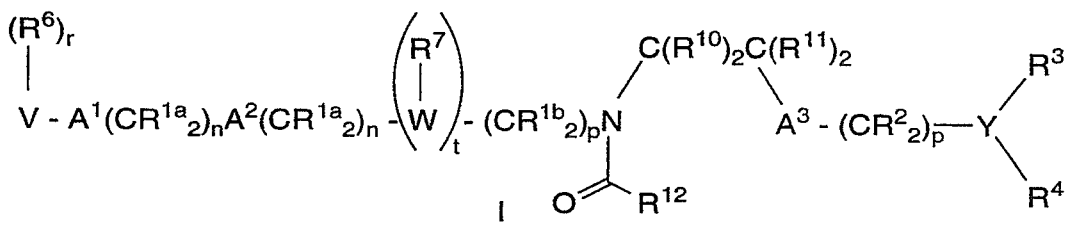
It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to

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

SUMMARY OF THE INVENTION

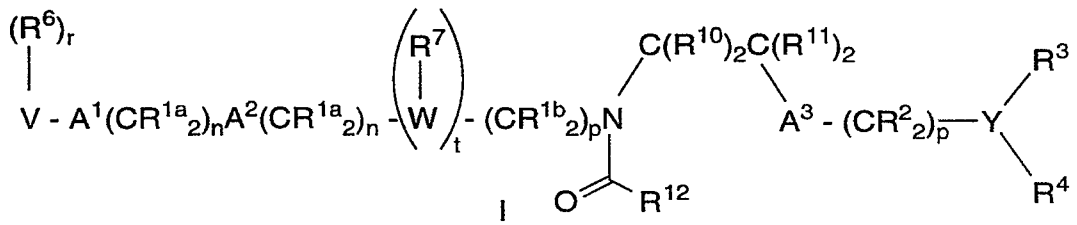
The present invention comprises small molecule peptidomimetic amide-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical 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.

The compounds of this invention are illustrated by the formula I:



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 I:



wherein:

R^{1a}, R^{1b} and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)$-NR^8-;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $CF_3(CH_2)_nO$-, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocyclic,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

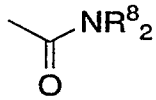
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-;

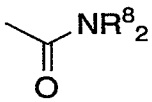
R^7 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is H, C_1-C_{10} alkyl, substituted or unsubstituted aryl or C_1-C_{10} alkyl which is substituted with a substituted or unsubstituted aryl ;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, or S(O)m;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

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

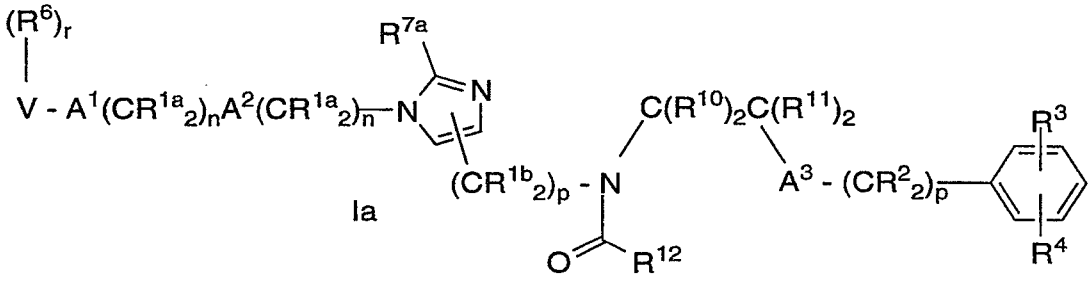
W is a heterocycle;

Y is aryl or heteroaryl;

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

or the pharmaceutically acceptable salts thereof.

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



Ia

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

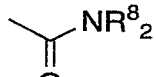
R^5 is selected from:
a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

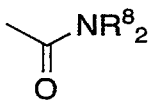
R^6 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{7a} is hydrogen or methyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is H, C_1-C_{10} alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or S(O)m;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

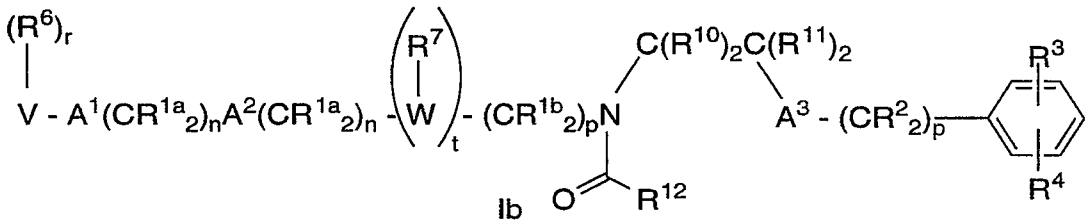
e) C_2-C_{20} alkenyl, and

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

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;

or the pharmaceutically acceptable salts thereof.

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



Ib

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN,

$(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,

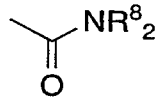
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

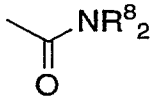
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^7 is selected from: hydrogen and C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or $S(O)_m$;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

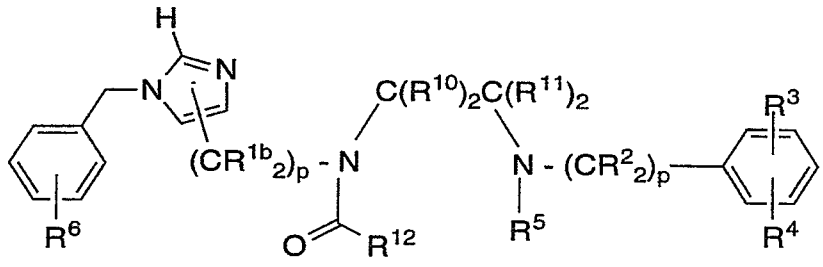
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

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

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

or the pharmaceutically acceptable salts thereof.

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



Ic

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-

$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

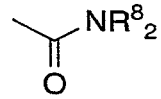
a) hydrogen,

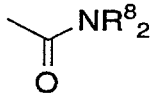
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_1-$_5$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

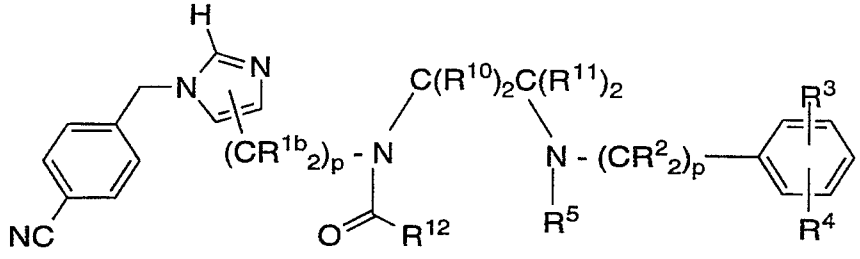
1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

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

or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula Id:



Id

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

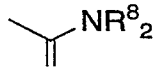
a) hydrogen,

and

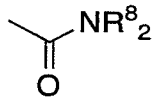
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_1-C_5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,

4) SR^9, SO_2R^9, or
5)  ;

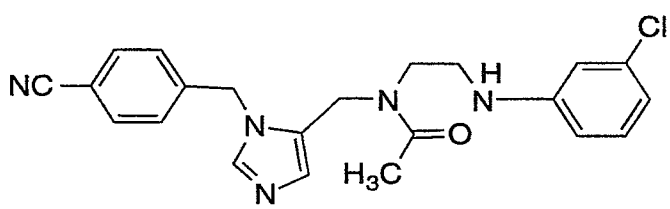
R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

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

or the pharmaceutically acceptable salts thereof.

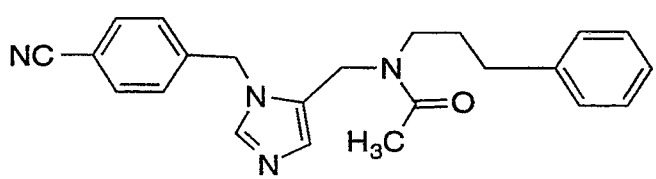
Specific examples of the compounds of the invention are:

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-[2-((3-chlorophenyl)amino)ethyl]acetamide



or

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-(3-phenylpropyl)acetamide



or the pharmaceutically acceptable salts thereof.

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, R^{1a}, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

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.

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, 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 heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl,

isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" 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 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, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)S(O)$_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Preferably, R^{1a}, R^{1b} and R^2 are independently selected from: hydrogen, $-N(R^8)_2$, $R^8C(O)NR^8-$ or C_1-C_6 alkyl unsubstituted or substituted by $-N(R^8)_2$, R^8O- or $R^8C(O)NR^8-$.

Preferably, R^3 and R^4 are independently selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, NO_2, $R^8{}_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8-$ and C_1-C_6 alkyl.

Preferably, R^5 is selected from hydrogen or C_1-C_6 alkyl substituted with hydrogen, $R^9S(O)_m-$, CF_3- or an unsubstituted or substituted aryl group.

Preferably, R^6 is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, NO_2, $R^8{}_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8-$ and C_1-C_6 alkyl.

Preferably, R^7 is hydrogen.

Preferably, R^8 is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, R^9 is selected from C_1-C_6 alkyl.

Preferably, R^{10} and R^{11} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, R^{12} is selected from C_1-C_6 alkyl. More preferably R^{12} is methyl.

Preferably, A^1 and A^2 are independently selected from: a bond, $-C(O)NR^8-$, $-NR^8C(O)-$, O, $-N(R^8)-$, $-S(O)_2N(R^8)-$ and- $N(R^8)S(O)_2-$.

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

Preferably, Y is selected from phenyl, furyl, thienyl and pyridyl. Most preferably, Y is phenyl.

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

Preferably t is 1.

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, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^8)_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

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 Schemes 1-12, 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 $R'CH_2$-, as shown in the Schemes, represent the substituents R^8, R^9 and others, depending on the compound of the instant invention that is being synthesized. The variable p' represents p-1.

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 1-12:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 1-2 illustrates the synthesis of one of the preferred embodiments of the instant invention, wherein the variable W is present as a imidazolyl moiety that is substituted with a suitably substituted benzyl group. Substituted protected imidazole alkanols II can be prepared by methods known in the art, such as those described by F. Schneider, *Z. Physiol. Chem.*, 3:206-210 (1961) and C.P. Stewart, *Biochem. Journal*, 17:130-133(1923). Benzylation and deprotection of the imidazole alkanol provides intermediate III which can be oxidized to the corresponding aldehyde IV.

The aldehyde whose synthesis is illustrated in Scheme 1 may be reacted with a suitably substituted diamine VI, which was prepared from the aniline V as shown in Scheme 2, to provide the intermediate compound VII. Compound VII can be selectively N-acylated under standard conditions, such as those illustrated, to provide the instant compound VIII. The analogous reaction directed towards compounds wherein A^3 is a bond is illustrated in Scheme 2a.

Schemes 3-6 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.

The diamine VI can be reacted with a variety of other aldehydes, such as IX, as shown in Scheme 7. The product X is first acylated and then can be deprotected to give the instant compound XI. The compound XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. As shown in Scheme 8, Compound XI can further be selectively protected to obtain XII which can subsequently be reductively alkylated with a second aldehyde, such as XIII, to obtain XIV. Removal of the

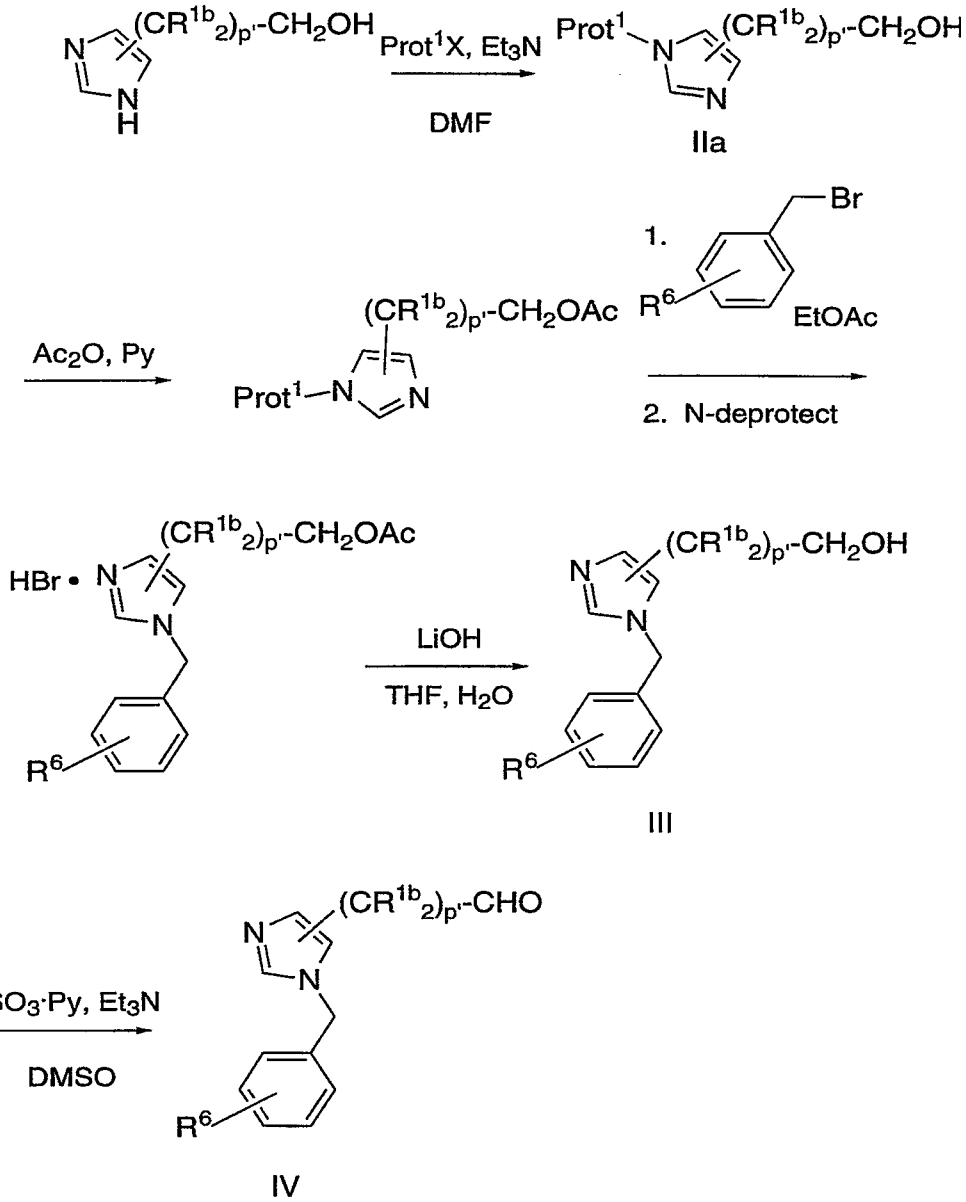
protecting group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

If the diamine VI is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XVI in Scheme 9, the product XVII can first be acylated and the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 9, 10). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXI. In addition, the fully deprotected amino alcohol XXII can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXIII (Scheme 10), or tertiary amines.

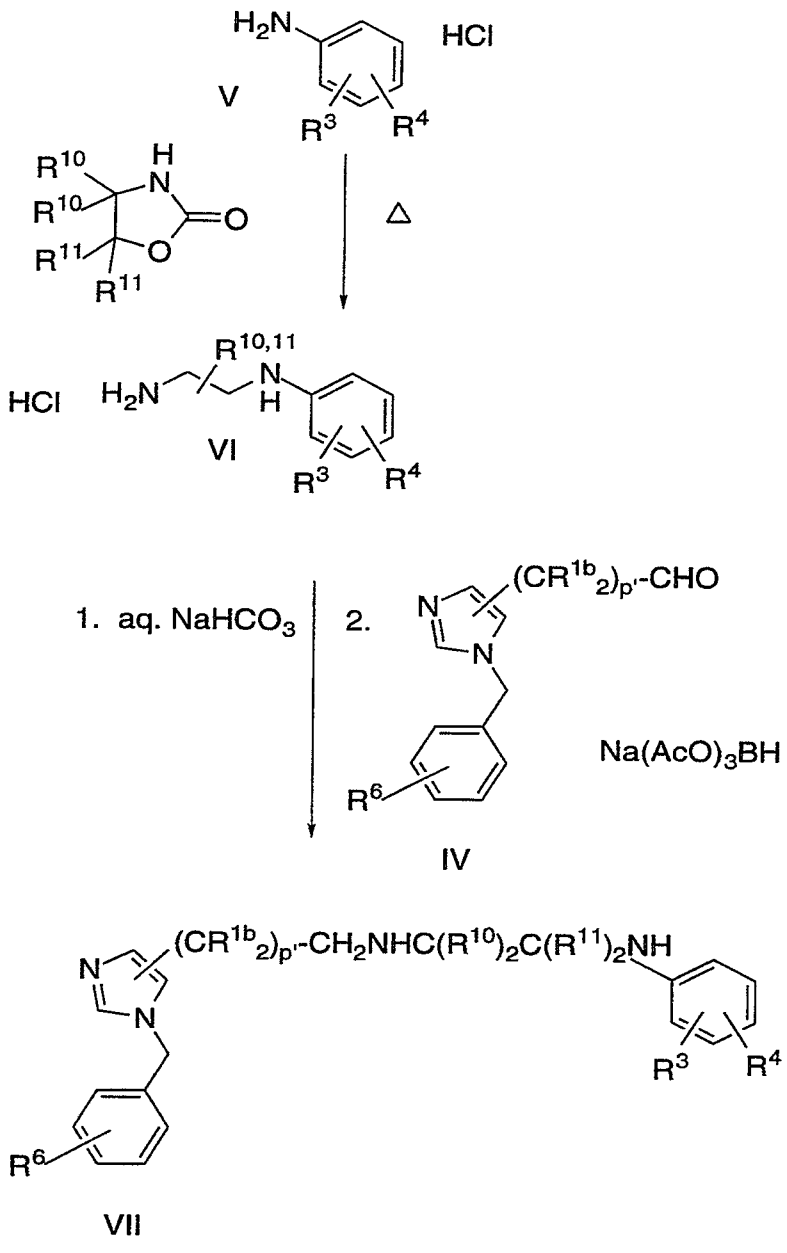
The Boc protected amino alcohol XIX can also be utilized to synthesize 2-aziridinylmethylamides such as XXIV (Scheme 11). Treating XIX with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide leads to the formation of aziridine XXIV. The aziridine may be reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXVI.

In addition, the diamine VI can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXII, as shown in Scheme 12. Intermediate XXXII is first acylated before it is further elaborated. When R' is an aryl group, XXXIII can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXIV. Alternatively, the amine protecting group in XXXIII can be removed, and O-alkylated phenolic amines such as XXXV produced.

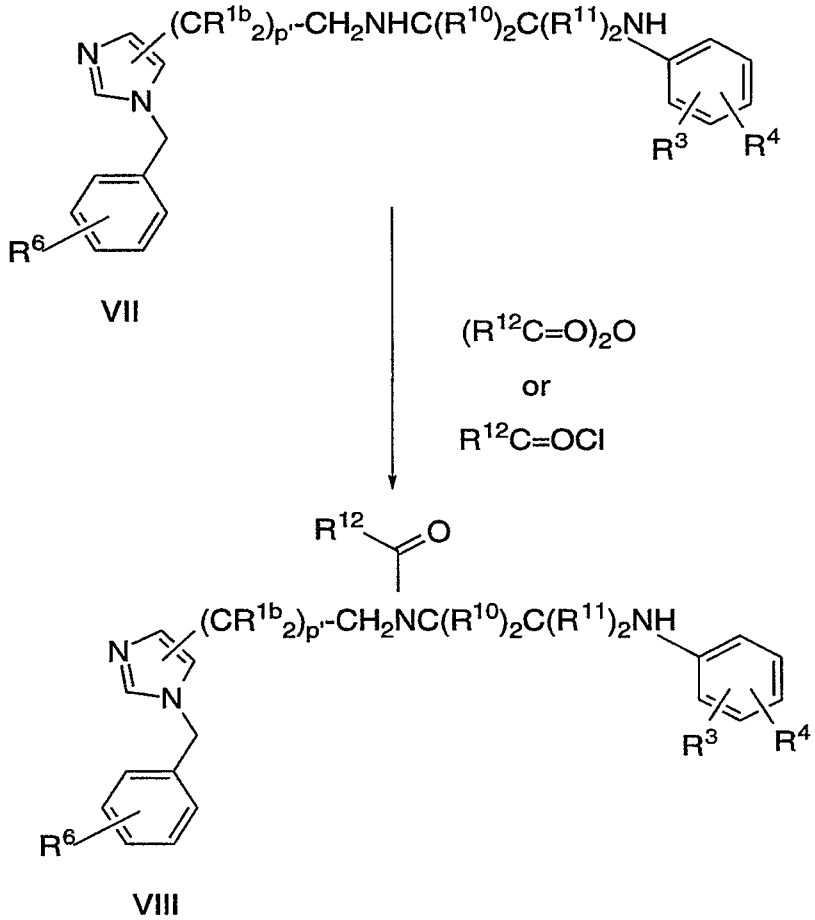
SCHEME 1


(CR1b2)p'-CH2OH
Prot1X, Et3N
DMF
Prot1
(CR1b2)p'-CH2OH
IIa
Br
1.
R6
EtOAc
2. N-deprotect
Ac2O, Py
(CR1b2)p'-CH2OAc
Prot1
HBr •
LiOH
THF, H2O
III
SO3·Py, Et3N
DMSO
(CR1b2)p'-CHO
IV

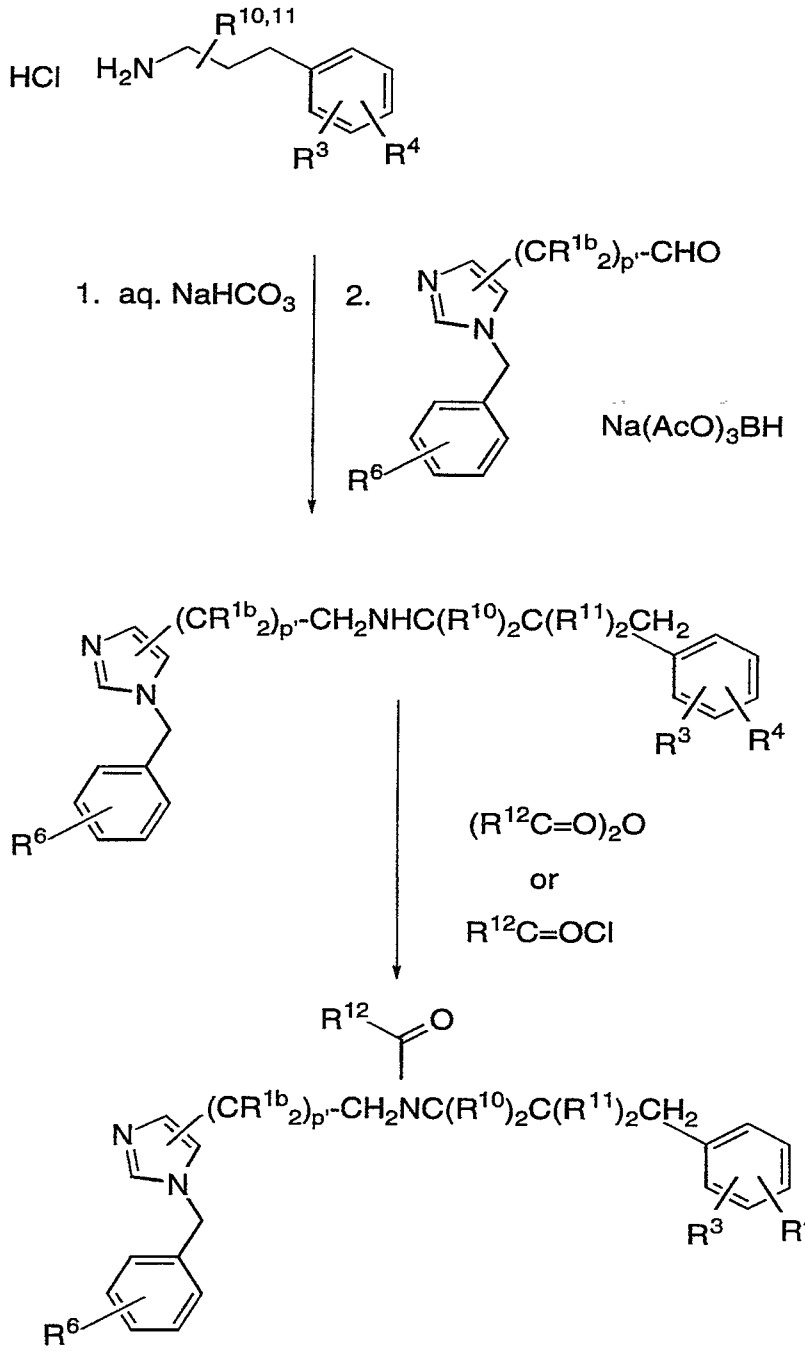
SCHEME 2


H2N
HCl
V
R3
R4
R10
R10
R11
R11
H
N
O
O
Δ
R10,11
HCl
H2N
N
H
VI
R3
R4
1. aq. NaHCO3
2.
(CR1b2)p'-CHO
N
N
R6
Na(AcO)3BH
IV
(CR1b2)p'-CH2NHC(R10)2C(R11)2NH
N
N
R6
R3
R4
VII

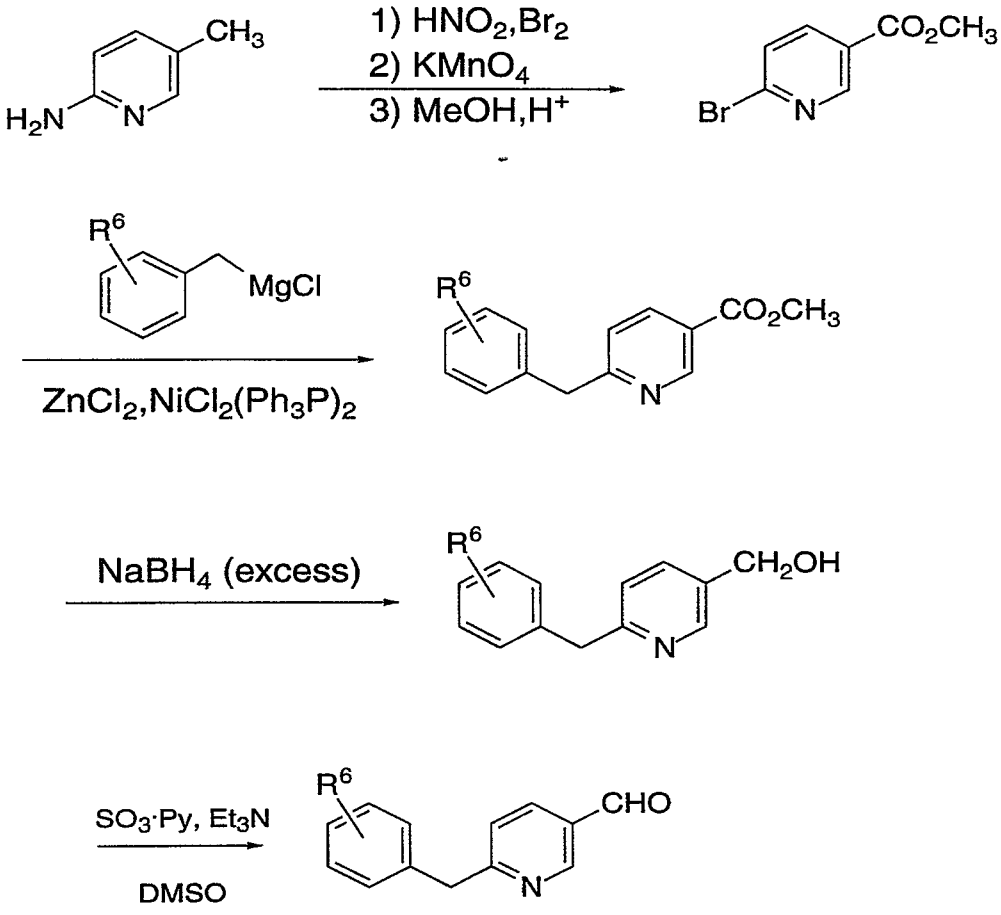
SCHEME 2 (continued)



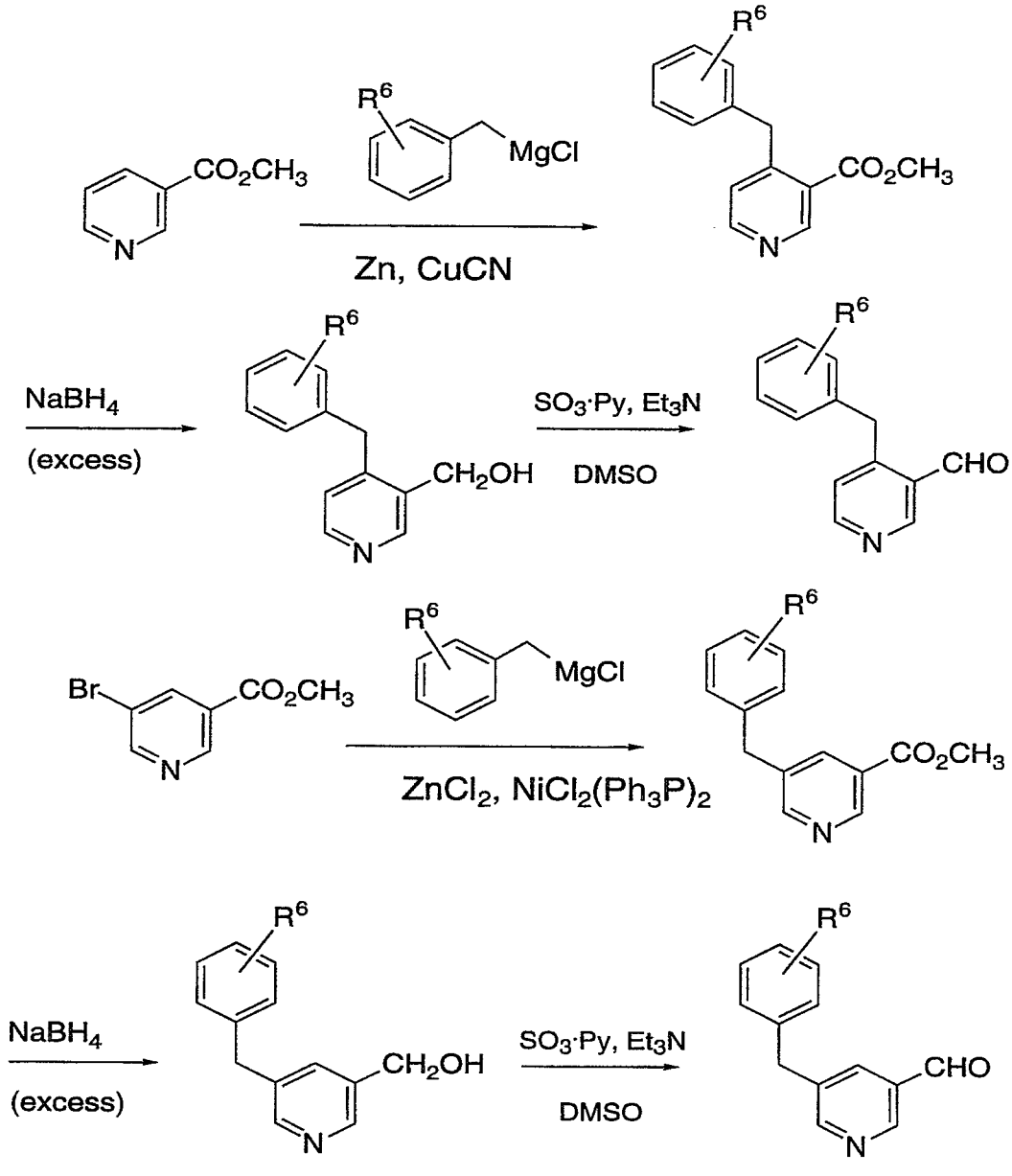
SCHEME 2a


HCl
H_2N
$R^{10,11}$
R^3
R^4
1. aq. $NaHCO_3$
2.
$(CR^{1b}_2)_{p'}$-CHO
$Na(AcO)_3BH$
R^6
$(CR^{1b}_2)_{p'}$-$CH_2NHC(R^{10})_2C(R^{11})_2CH_2$
$(R^{12}C=O)_2O$
or
$R^{12}C=OCl$
R^{12}
O
$(CR^{1b}_2)_{p'}$-$CH_2NC(R^{10})_2C(R^{11})_2CH_2$

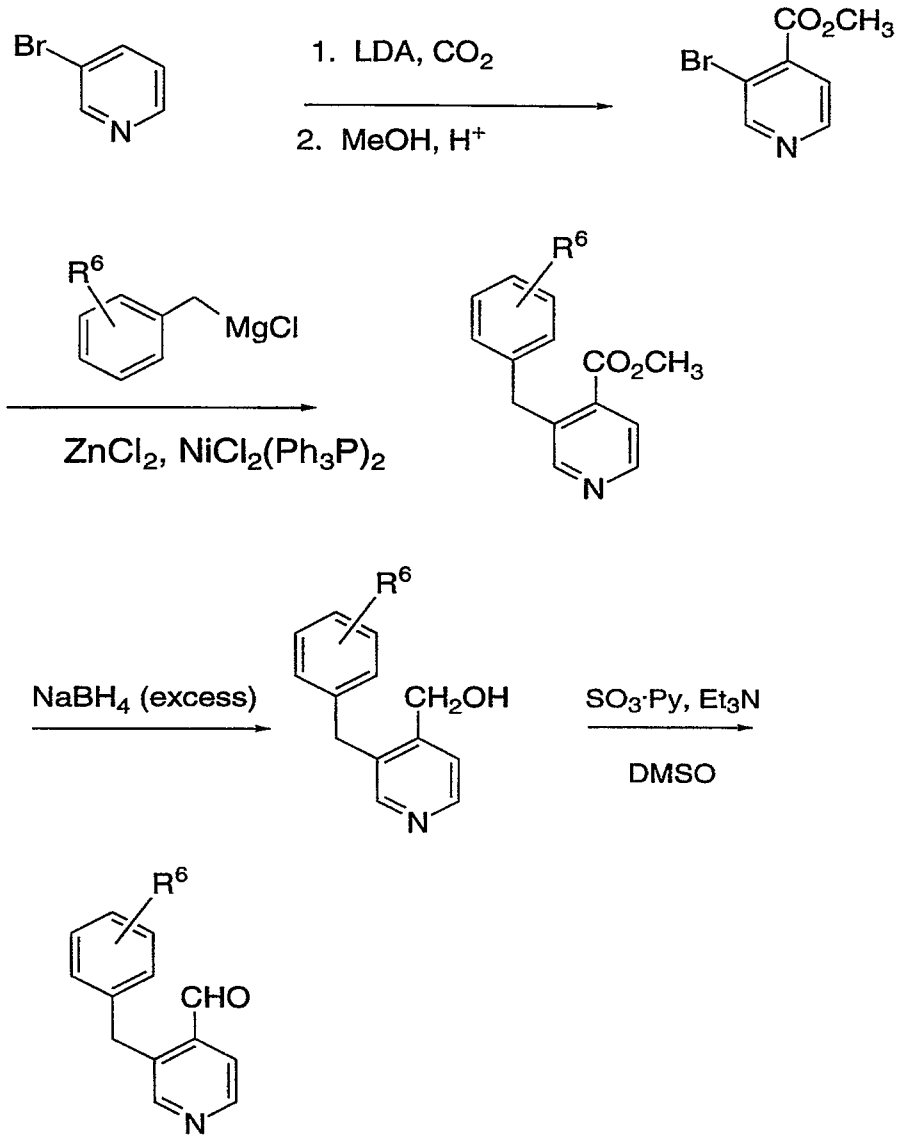
SCHEME 3


1) HNO_2,Br_2
2) $KMnO_4$
3) MeOH,H^+
CH_3
H_2N
N
CO_2CH_3
Br
R^6
MgCl
$ZnCl_2$,$NiCl_2(Ph_3P)_2$
CO_2CH_3
$NaBH_4$ (excess)
CH_2OH
SO_3·Py, Et_3N
DMSO
CHO

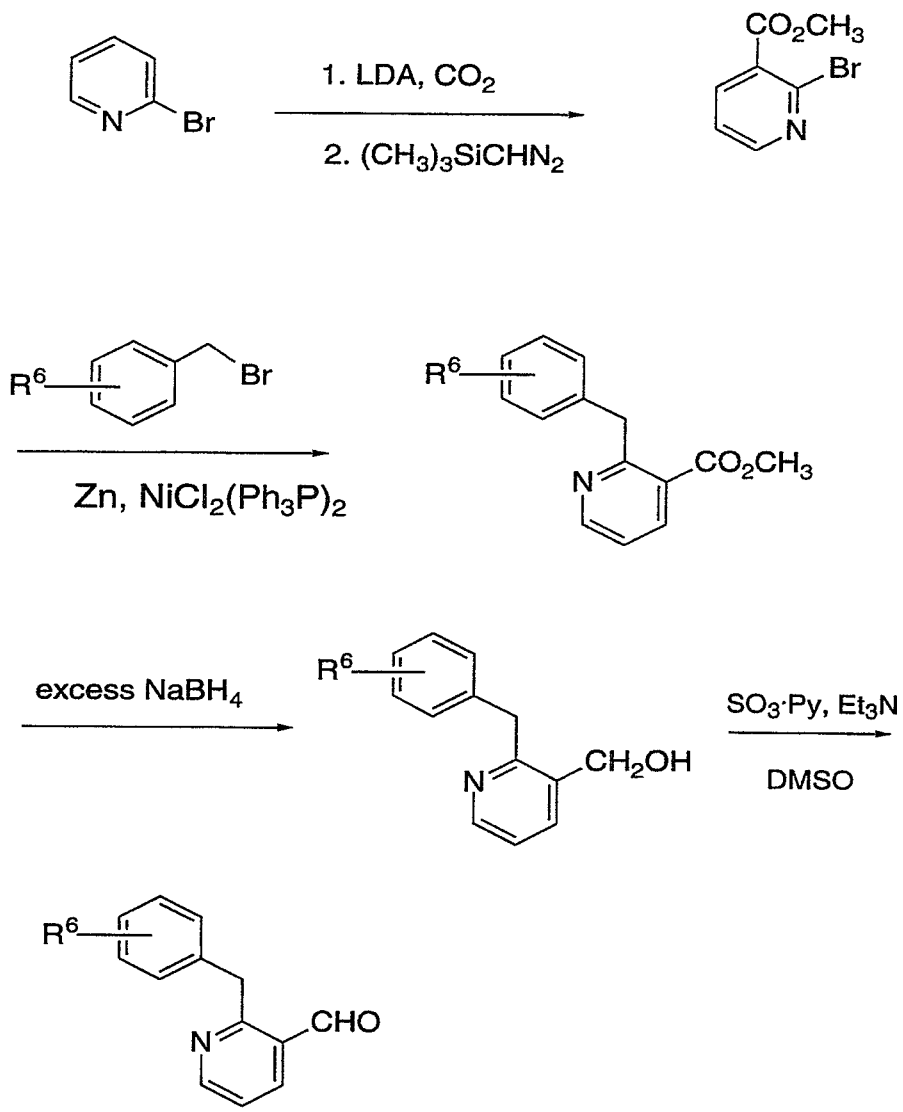
SCHEME 4


R6
MgCl
CO2CH3
N
Zn, CuCN
NaBH4
(excess)
CH2OH
SO3·Py, Et3N
DMSO
CHO
Br
ZnCl2, NiCl2(Ph3P)2

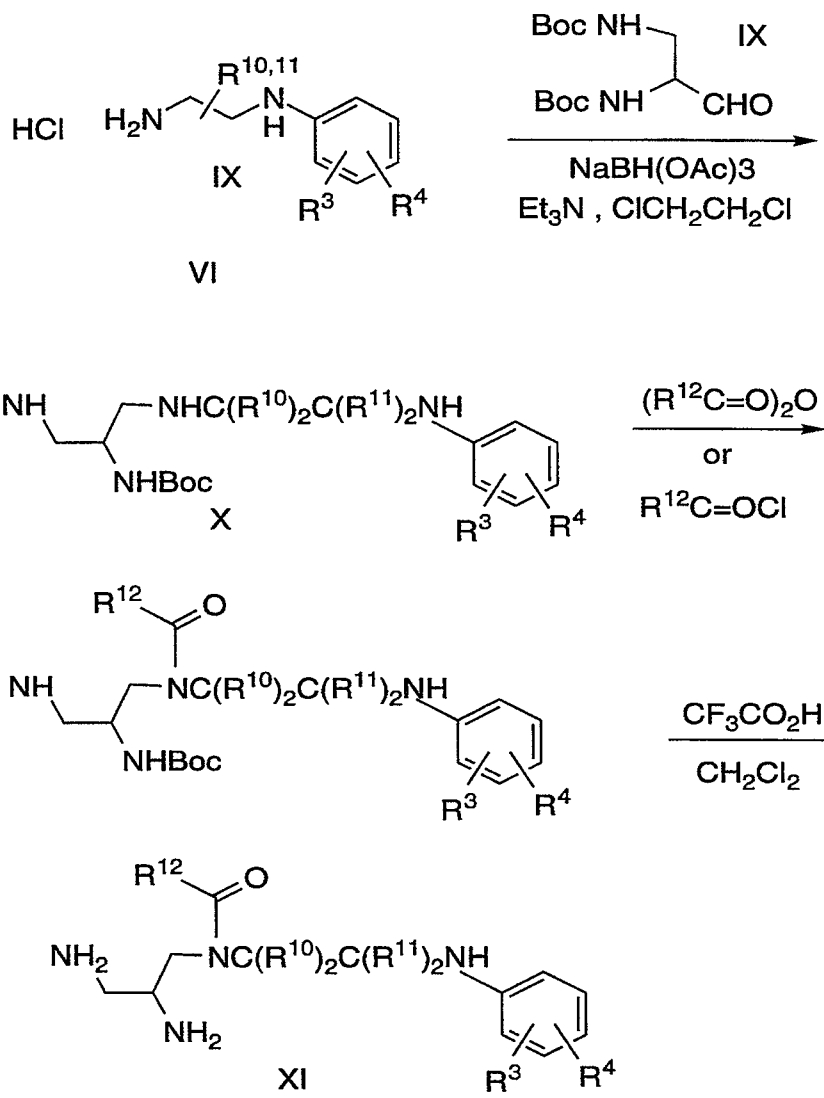
SCHEME 5


Br
N
1. LDA, CO_2
2. MeOH, H^+
CO_2CH_3
Br
N
R^6
MgCl
$ZnCl_2$, $NiCl_2(Ph_3P)_2$
R^6
CO_2CH_3
N
$NaBH_4$ (excess)
R^6
CH_2OH
N
SO_3·Py, Et_3N
DMSO
R^6
CHO
N

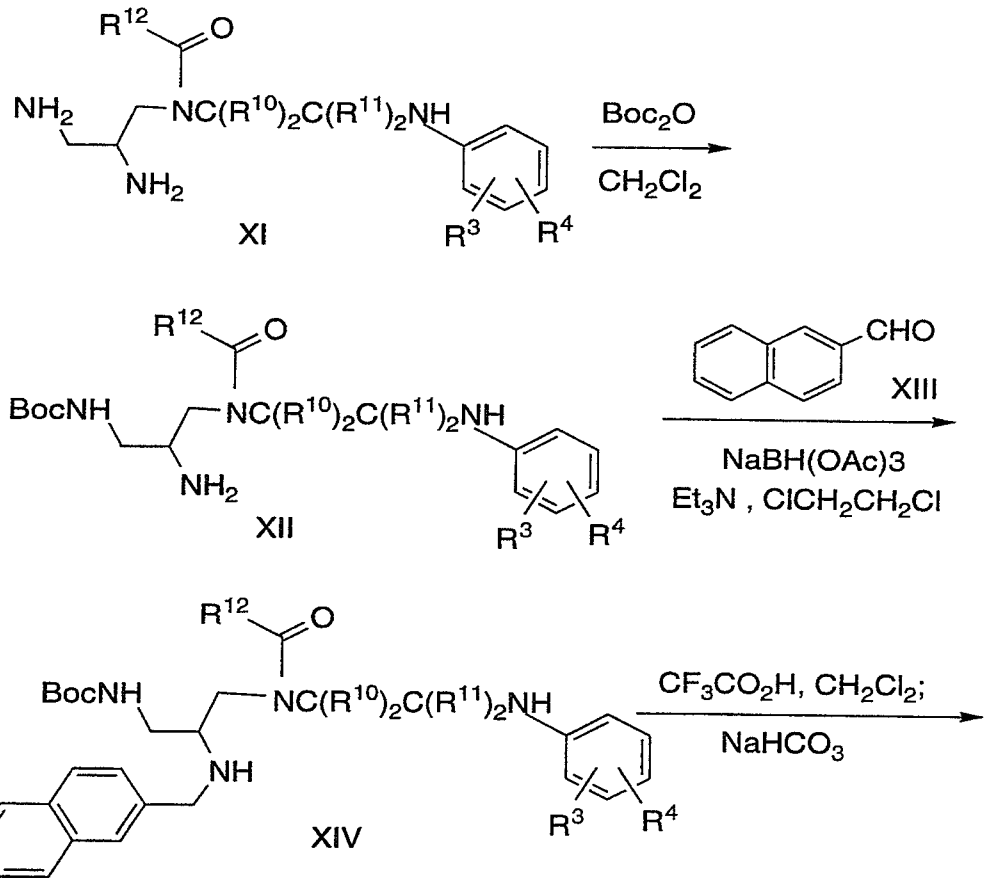
SCHEME 6


1. LDA, CO_2
2. $(CH_3)_3SiCHN_2$
CO_2CH_3
Br
N
R^6
Br
Zn, $NiCl_2(Ph_3P)_2$
CO_2CH_3
excess $NaBH_4$
CH_2OH
SO_3·Py, Et_3N
DMSO
CHO

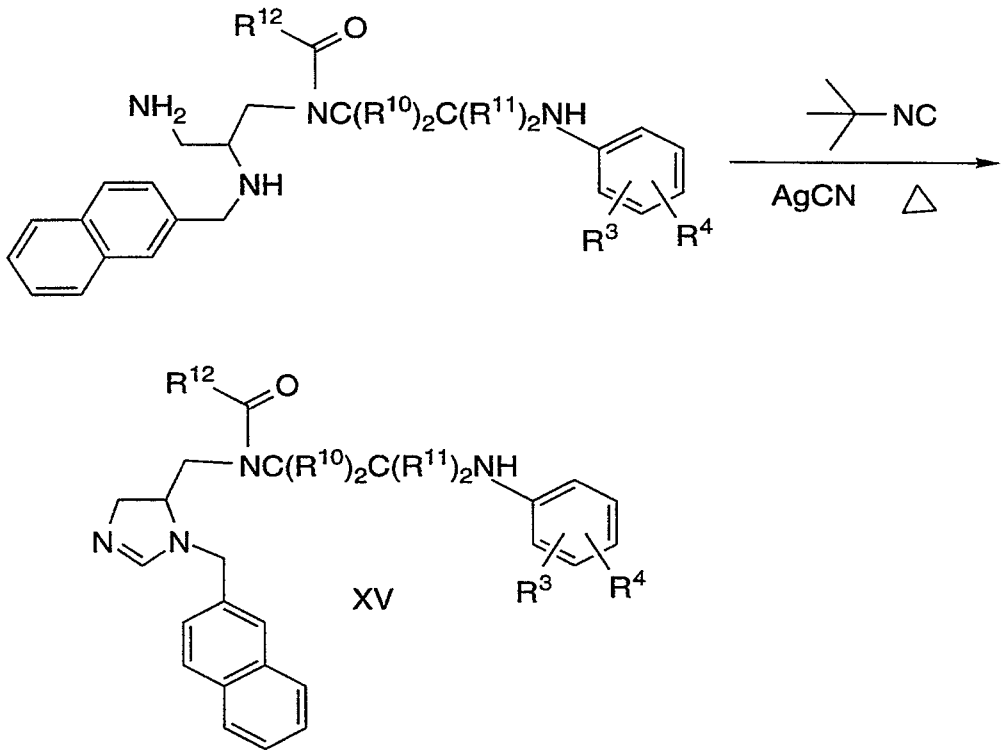
SCHEME 7


HCl
H2N
R10,11
N
H
IX
R3
R4
VI
Boc NH
IX
Boc NH
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl
Boc NH
NHC(R10)2C(R11)2NH
NHBoc
X
R3
R4
(R12C=O)2O
or
R12C=OCl
R12
O
Boc NH
NC(R10)2C(R11)2NH
NHBoc
R3
R4
CF3CO2H
CH2Cl2
R12
O
NH2
NC(R10)2C(R11)2NH
NH2
XI
R3
R4

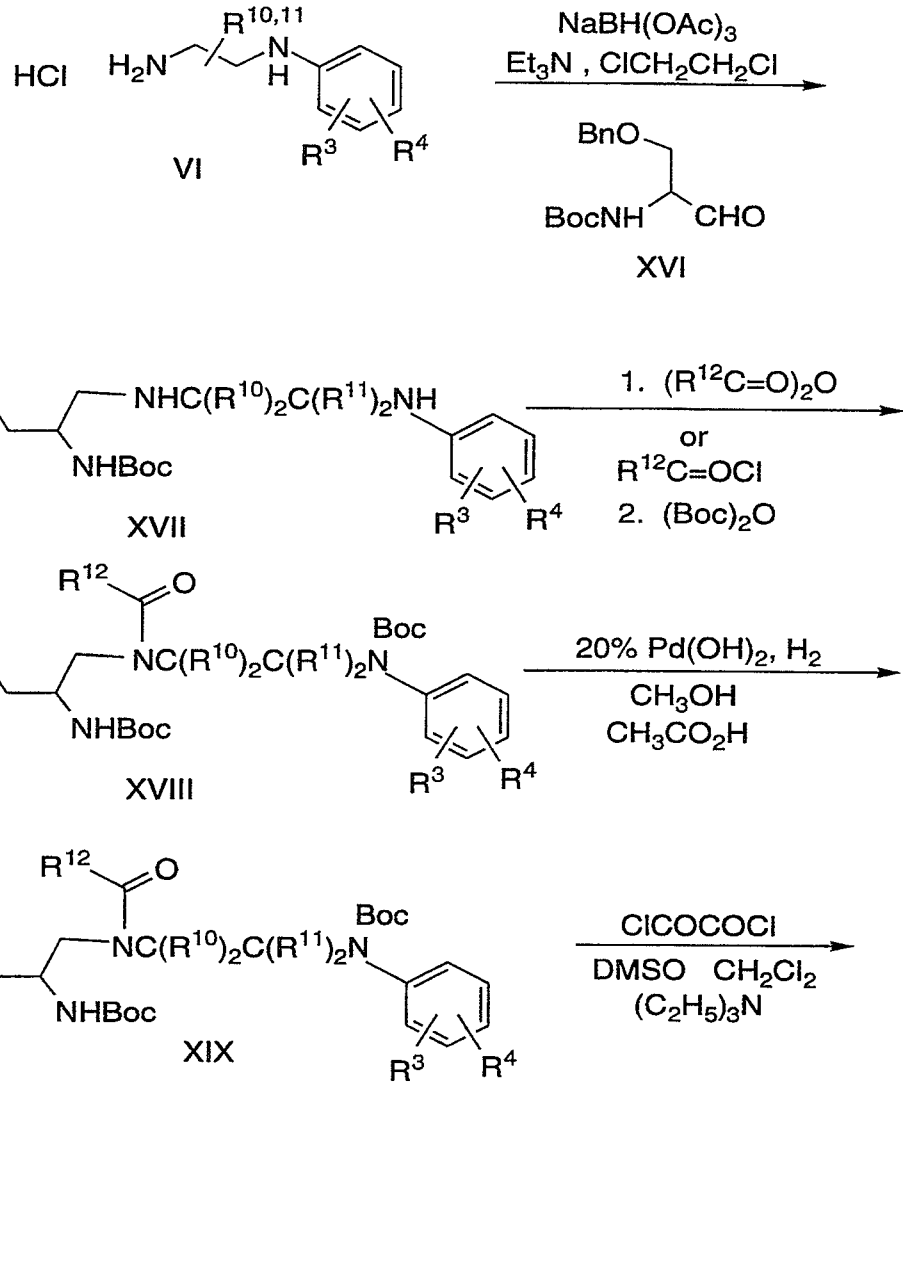
SCHEME 8


R12
O
NH2
NC(R10)2C(R11)2NH
NH2
XI
R3
R4
Boc2O
CH2Cl2
BocNH
XII
CHO
XIII
NaBH(OAc)3
Et3N , ClCH2CH2Cl
NH
XIV
CF3CO2H, CH2Cl2;
NaHCO3

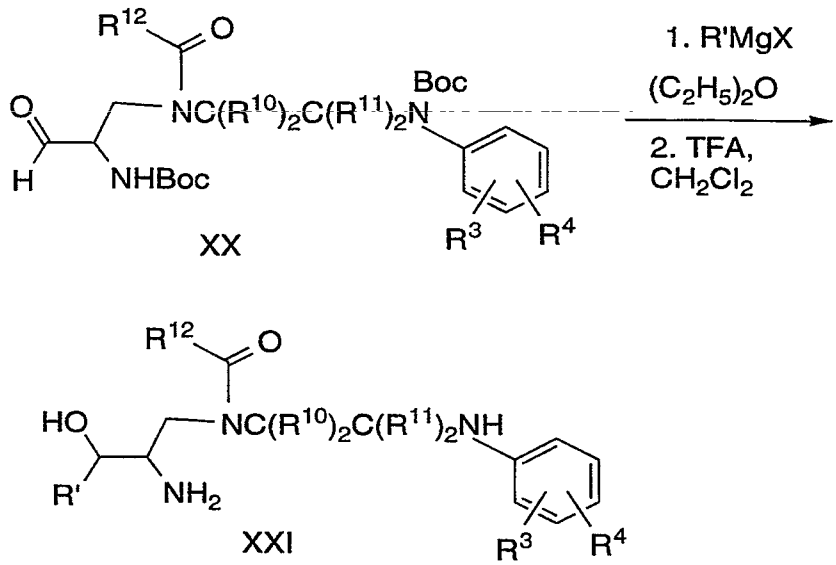
SCHEME 8 (continued)



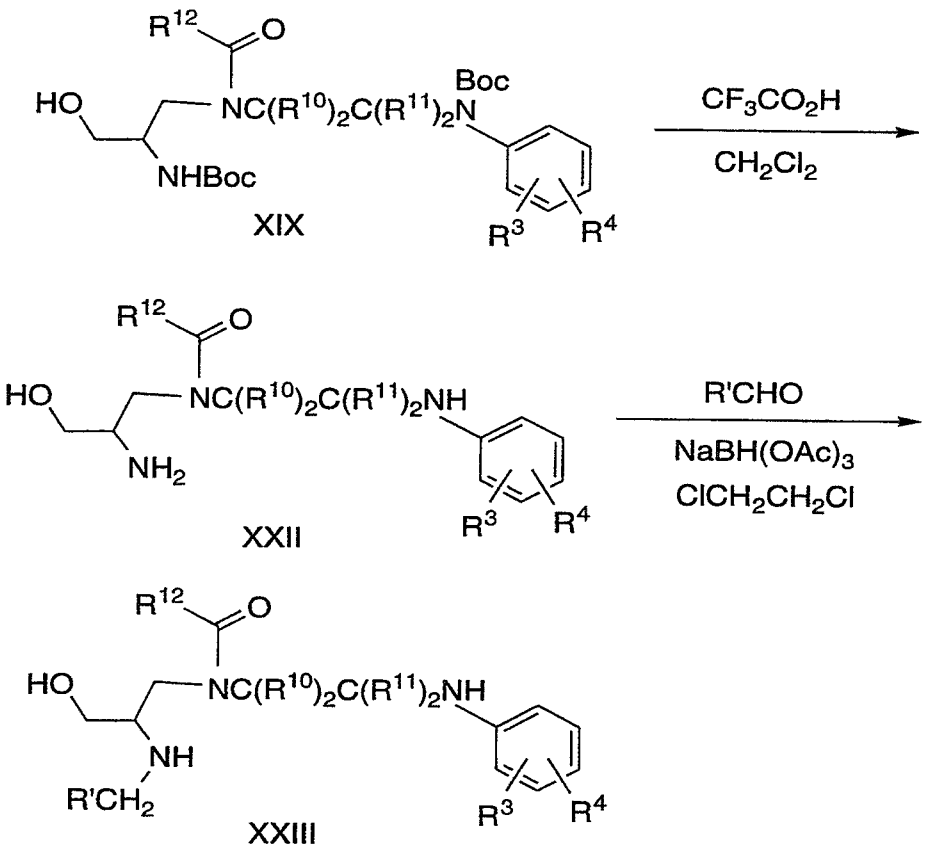
SCHEME 9


HCl
H2N
R10,11
N
H
R3
R4
VI
NaBH(OAc)3
Et3N , ClCH2CH2Cl
BnO
BocNH
CHO
XVI
BnO
NHC(R10)2C(R11)2NH
NHBoc
XVII
1. (R12C=O)2O
or
R12C=OCl
2. (Boc)2O
R12
O
BnO
NC(R10)2C(R11)2N
Boc
NHBoc
XVIII
20% Pd(OH)2, H2
CH3OH
CH3CO2H
HO
XIX
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N

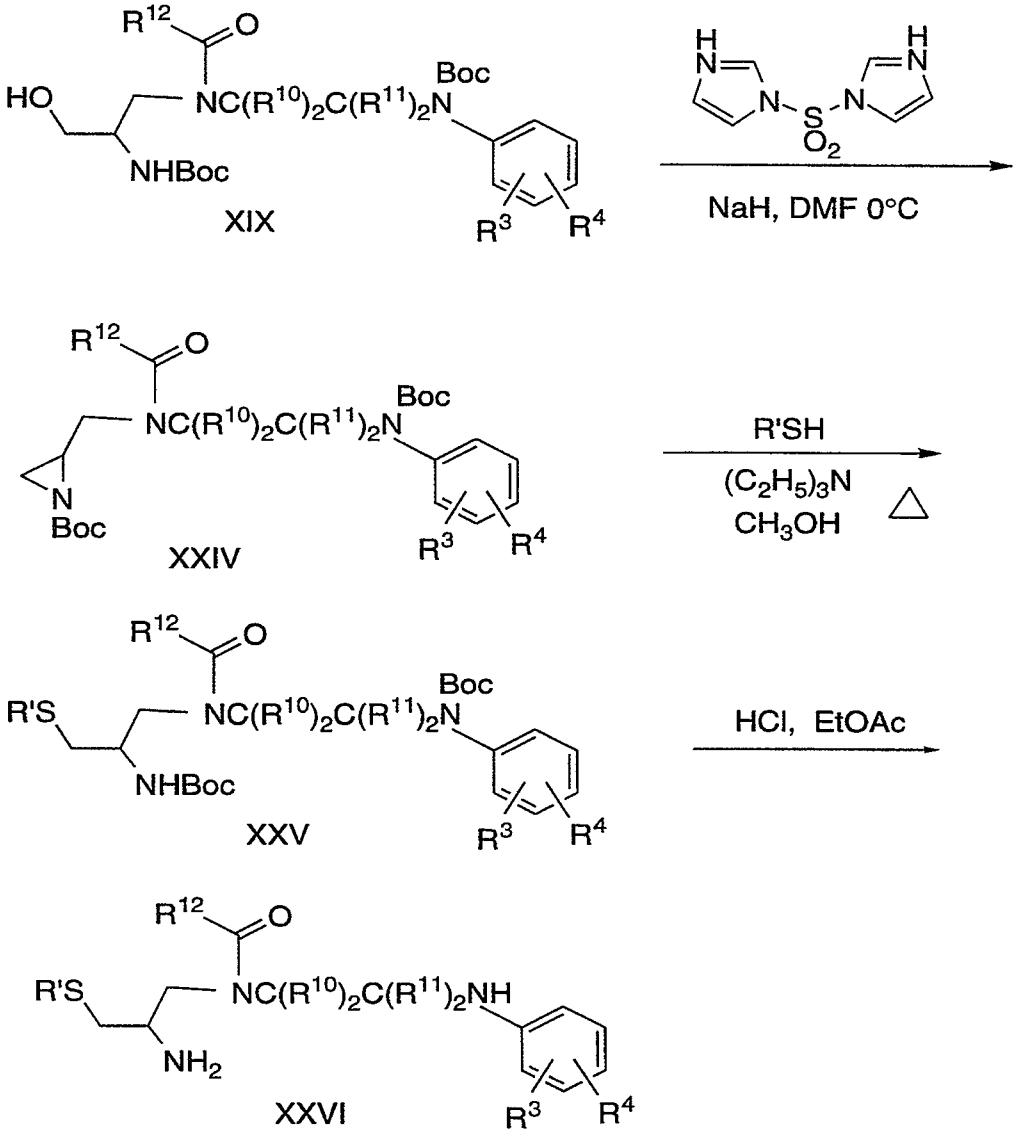
SCHEME 9 (CONTINUED)



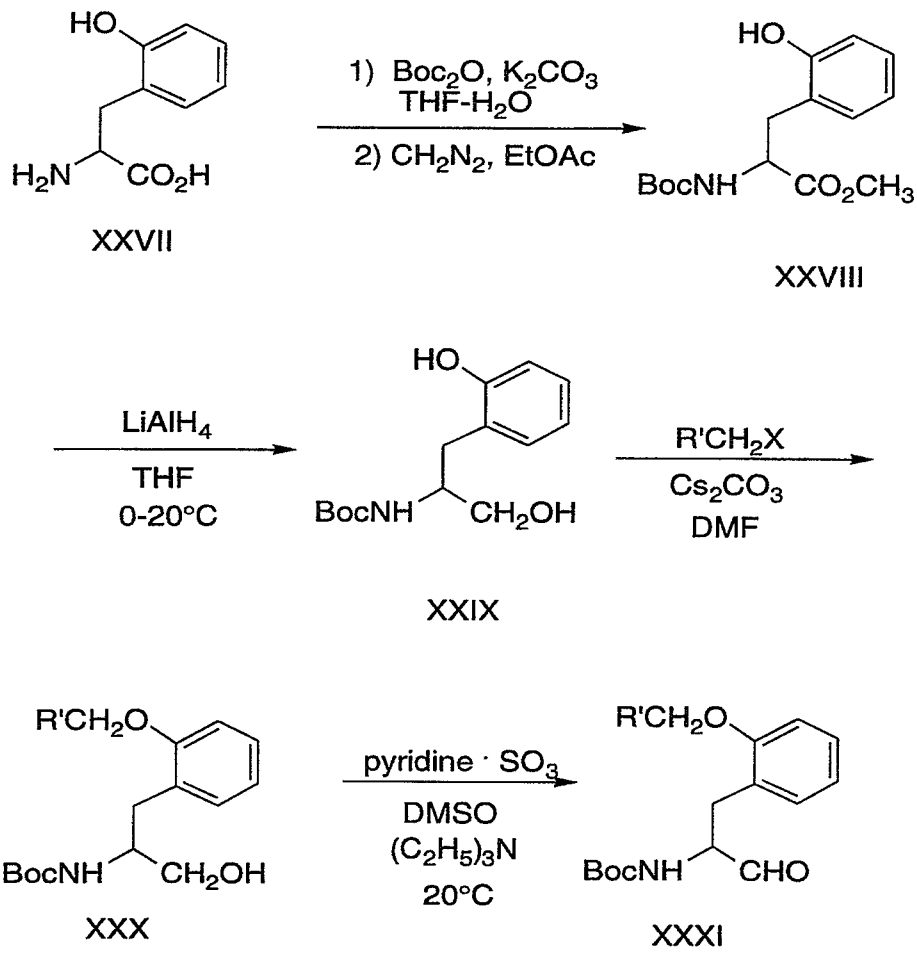
SCHEME 10


R12
O
HO
NC(R10)2C(R11)2N
Boc
NHBoc
XIX
R3
R4
CF3CO2H
CH2Cl2
R12
O
HO
NC(R10)2C(R11)2NH
NH2
XXII
R3
R4
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
R12
O
HO
NC(R10)2C(R11)2NH
NH
R'CH2
XXIII
R3
R4

SCHEME 11

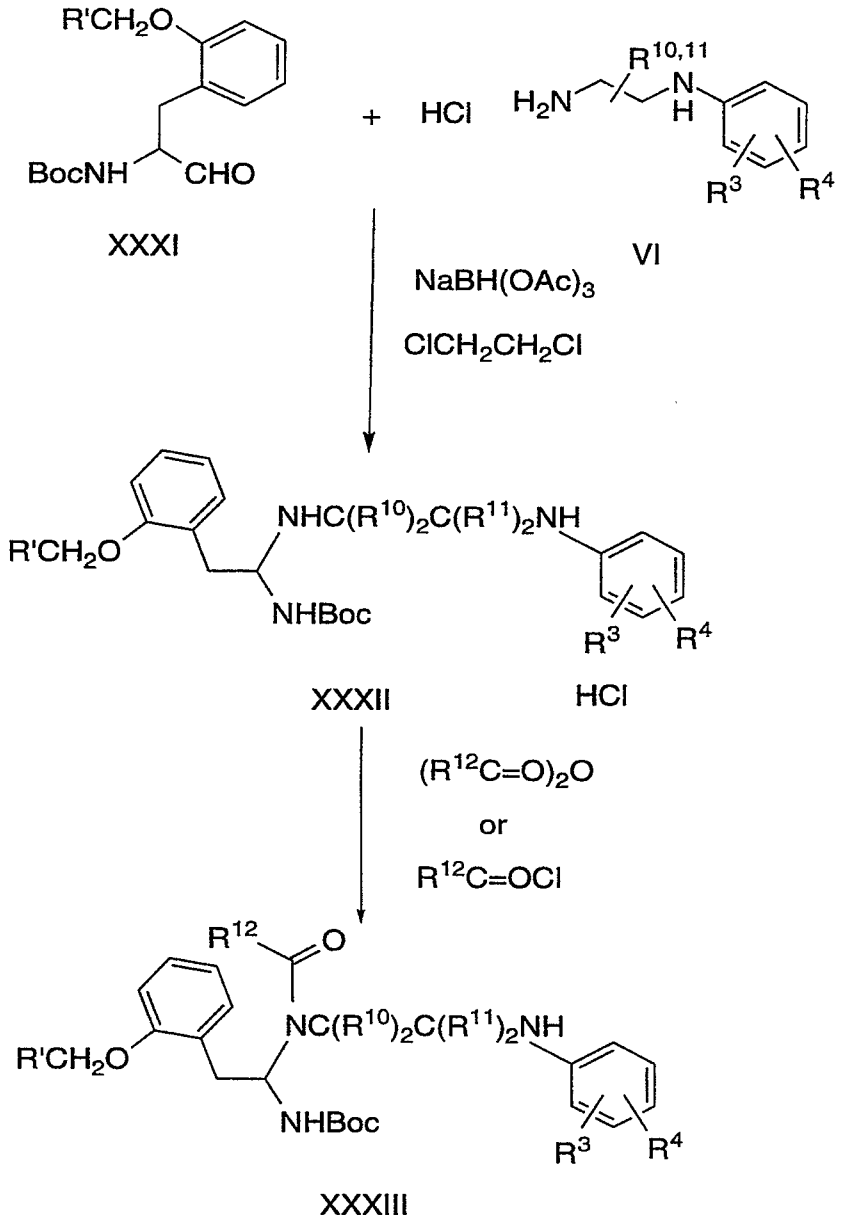

R12
O
HO
NC(R10)2C(R11)2N
Boc
NHBoc
XIX
R3
R4
H
N
N
S
O2
NaH, DMF 0°C
XXIV
N
Boc
R'SH
(C2H5)3N
CH3OH
XXV
R'S
XXVI
NH2
NC(R10)2C(R11)2NH
HCl, EtOAc

SCHEME 12

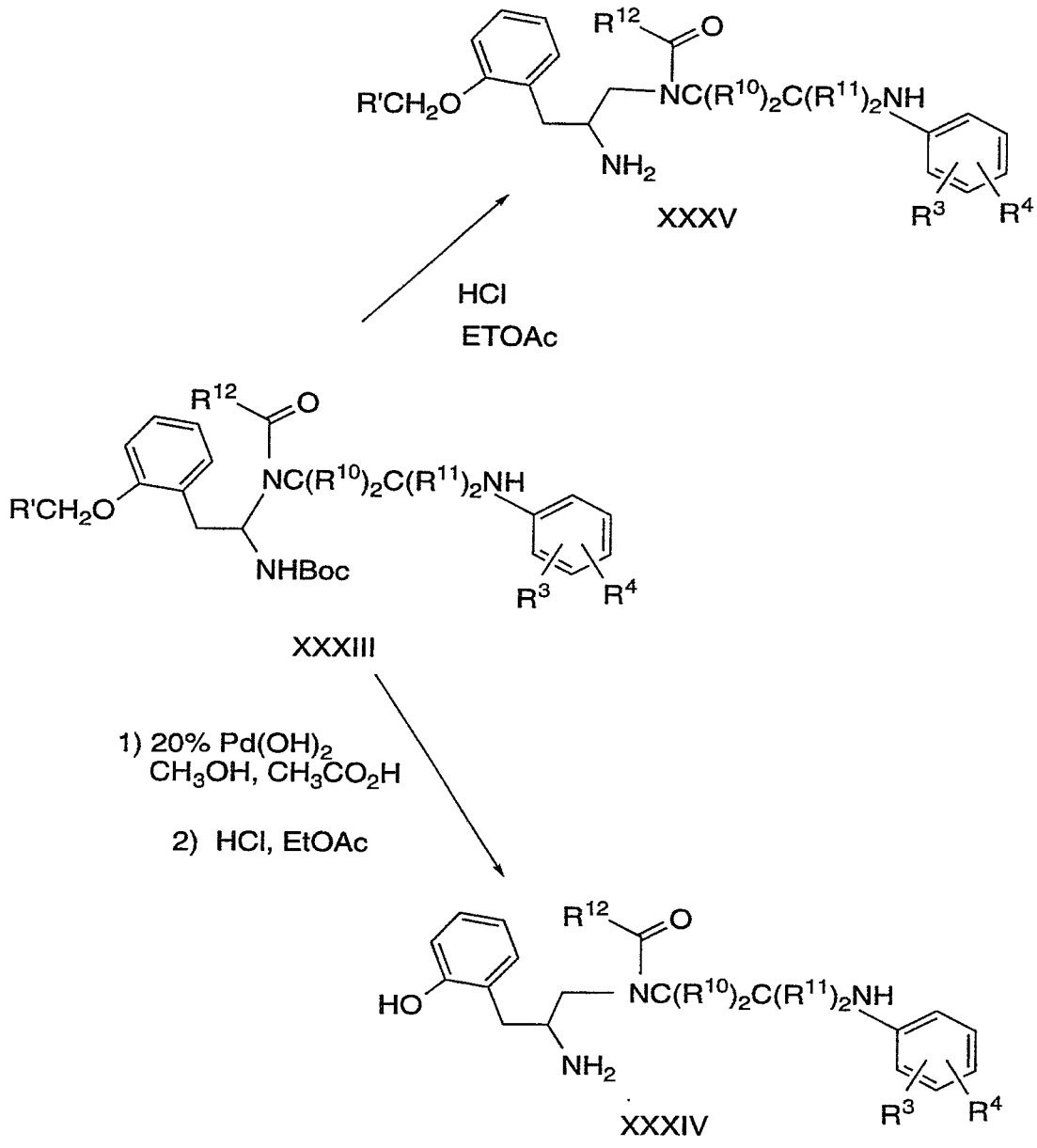


XXVII XXVIII XXIX XXX XXXI

SCHEME 12 (continued)



SCHEME 12 (continued)



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras formation (i.e., neurofibromen (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 angiogenisis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenisis 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.

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

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

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

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

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous

solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

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

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 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 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 Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

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

EXAMPLE 1

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-[2-((3-chlorophenyl)amino)ethyl]acetamide dihydrochloride (**1**)

Step 1: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole (**2**)

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35 g) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL). A white solid precipitated from the

solution. Chlorotriphenylmethane (76.1 g) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide **2** as a white solid which was sufficiently pure for use in the next step.

Step 2: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole (**3**)

Alcohol **2** (prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate **3** was isolated as a white powder which was sufficiently pure for use in the next step.

Step 3: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide (**4**)

A solution of **3** (85.8 g) and α-bromo-*p*-tolunitrile (50.1 g) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step 4: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole (**5**)

To a solution of the acetate **4** (50.4 g) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step 5: Preparation of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde (**6**)

To a solution of the alcohol **5** (21.5 g) in 500 mL of DMSO at room temperature was added triethylamine (56 mL), then SO_3-pyridine complex (40.5 g). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde **6** as a white powder which was sufficiently pure for use in the next step without further purification.

Step 6: Preparation of *N*-(2-aminoethyl)-3-chloroaniline hydrochloride (**7**)

To a solution of 3-chloroaniline (30 mL) in 500 mL of dichloromethane at 0 °C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g) was heated under nitrogen atmosphere at 160 °C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the titled compound **7** as a pale brown solid.

Step 7: Preparation of *N*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(3-chlorophenyl)ethylenediamine (**8**)

The amine hydrochloride **7** (978 mg) was partitioned between dilute aqueous $NaHCO_3$ solution and methylene chloride. The aqueous layer was washed with three portions of CH_2Cl_2, and the combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the free amine. To a solution of the amine in 11 mL of 1,2-dichloroethane at 0 °C was added 4Å powdered molecular sieves (2 g), followed by sodium triacetoxyborohydride (3.04 g). The aldehyde **6** (1.21 g) was added, and the reaction was stirred at 0 °C. After 15 hours, the reaction was poured into EtOAc, washed with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was taken up in 60 mL of 5:1 benzene:CH_2Cl_2, and propylamine (10 mL) was added. The reaction was stirred for 12 hours, then concentrated *in vacuo*, and purified by silica gel chromatography (5% MeOH/$CHCl_3$) to provide the titled compound **8** as a white foam..

Step 8: Preparation of *N*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-[2-((3-chlorophenyl)amino)ethyl]acetamide dihydrochloride (**1**)

To a solution of the diamine **8** (150 mg) in 2.5 mL of CH_2Cl_2 was added triethylamine (0.057 mL). The solution was cooled to 0 °C, and acetic anyhydride (0.019 mL) was added. The reaction was stirred overnight, allowing it to gradually warm to room temperature. The mixture was poured into EtOAc and washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. This material was purified by silica gel chromatography (2.5-5% MeOH/CH_2Cl_2), taken up in CH_2Cl_2 and treated with 1 M HCl/ether solution, and concentrated *in vacuo*. The product hydrochloride **1** was isolated as a white solid.

FAB mass spectrum m/e 408 (M+1).
Analysis calculated for $C_{22}H_{22}ClN_5O \cdot 2.00\ HCl \cdot 0.50\ H_2O$:
C, 53.95; H, 5.14; N, 14.30;
Found: C, 53.93; H, 5.42; N, 13.42.

EXAMPLE 2

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-(3-phenylpropyl)acetamide hydrochloride (9)

Step 1: Preparation of *N*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-(3-phenylpropyl)amine (**10**)

To a solution of 3-phenylpropylamine (0.202 mL, 1.42 mmol) in 5 mL of 1,2-dichloroethane at 0 °C was added 4Å powdered molecular sieves (0.38 g), followed by sodium triacetoxyborohydride (301 mg, 1.42 mmol g). The aldehyde **6** from Step 5 of Example 1 (200 mg, 0.947 mmol) was added, and the reaction was allowed to warm to room temperature. After 2 days, the reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was taken up in 12 mL of 20% CH_2Cl_2/ propylamine, stirred for 12 hours, concentrated *in vacuo*, and purified by preparative HPLC. Thus, the product was taken up in water/MeOH solution and was injected directly onto a Delta-Pak (C-18, 100A, 15 mm, 40 mm x 100 mm) prep HPLC column using a gradient with 0.1% trifluoroacetic acid/water and 0.1% trifluoroacetic acid/acetonitrile as solvents. A portion of the pure fractions was then partitioned between methylene chloride and water, and the organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product **10** as a white solid.

Step 2: Preparation of *N*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-(3-phenylpropyl)acetamide hydrochloride (**9**)

To a solution of the amine **10** from Step 1 (41 mg, 0.125 mmol) in 2 mL of CH_2Cl_2 was added triethylamine (0.035 mL, 0.250 mmol). The solution was cooled to 0 °C, and acetic anyhydride (0.012 mL, 0.125 mmol) was added. After 1 hour, the mixture was poured into EtOAc and washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. This material was purified by silica gel chromatography (70% acetone/hexane), taken up in CH_2Cl_2 and treated with 1 M HCl/ether solution, and concentrated *in vacuo*. The titled product hydrochloride **9** was isolated as a white solid.

FAB mass spectrum m/e 373 (M+1).
Analysis calculated for $C_{23}H_{24}N_4O \cdot 1.00\ HCl \cdot 0.90\ H_2O$:
C, 64.98; H, 6.35; N, 13.18;
Found: C, 65.10; H, 6.32; N, 12.82.

EXAMPLE 3

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified 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 µl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 µg/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. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, 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 [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., 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 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compound of the instant invention described hereinabove in Example 1 was tested for inhibitory activity against human FPTase by the assay described above and was found to have IC_{50} of < 10 μM.

EXAMPLE 4

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]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 $MgCl_2$/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

of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 5

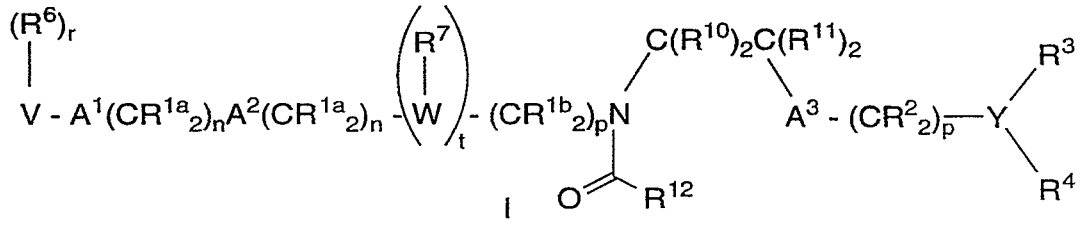
In vivo growth inhibition assay

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

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 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 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.

WHAT IS CLAIMED IS:

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



wherein:

R^{1a}, R^{1b} and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)$-NR^8-;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $CF_3(CH_2)_nO$-, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocyclic,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

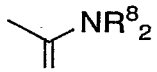
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-;

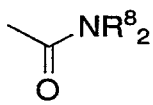
R^7 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is H, C_1-C_{10} alkyl, substituted or unsubstituted aryl or C_1-C_{10} alkyl which is substituted with a substituted or unsubstituted aryl ;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)2-, or S(O)m;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

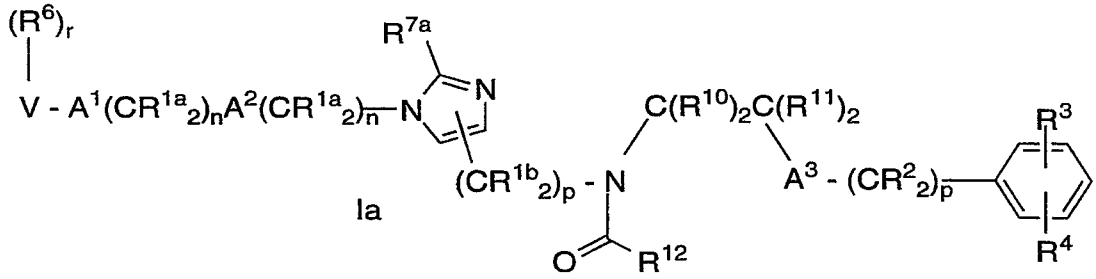
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

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

or an optical isomer or pharmaceutically acceptable salt thereof.

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



Ia

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

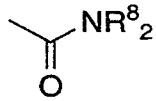
R^5 is selected from:
a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

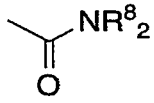
R^6 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{7a} is hydrogen or methyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is H, C_1-C_{10} alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or S(O)$_m$;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

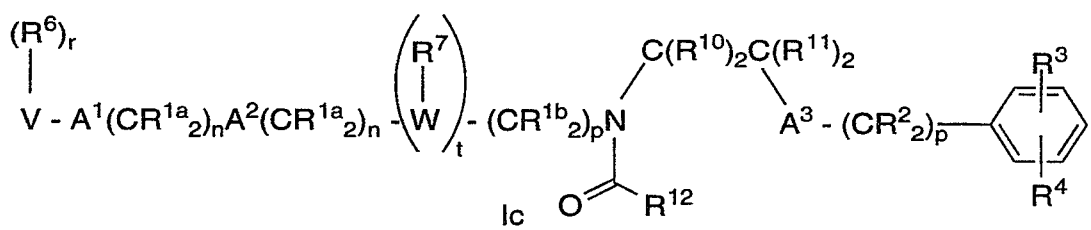
e) C_2-C_{20} alkenyl, and

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

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;

or an optical isomer or pharmaceutically acceptable salt thereof.

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



Ic

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-

C(NH)-, (R^8)C(O)-, (R^8)OC(O)-, N_3, CN, (R^9)OC(O)NR^8-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, N(R^8)$_2$, CF_3, NO_2, (R^8)O-, (R^9)S(O)$_m$-, (R^8)C(O)NH-, H_2N-C(NH)-, (R^8)C(O)-, (R^8)OC(O)-, N_3, CN (R^9)OC(O)NR^8-;

R^6 is independently selected from:

a) hydrogen,

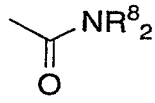
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, R^8C(O)NR^8-, CN, NO_2, (R^8)$_2$N-C(NR^8)-, R^8C(O)-, R^8OC(O)-, -N(R^8)$_2$, or R^9OC(O)NR^8-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, R^8C(O)NR^8-, (R^8)$_2$N-C(NR^8)-, R^8C(O)-, R^8OC(O)-, -N(R^8)$_2$, or R^9OC(O)NR^8-;

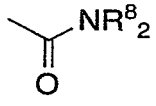
R^7 is selected from: hydrogen and C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or

C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or $S(O)_m$;

A^3 is selected from: -NR^5- or a bond;

V is selected from:

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

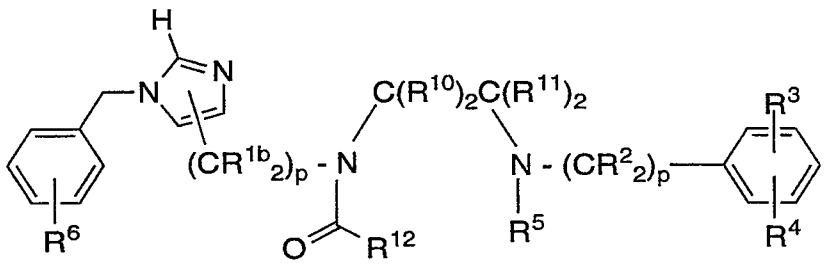
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

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

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

or an optical isomer or pharmaceutically acceptable salt thereof.

10 4. The compound according to Claim 1 of the formula Ic:



Ic

wherein:

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R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

20 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

25 R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN,

$(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

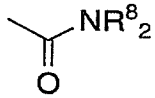
a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

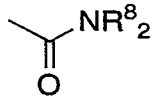
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_1-C_5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

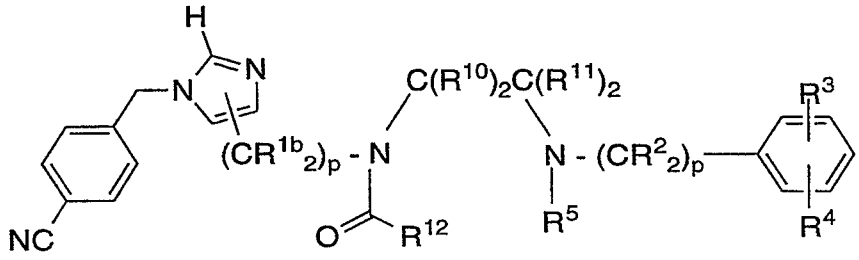
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5) 
;

R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

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

or an optical isomer or pharmaceutically acceptable salt thereof.

5. The compound according to Claim 4 of the formula Id:



Id

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^5 is selected from:

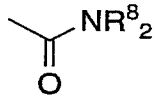
a) hydrogen,

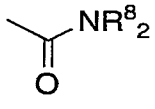
and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} and R^{11} are independently selected from: H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^8,
4) SR^9, SO_2R^9, or
5)  ;

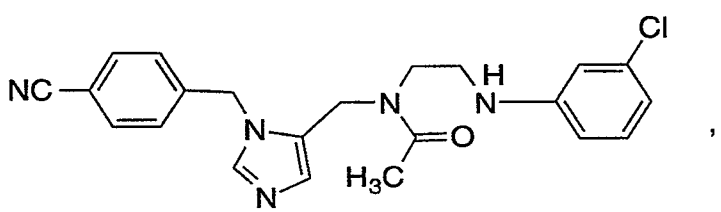
R^{12} is C_1-C_{10} alkyl and substituted or unsubstituted aryl;

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

or an optical isomer or pharmaceutically acceptable salt thereof.

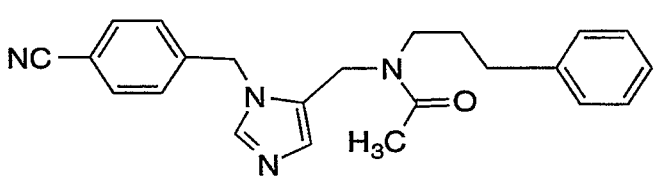
6. A compound which inhibits farnesyl-protein transferase which is selected from:

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-[2-((3-chlorophenyl)amino)ethyl]acetamide



and

N-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N*-(3-phenylpropyl)acetamide



or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

8. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

9. 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 7.

10. 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 8.

11. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

12. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

13. A method for treating neurofibromen benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

14. 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 7.

15. 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 7.

16. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

17. 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 7.

18. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

19. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.