



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>C07D 233/70, 233/66, 233/60, A61K 31/415</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 97/36877</b><br><b>(43) International Publication Date:</b> 9 October 1997 (09.10.97)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>(21) International Application Number:</b> PCT/US97/05295<br><b>(22) International Filing Date:</b> 31 March 1997 (31.03.97)<br><b>(30) Priority Data:</b><br>60/014,794            3 April 1996 (03.04.96)            US<br>9609334.9           3 May 1996 (03.05.96)            GB<br><b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).<br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> HUTCHINSON, John, H. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).<br><b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). |           | <b>(81) Designated States:</b> 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).<br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| <b>(54) Title:</b> INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>(57) Abstract</b><br><br><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>                                                                                                                                                                                                                                                                                        |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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## TITLE OF THE INVENTION

### INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

## BACKGROUND OF THE INVENTION

5           The present invention relates to compounds which inhibit farnesyl protein transferase, a protein which is implicated in the oncogenic pathway mediated by Ras. 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<sup>1</sup>-Aaa<sup>2</sup>-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<sub>15</sub> or C<sub>20</sub> isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann.*

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*Rev. Genetics* 30:209-237 (1992)). Ras proteins 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.,  
5 *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  
10 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.*,  
15 *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*  
20 *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  
25 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.*,  
30 *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 thus preferable.

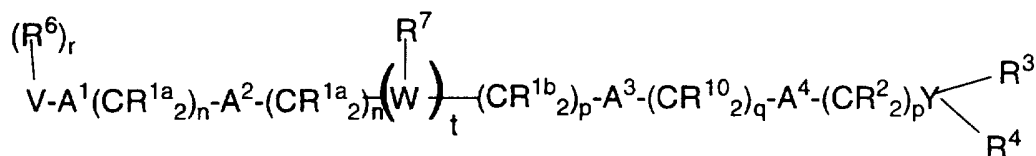
Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described 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)).

It has recently been reported that FPT-ase inhibitors also inhibit the proliferation of vascular smooth muscle cells and are therefore useful in the prevention and treatment 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).  
20 Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

## SUMMARY OF THE INVENTION

The present invention addresses a compound of formula I:



25

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup> and R<sup>10</sup> are independently selected from the group consisting of: hydrogen, aryl, substituted aryl, C<sub>3</sub>-C<sub>10</sub>

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cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>,  
 -N(R<sup>8</sup>)<sub>2</sub>, R<sup>9</sup>OC(O)NR<sup>8</sup>- and C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted or substituted  
 5 with 1-3 groups selected from the group consisting of: halo, aryl,  
 heterocyclyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-,  
 R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-,  
 N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub> and R<sup>9</sup>OC(O)NR<sup>8</sup>-;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group  
 10 consisting of: H, F, Cl, Br, -N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 R<sup>8</sup>C(O)NH-, H<sub>2</sub>NC(NH)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, CN,  
 R<sup>9</sup>OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and  
 substituted or unsubstituted heterocyclyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from the group  
 15 consisting of: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>8</sup>-,  
 -NR<sup>8</sup>C(O)-, -O-, -N(R<sup>8</sup>)-, -S(O)<sub>2</sub>N(R<sup>8</sup>)-, -N(R<sup>8</sup>)S(O)<sub>2</sub>-, and S(O)<sub>m</sub>;

A<sup>3</sup> is selected from the group consisting of: -C(O)-, -O-,  
 20 -S(O)<sub>m</sub>-, -OC(O)-, -C(O)O-, -NR<sup>5</sup>-, -NR<sup>5</sup>S(O)<sub>m</sub>- or S(O)<sub>m</sub>NR<sup>5</sup>-;

A<sup>4</sup> is selected from -O-, -S(O)<sub>m</sub>-, -NR<sup>5</sup>-, -NR<sup>5</sup>C(O)-,  
 -C(O)NR<sup>5</sup>-, -OC(O)-, -C(O)O-, -NR<sup>5</sup>S(O)<sub>m</sub>- and -S(O)<sub>m</sub>NR<sup>5</sup>-;

25 m represents 0, 1 or 2;

each R<sup>5</sup> is independently selected from the group consisting  
 of: hydrogen, unsubstituted or substituted aryl, unsubstituted or  
 substituted heterocyclyl, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  
 30 and C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1-3 members selected  
 from the group consisting of: unsubstituted or substituted aryl,  
 unsubstituted or substituted heterocyclyl, unsubstituted or substituted  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-,

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$(R^8)C(O)NH-$ ,  $H_2N-C(NH)-$ ,  $(R^8)C(O)-$ ,  $(R^8)OC(O)-$ ,  $N_3$ ,  $CN$   
 $(R^9)OC(O)NR^8-$ ;

$R^6$  and  $R^7$  are independently selected from the group  
 5 consisting of: hydrogen, aryl, heterocyclyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
 alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1-6</sub> perfluoroalkyl, F, Cl, Br,  $R^8O-$ ,  
 $R^9S(O)_m-$ ,  $R^8C(O)NR^8-$ , CN, NO<sub>2</sub>,  $(R^8)_2NC(NR^8)-$ ,  $R^8C(O)-$ ,  
 $R^8OC(O)-$ ,  $N_3$ ,  $-N(R^8)_2$ ,  $R^9OC(O)NR^8-$  and C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted  
 10 or substituted by 1-3 groups selected from: aryl, heterocyclyl, C<sub>3</sub>-C<sub>10</sub>  
 cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br,  
 $R^8O-$ ,  $R^9S(O)_m-$ ,  $R^8C(O)NR^8-$ , CN,  $(R^8)_2NC(NR^8)-$ ,  $R^8C(O)-$ ,  
 $R^8OC(O)-$ ,  $N_3$ ,  $-N(R^8)_2$  and  $R^9OC(O)NR^8-$ ;

each  $R^8$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>  
 15 alkyl, aryl and aralkyl;

each  $R^9$  is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and  
 aryl;

20 V is selected from the group consisting of: hydrogen,  
 heterocyclyl, aryl, C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
 replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub>  
 alkenyl,  
 provided that V is not hydrogen if  $A^1$  is  $S(O)_m$  and V is not hydrogen  
 25 if  $A^1$  is a bond, n is 0 and  $A^2$  is  $S(O)_m$ ;

W represents heterocyclyl;

Y represents aryl;

30

each n and p independently represents 0, 1, 2, 3 or 4;

q is 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.

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### DETAILED DESCRIPTION OF THE INVENTION

5 The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras, and thus are useful for the treatment of cancer.

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  
10 isomers, being included in the present invention.

When any variable (e.g. aryl, heterocycle, R<sup>1</sup>, R<sup>2</sup> etc.) occurs more than one time in any constituent, each definition is independent.

15 The term "alkyl" and the alkyl portion of alkoxy, aralkyl and similar terms, is intended to include branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, or 1-6 carbon atoms if unspecified. Cycloalkyl means 1-2 carbocyclic rings which are saturated and contain from 3-10 atoms.

"Halogen" or "halo" as used herein means fluoro, chloro,  
20 bromo and iodo.

As used herein, "aryl" and the aryl portion of aralkyl, are 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,  
25 tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. A preferred aralkyl group is benzyl.

The terms heterocyclyl, heterocycle and heterocyclic, as used herein, mean a 5- to 7-membered monocyclic or 8- to 11-membered bicyclic heterocyclic rings, either saturated or unsaturated,  
30 aromatic, partially aromatic or non-aromatic, and which consist of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S. Thus, it includes any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The ring or ring system may be attached at any heteroatom or carbon

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atom which results in a stable structure, and may contain 1-3 carbonyl groups. Examples of such heterocycles 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, imidazolynyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 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.

"Heteroaryl" is a subset of heterocyclic, and means a monocyclic or bicyclic ring system, with 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 include 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.

Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the substitutable ring atoms.

The term "substituted", as used in, e.g., with respect to substituted alkyl, substituted aryl, substituted heterocyclyl and

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substituted cycloalkyl means alkyl, aryl, heterocyclyl and cycloalkyl groups, respectively, having from 1-3 substituents which are selected from: halo, aryl, heterocyclyl, C<sub>1-6</sub> alkyl, C<sub>3-10</sub> cycloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub> and R<sup>9</sup>OC(O)NR<sup>8</sup>-.  
 5 When for example, a substituted alkyl group is substituted with a "substituted aryl group", the aryl portion is substituted with 1-3 groups as defined above.

Preferably 1-2 groups are present on substituted alkyl, substituted aryl, substituted heterocyclyl and substituted cycloalkyl, which are selected from: halo, aryl, R<sup>8</sup>O-, CN, R<sup>8</sup>C(O)- and -N(R<sup>8</sup>)<sub>2</sub>.  
 10

Preferably, R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup> and R<sup>10</sup> are independently selected from: hydrogen, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>C(O)NR<sup>8</sup>- or unsubstituted or substituted C<sub>1-C6</sub> alkyl wherein the substituent on the substituted C<sub>1-C6</sub> alkyl is selected from unsubstituted or substituted aryl, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>O- and R<sup>8</sup>C(O)NR<sup>8</sup>-. Preferably, R<sup>3</sup> and R<sup>4</sup> are selected from: hydrogen and C<sub>1-C6</sub> alkyl.  
 15

Preferably, R<sup>6</sup> represents CN, NO<sub>2</sub> or R<sup>8</sup>O-.

Preferably R<sup>7</sup> represent hydrogen, unsubstituted or substituted C<sub>1-C6</sub> alkyl.  
 20

Preferably, R<sup>8</sup> represents H or C<sub>1-6</sub> alkyl, and R<sup>9</sup> is C<sub>1-6</sub> alkyl.

Preferably, A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -C(O)NR<sup>8</sup>-, -NR<sup>8</sup>C(O)-, -O-, -N(R<sup>8</sup>)-, -S(O)<sub>2</sub>N(R<sup>8</sup>)- and -N(R<sup>8</sup>)S(O)<sub>2</sub>-.  
 25

Preferably, A<sup>3</sup> represents O, S, NR<sup>5</sup> or NR<sup>5</sup>S(O)<sub>m</sub>, wherein m represents 2 and R<sup>5</sup> represents hydrogen.

Preferably A<sup>4</sup> represents -C(O)NR<sup>5</sup>- or -NR<sup>5</sup>C(O)-, with R<sup>5</sup> representing H.

Preferably, V is selected from hydrogen, heterocyclyl and aryl. More preferably V is phenyl.  
 30

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

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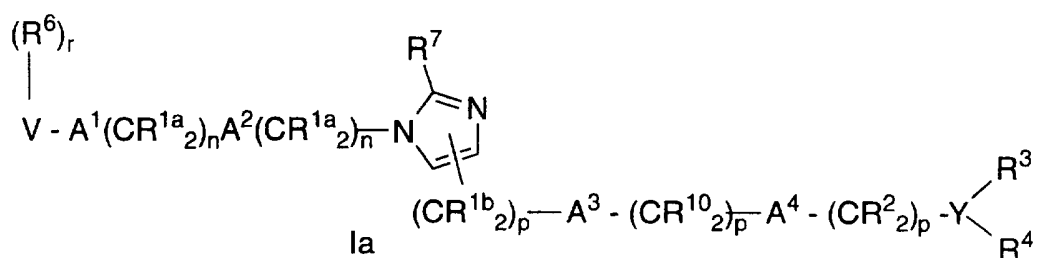
Preferably, m is 0 or 2.

Preferably n and p are 0, 1, 2 or 3.

Preferably t is 1.

A subset of compounds of the invention is represented by

5 formula Ia:



wherein:

10  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{A}^3$ ,  $\text{A}^4$ , Y,  $\text{R}^8$ ,  $\text{R}^9$ , m, n, p and r are as originally defined;

each  $\text{R}^{1a}$ ,  $\text{R}^{1b}$ ,  $\text{R}^2$  and  $\text{R}^{10}$  is independently selected from hydrogen and C1-C6 alkyl;

15  $\text{R}^5$  is selected from the group consisting of: hydrogen and C1-C6 alkyl, unsubstituted or substituted with 1-3 members selected from the group consisting of: unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C3-C10 cycloalkyl,  $-\text{N}(\text{R}^8)_2$ ,  $-\text{CF}_3$ ,  $-\text{NO}_2$ ,  $(\text{R}^8)\text{O}-$ ,  $(\text{R}^9)\text{S}(\text{O})_m-$ ,  
 20  $(\text{R}^8)\text{C}(\text{O})\text{NH}-$ ,  $\text{H}_2\text{NC}(\text{NH})-$ ,  $(\text{R}^8)\text{C}(\text{O})-$ ,  $(\text{R}^8)\text{OC}(\text{O})-$ ,  $\text{N}_3$ , CN and  $(\text{R}^9)\text{OC}(\text{O})\text{NR}^8-$ ;

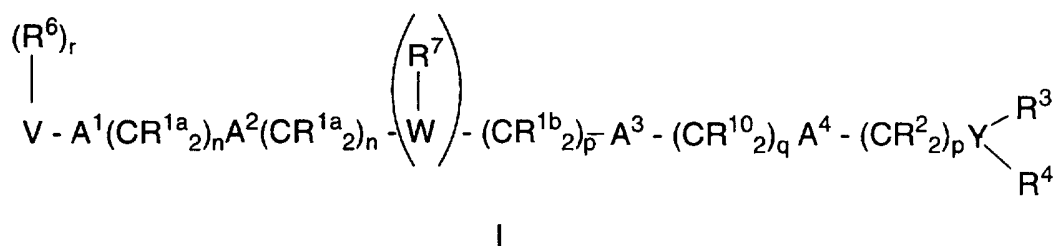
$\text{R}^6$  and  $\text{R}^7$  are independently selected from: hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $\text{R}^8\text{O}-$ ,  $\text{R}^8\text{C}(\text{O})\text{NR}^8-$ , CN,  $\text{NO}_2$ ,  $(\text{R}^8)_2\text{N}-\text{C}(\text{NR}^8)-$ ,  $\text{R}^8\text{C}(\text{O})-$ ,  $\text{R}^8\text{OC}(\text{O})-$ ,  
 25  $-\text{N}(\text{R}^8)_2$ , or  $\text{R}^9\text{OC}(\text{O})\text{NR}^8-$ , and C1-C6 alkyl substituted by C1-C6 perfluoroalkyl,  $\text{R}^8\text{O}-$ ,  $\text{R}^8\text{C}(\text{O})\text{NR}^8-$ ,  $(\text{R}^8)_2\text{N}-\text{C}(\text{NR}^8)-$ ,  $\text{R}^8\text{C}(\text{O})-$ ,  $\text{R}^8\text{OC}(\text{O})-$ ,  $-\text{N}(\text{R}^8)_2$  and  $\text{R}^9\text{OC}(\text{O})\text{NR}^8-$ ;

- 10 -

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

and  $V$  is selected from: hydrogen; aryl; heterocyclyl  
 5 selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl and thienyl;  $\text{C}_1$ - $\text{C}_{20}$  alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from  $\text{O}$ ,  $\text{S}$ , and  $\text{N}$ , and  $\text{C}_2$ - $\text{C}_{20}$  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  
 10 bond and  $A^2$  is  $\text{S}(\text{O})_m$ .

A second subset of compounds of the present invention is represented by formula I:



15 wherein:

$\text{R}^3$ ,  $\text{R}^4$ ,  $\text{A}^3$ ,  $\text{A}^4$ ,  $\text{Y}$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $m$ ,  $n$ ,  $p$  and  $r$  are as originally defined;

20 each  $\text{R}^{1a}$ ,  $\text{R}^{1b}$ ,  $\text{R}^2$  and  $\text{R}^{10}$  is independently selected from hydrogen and  $\text{C}_1$ - $\text{C}_6$  alkyl;

$\text{R}^5$  is selected from the group consisting of: hydrogen and  $\text{C}_1$ - $\text{C}_6$  alkyl, unsubstituted or substituted with 1-3 members selected  
 25 from the group consisting of: unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted  $\text{C}_3$ - $\text{C}_{10}$  cycloalkyl,  $-\text{N}(\text{R}^8)_2$ ,  $-\text{CF}_3$ ,  $-\text{NO}_2$ ,  $(\text{R}^8)\text{O}-$ ,  $(\text{R}^9)\text{S}(\text{O})_m-$ ,  $(\text{R}^8)\text{C}(\text{O})\text{NH}-$ ,  $\text{H}_2\text{NC}(\text{NH})-$ ,  $(\text{R}^8)\text{C}(\text{O})-$ ,  $(\text{R}^8)\text{OC}(\text{O})-$ ,  $\text{N}_3$ ,  $\text{CN}$  and  $(\text{R}^9)\text{OC}(\text{O})\text{NR}^8-$ ;

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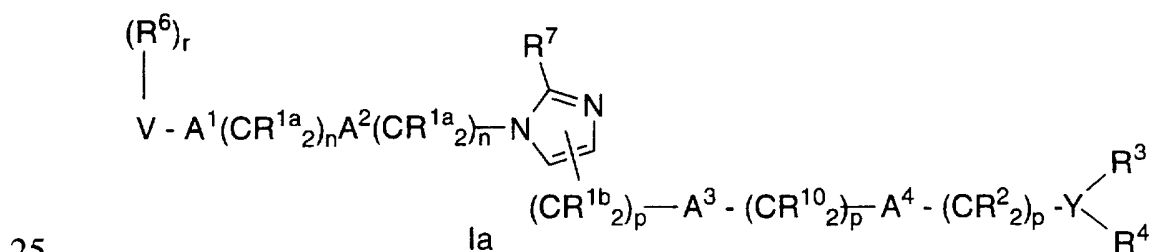
$R^6$  and  $R^7$  are independently selected from: hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $R^8O-$ ,  $R^8C(O)NR^8-$ , CN, NO<sub>2</sub>,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  
 5  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$ , and C1-C6 alkyl substituted by C1-C6 perfluoroalkyl,  $R^8O-$ ,  $R^8C(O)NR^8-$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$  and  $R^9OC(O)NR^8-$ ;

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

and V is selected from: hydrogen; aryl; heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl and thienyl; C1-C20  
 15 alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and C2-C20 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 and  $A^2$  is  $S(O)_m$ ; and

W represents heterocyclyl selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl and isoquinolinyl.  
 20

A third subset of compounds of the invention is represented by formula Ia:



wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^2$ ,  $R^{10}$ ,  $A^1$ ,  $A^2$ ,  $A^4$ , Y,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^8$ ,  $R^9$ ,  
 m, n, p, q and r are as originally defined;

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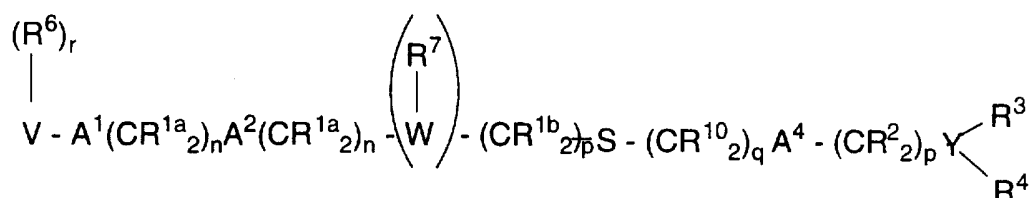
$R^7$  is selected from: hydrogen and  $C_1$ - $C_6$  alkyl;

$A^3$  represents -S-;

5           V is selected from: hydrogen, heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, aryl,  $C_1$ - $C_{20}$  alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and  $C_2$ - $C_{20}$  alkenyl,  
10 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  $S(O)_m$ ; and

15           W represents heterocyclyl selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl and isoquinolinyl.

A fourth subset of compounds of the present invention is represented by formula Ib:



20

Ib

wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^2$ ,  $R^{10}$ ,  $A^1$ ,  $A^2$ ,  $A^4$ , Y,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^8$ ,  $R^9$ ,  
m, n, p, q and r are as originally defined;

25

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

V is selected from: hydrogen, heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-

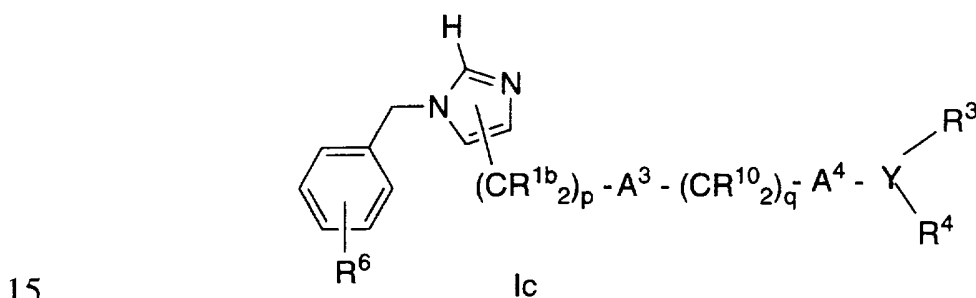
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oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, aryl, C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub> alkenyl,

- 5 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>; and

W represents heterocyclyl selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl  
10 and isoquinolinyl.

A fifth subset of the invention is described in accordance with formula Ic:



wherein:

20 each R<sup>1b</sup> and R<sup>10</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup>, R<sup>9</sup>, m, p, and q are as originally defined;

25 A<sup>3</sup> represents -O-, -S- or -NH-;

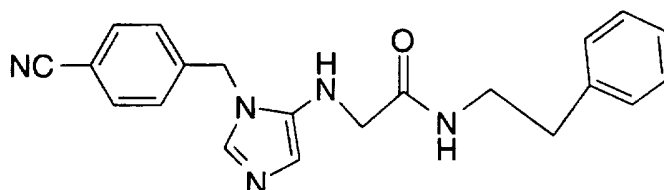
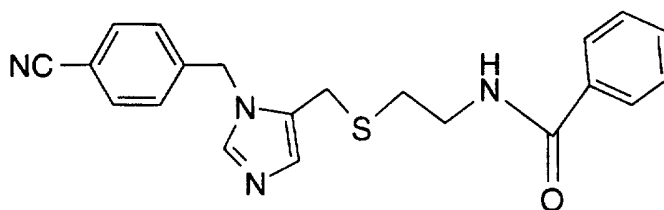
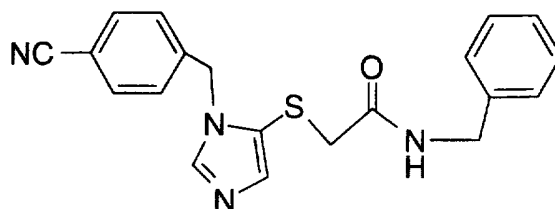
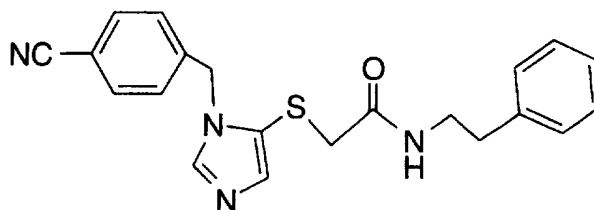
A<sup>4</sup> represents -C(O)NH- or -NHC(O)-;

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- and  $R^6$  is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl,  $R^8O-$ ,  $R^8C(O)NR^8-$ , CN, NO<sub>2</sub>,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$  and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by
- 5 C<sub>1</sub>-C<sub>6</sub> 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  $R^9OC(O)NR^8-$ .

Specific examples of compounds of the invention are:

10



- 15 -

and the pharmaceutically acceptable salts thereof.

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  
5 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,  
10 phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, 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  
15 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  
20 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<sub>2</sub>-  
25 , as shown in the Schemes, represent the substituents R<sup>8</sup>, R<sup>9</sup> 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  
30 synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

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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  
5 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,  
10 *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 amine VI, which was  
15 prepared from the aniline V as shown in Scheme 2, to provide compound VII.

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  
20 for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

The amine 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.  
25 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 Boc  
30 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

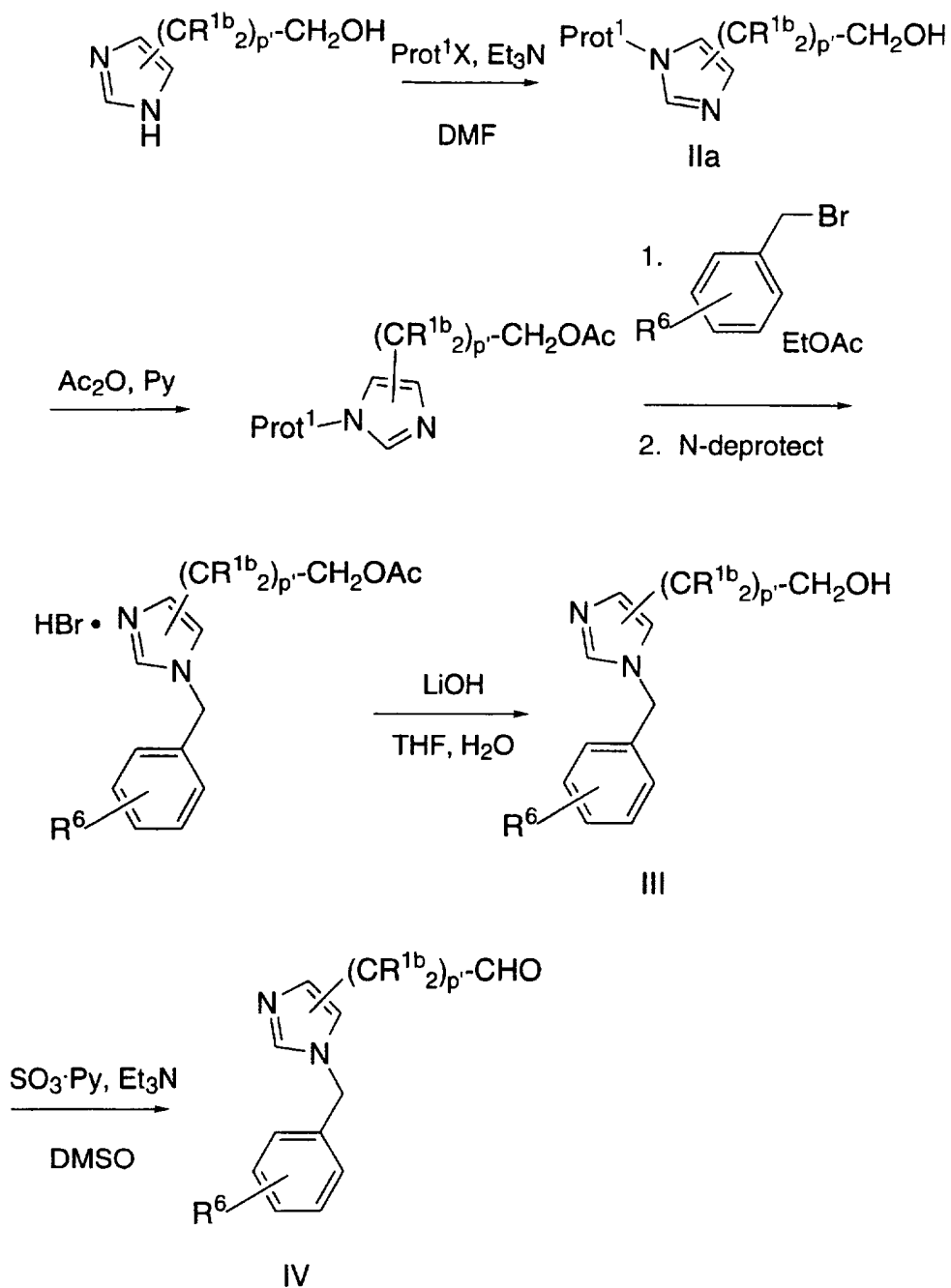
- 17 -

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  
5 XXI. In addition, the 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  
10 to synthesize 2-aziridinylmethanamines such as XXIV (Scheme 11). Protecting group manipulation of XVII followed by treatment 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  
15 presence of base to yield (after deprotection) the ring-opened product XXVI.

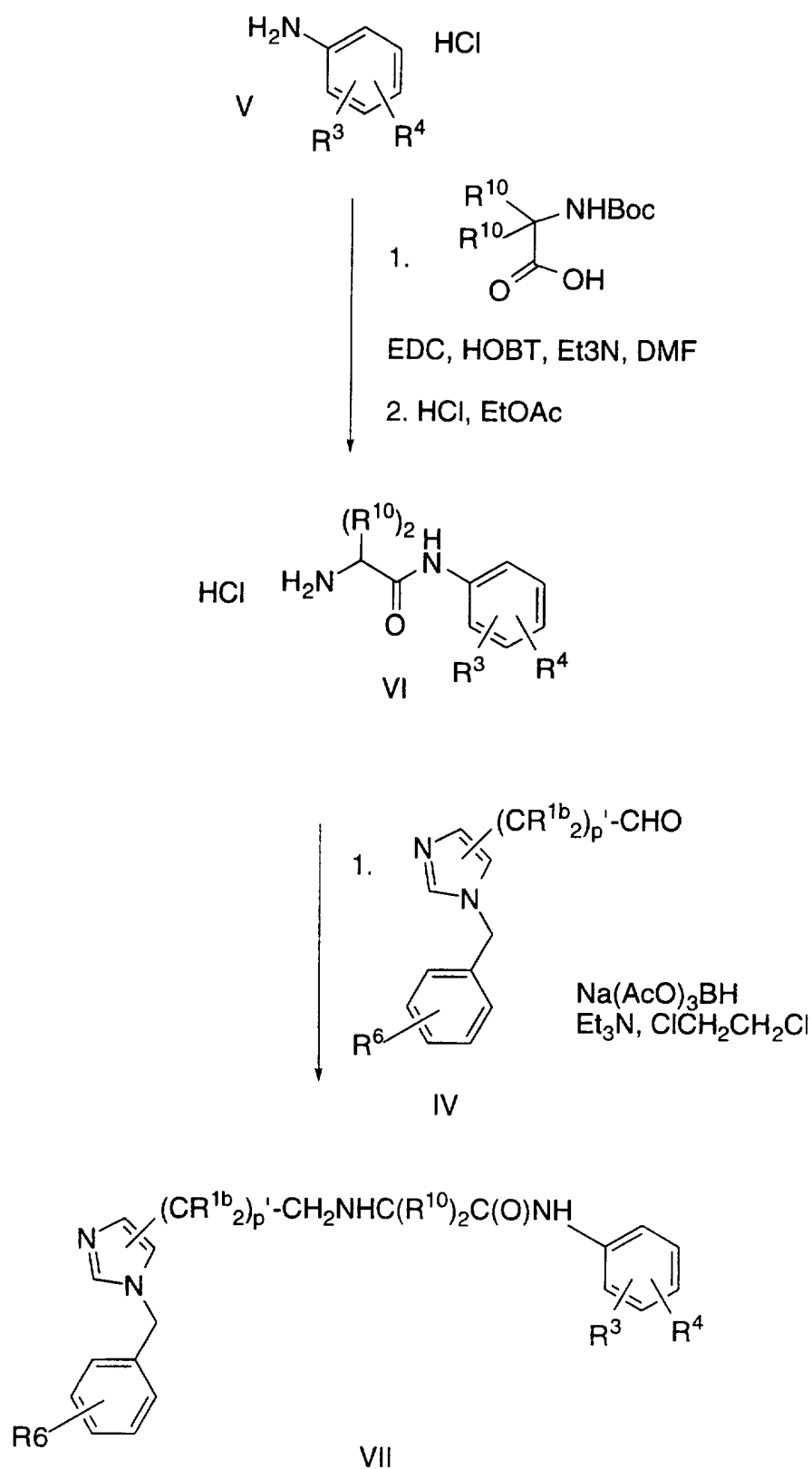
In addition, the diamine VI can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXII, as shown in  
20 Scheme 12. Intermediate XXXII is first acylated before it is further elaborated. When R' is an aryl group, 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  
25 as XXXV produced.

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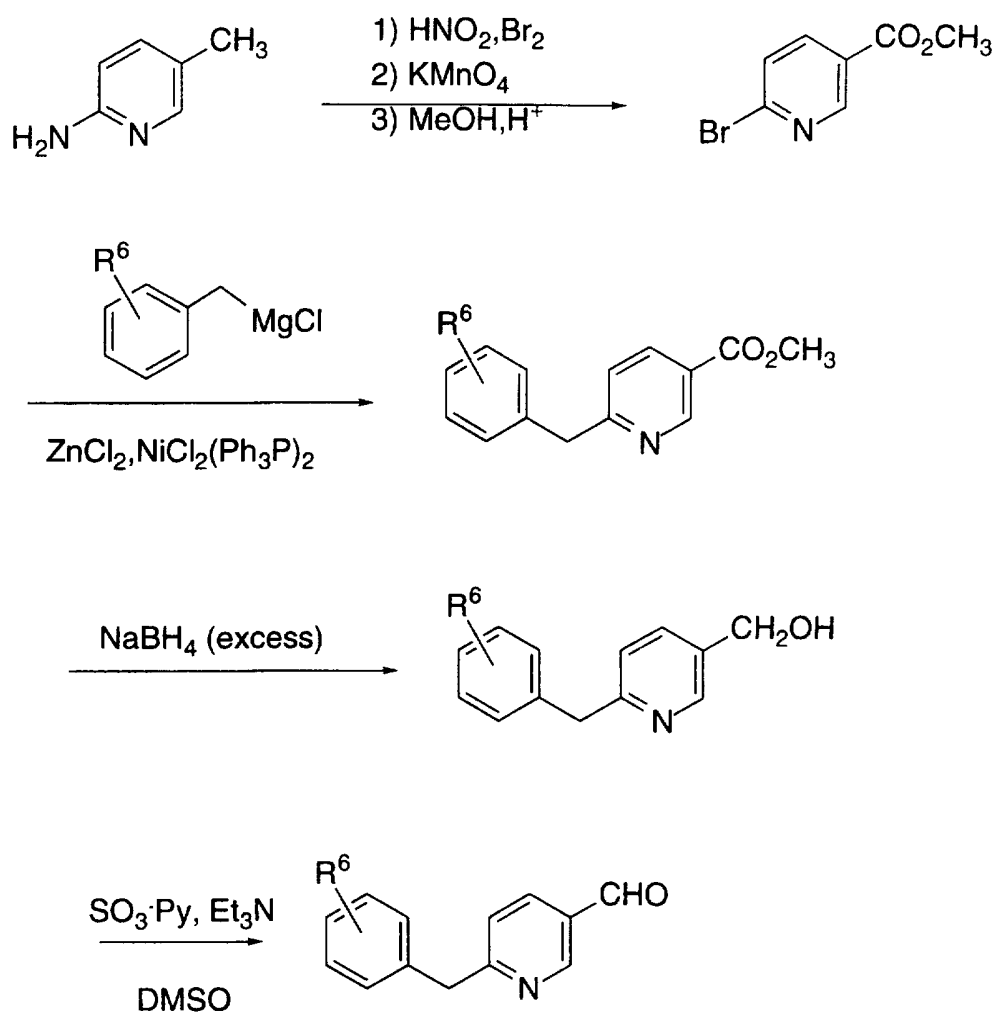
SCHEME 1

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## SCHEME 2

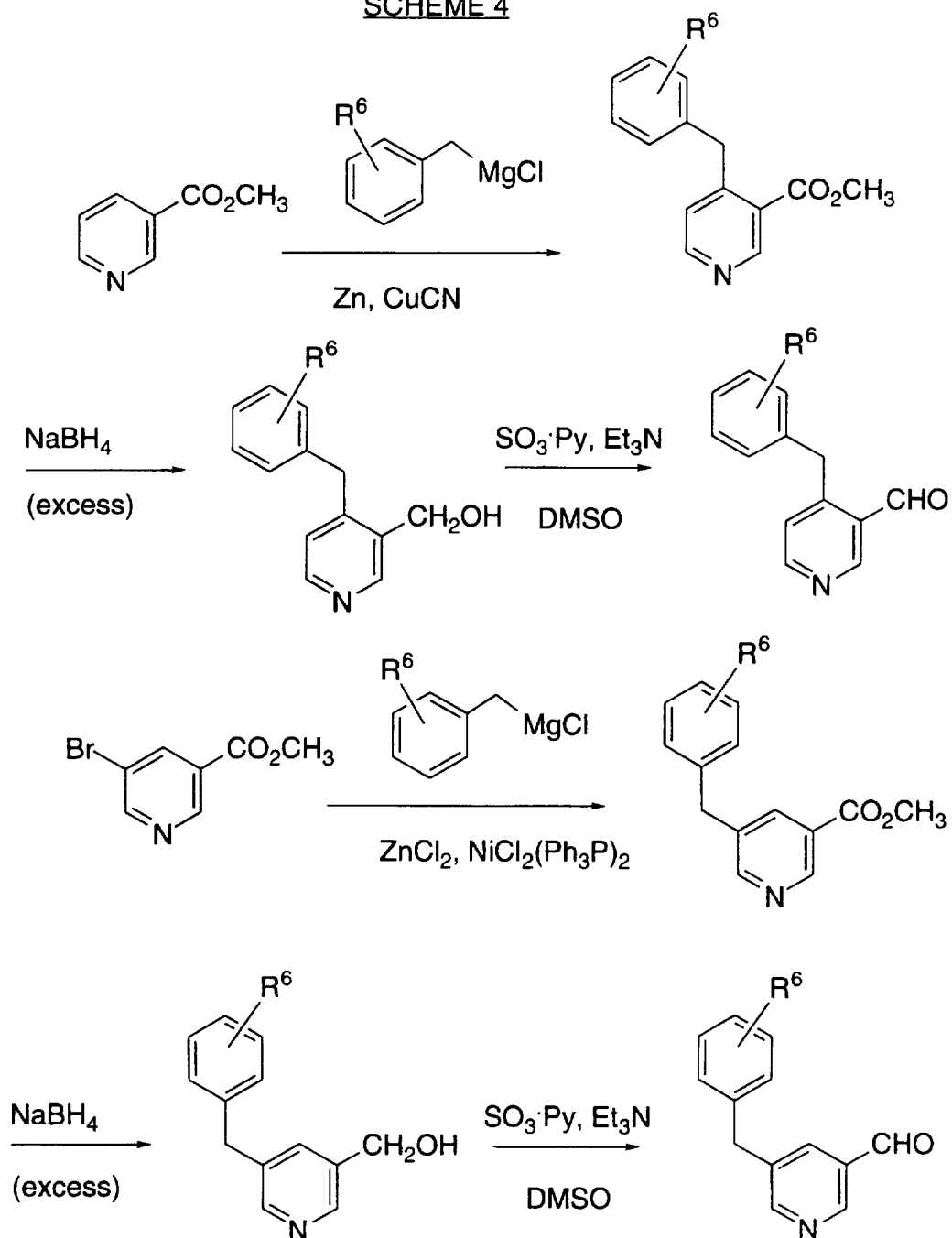


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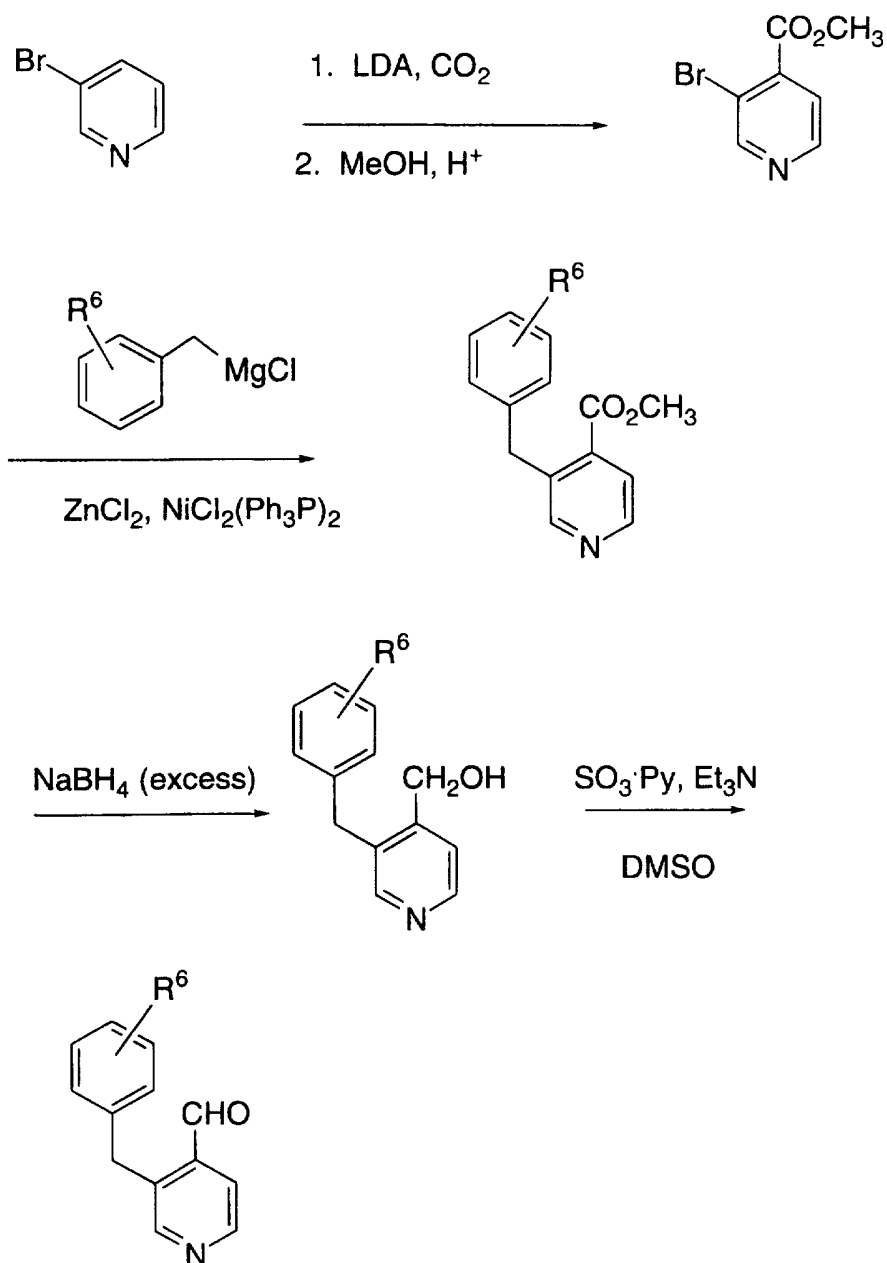
SCHEME 3

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## SCHEME 4

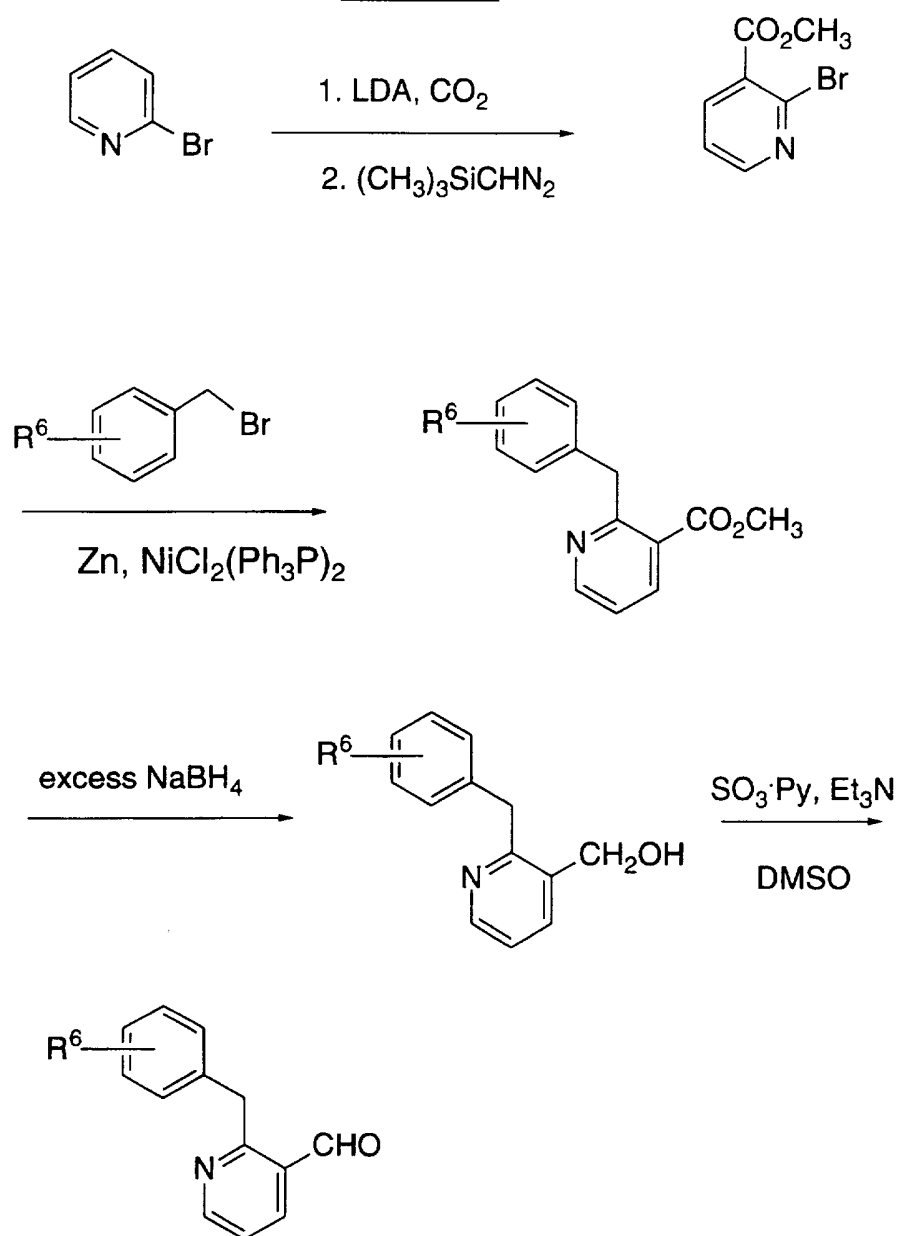


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SCHEME 5

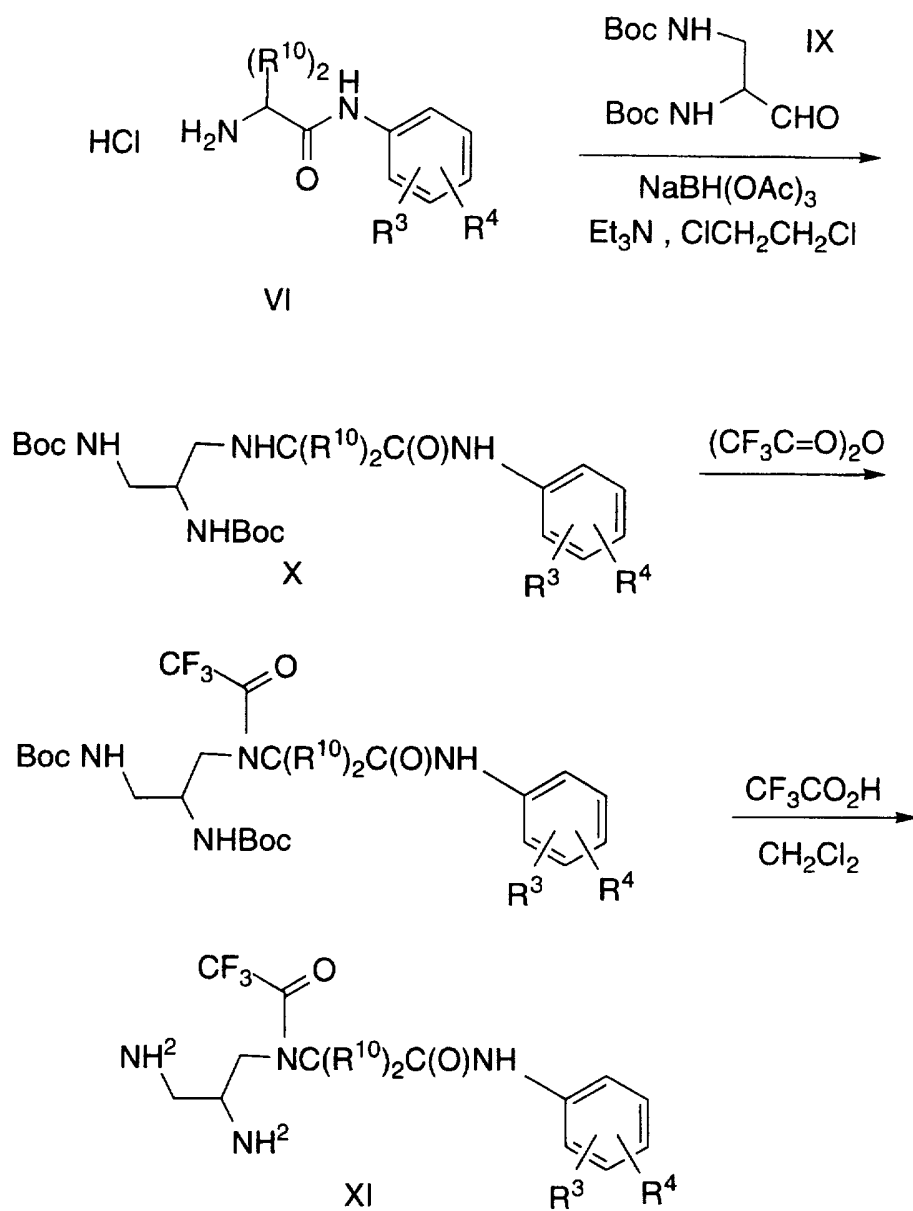
- 23 -

## SCHEME 6

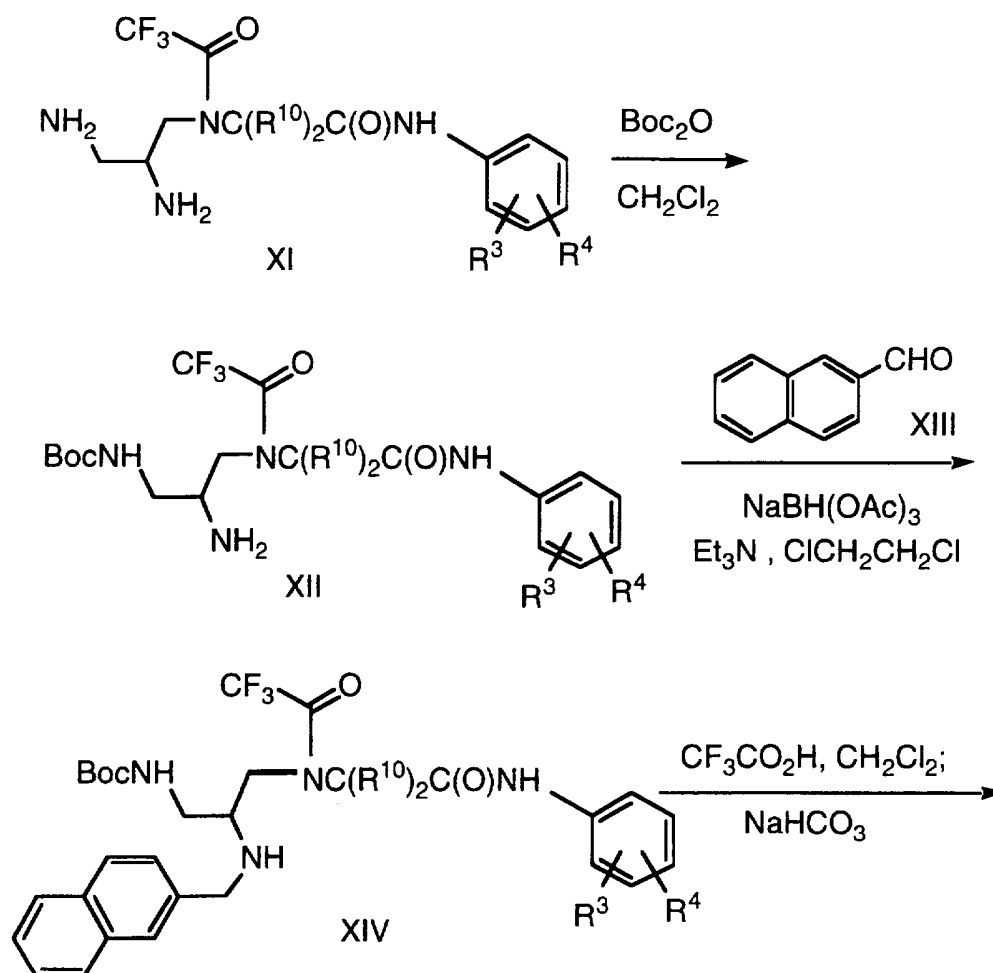


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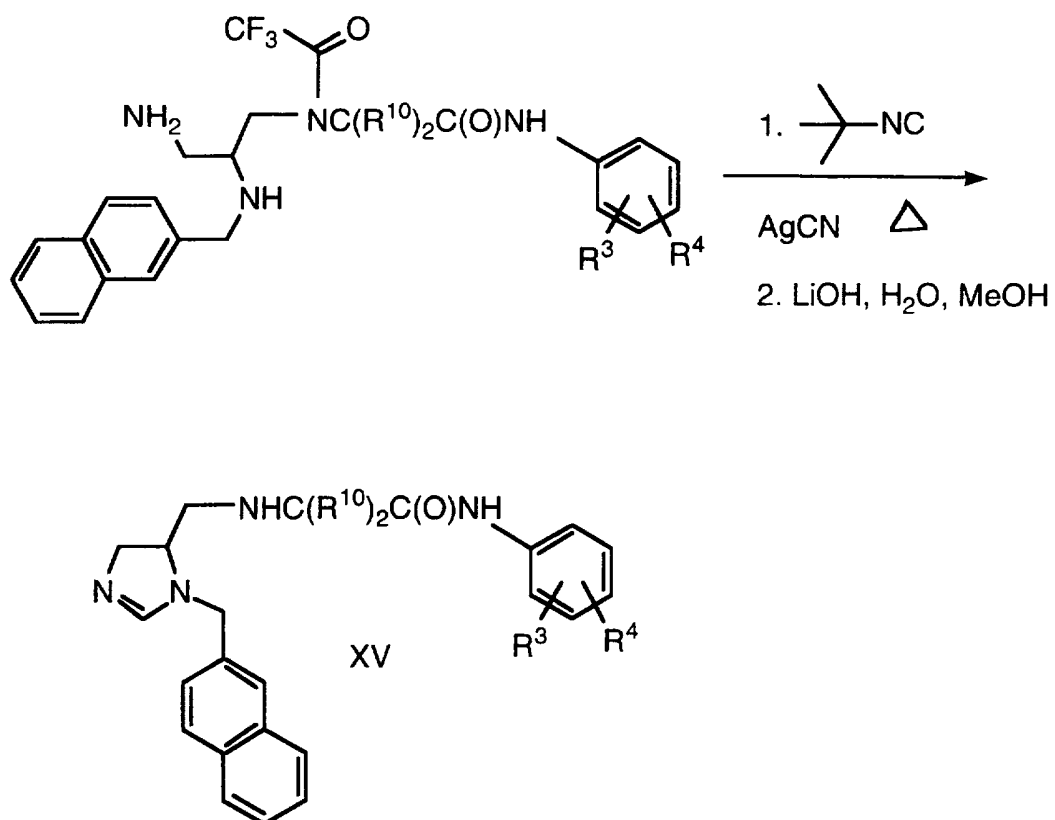
## SCHEME 7



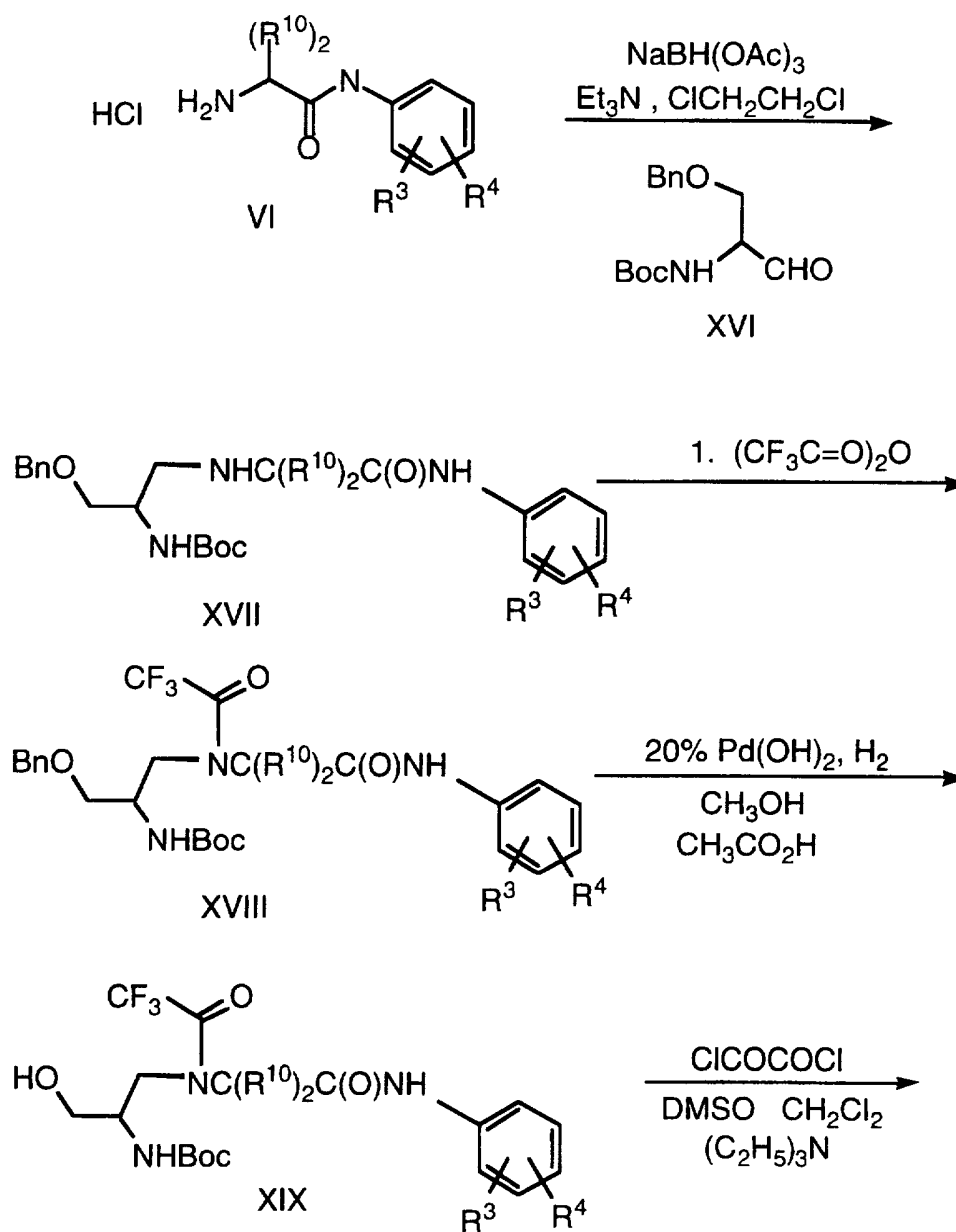
- 25 -

SCHEME 8

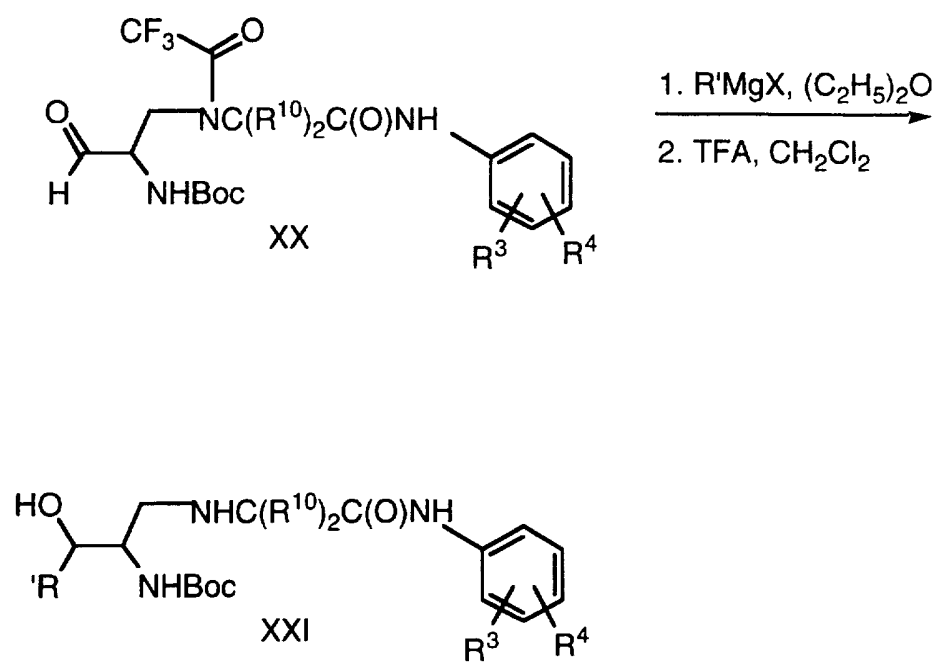
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SCHEME 8 (continued)

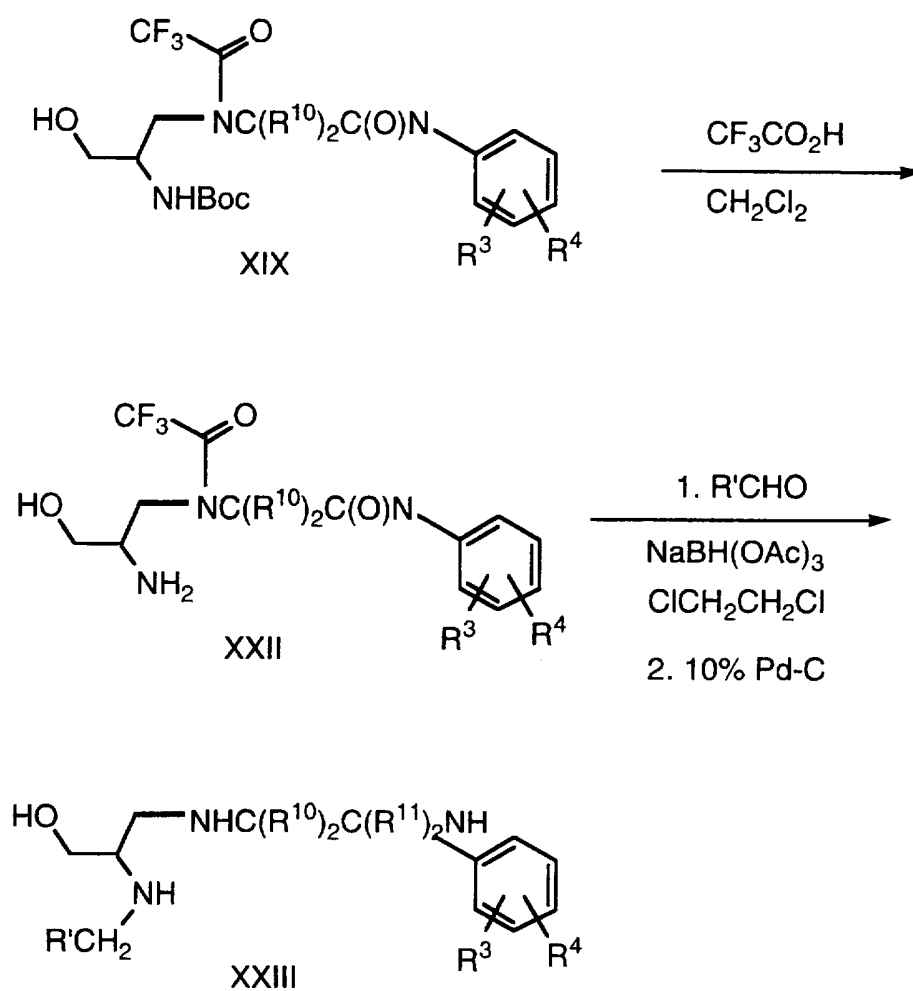
- 27 -

SCHEME 9

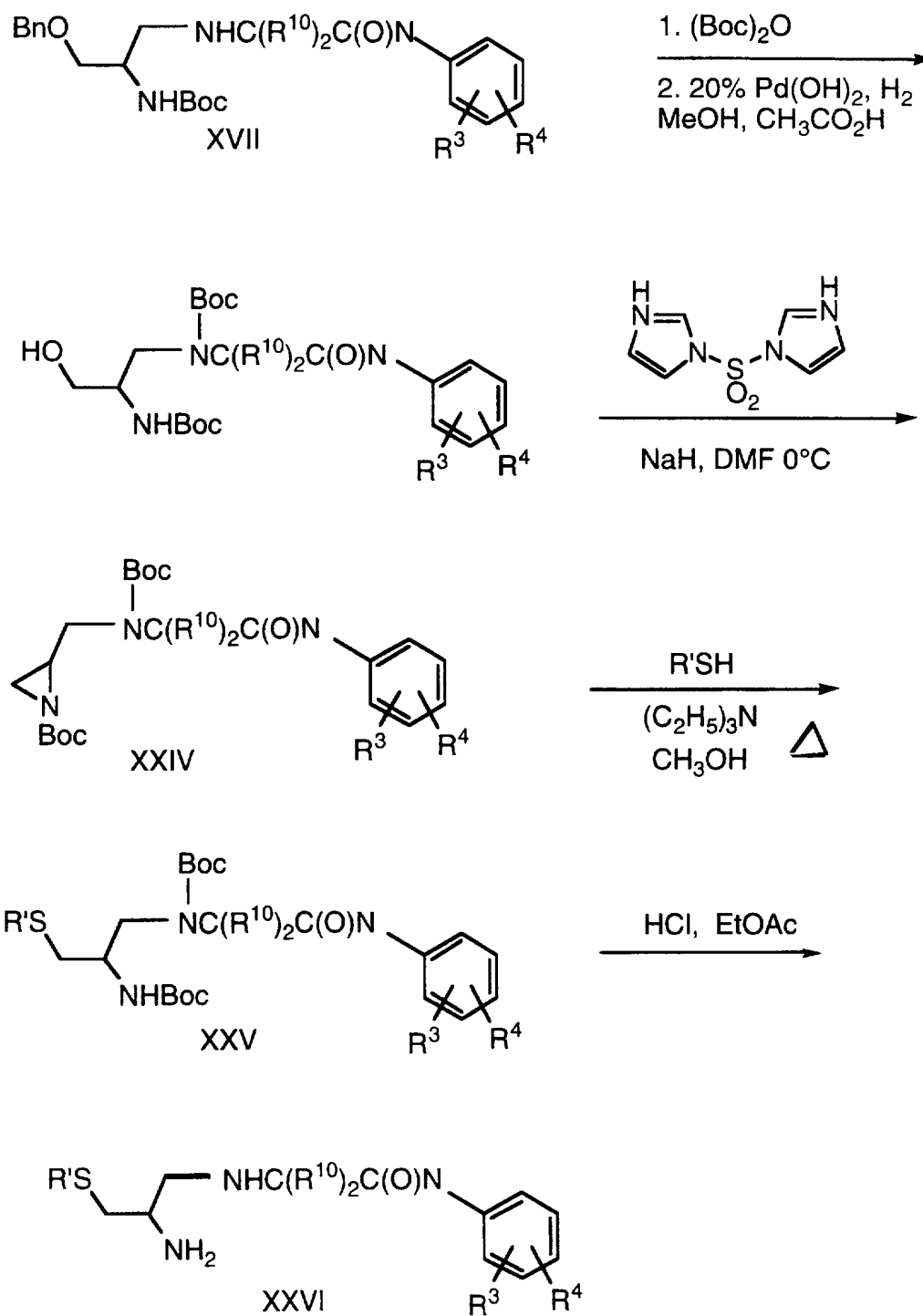
- 28 -

SCHEME 9 (CONTINUED)

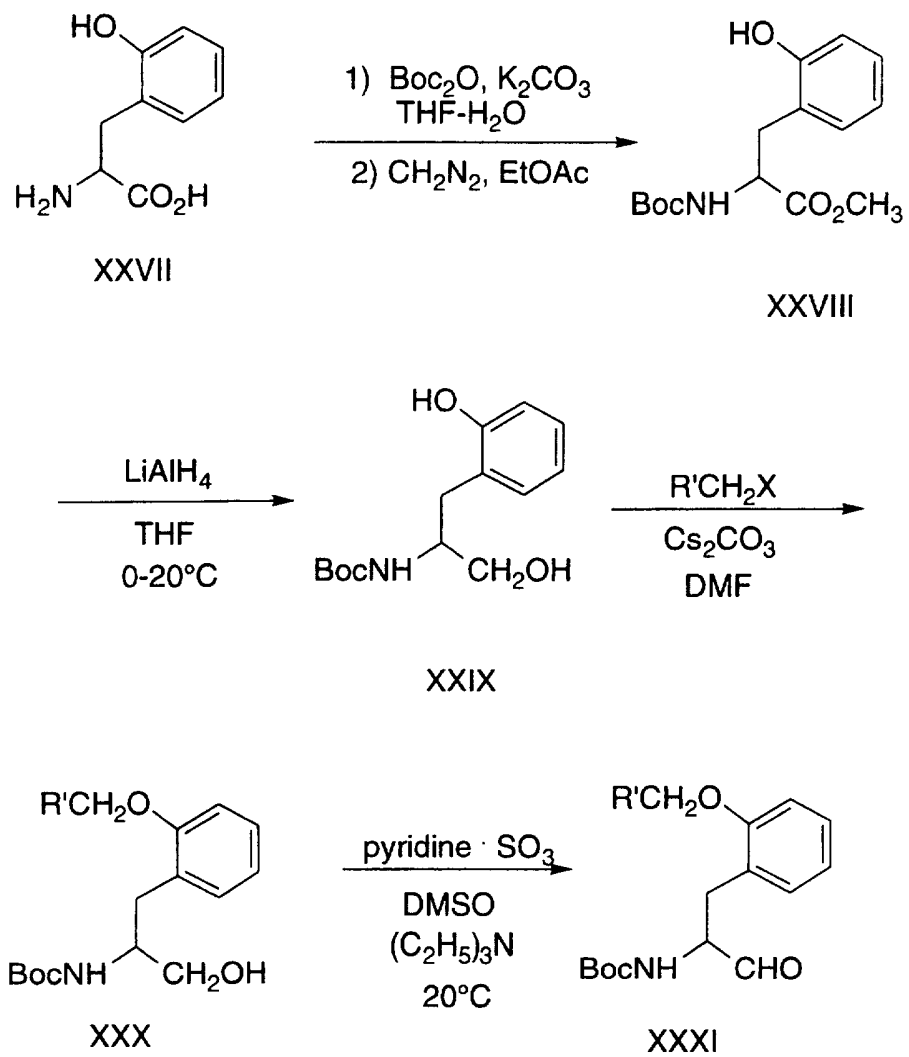
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SCHEME 10

- 30 -

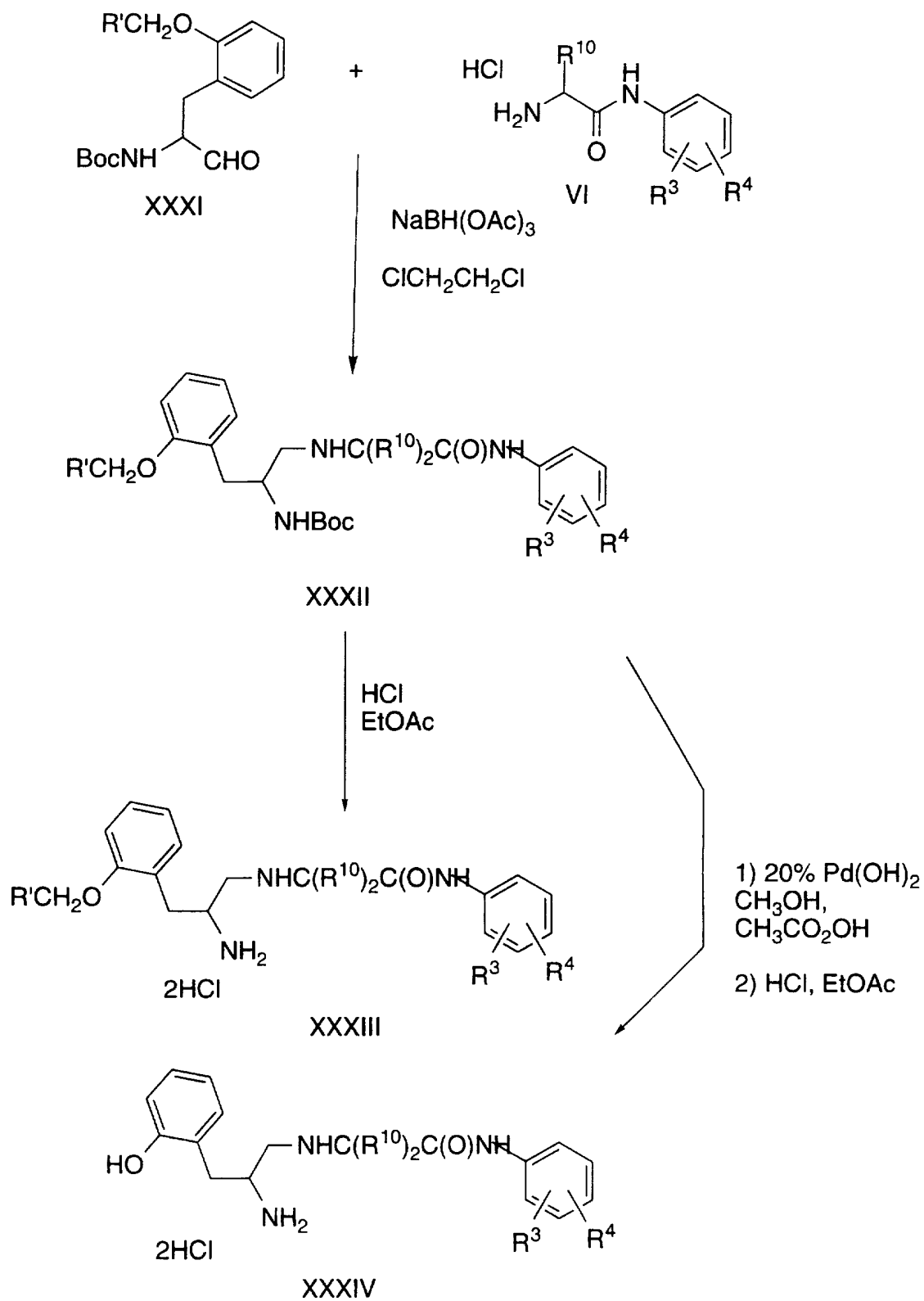
SCHEME 11

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SCHEME 12

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## SCHEME 12 (continued)



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The instant compounds are useful in the treatment of cancer. Cancers which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine  
5 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-  
10 protein transferase and 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-angiogenic properties of the instant compounds may also be useful in the treatment of certain forms of blindness related  
15 to retinal vascularization.

The compounds of this invention are also useful for inhibiting or treating other diseases where 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  
20 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  
25 of 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  
30 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)).

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

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, in the form of a pharmaceutical composition, which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier. The compounds can be administered orally, topically, rectally, vaginally transdermally or parenterally, including the intravenous, intramuscular, intraperitoneal and subcutaneous routes of administration.

For oral use, the compound is administered, for example, in the form of tablets or capsules, or as a solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch; lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, diluents also 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, the pH of the solution is suitably adjusted and the product is buffered. For intravenous use, the total concentration is controlled to render the preparation substantially isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected 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, retinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

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If formulated as a fixed dose, such combination products employ a compound of this invention substantially within the dosage range described below and other pharmaceutically active agent(s) typically within the acceptable 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 daily dosage will normally be determined by the prescribing physician, who may vary the dosage according to the age, weight, and response of the individual patient, as well as the severity of the patient's condition.

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

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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.

20

### EXAMPLE 1

#### 1-(4-CYANOBENZYL)-5-(HYDROXYMETHYL)IMIDAZOLE

##### 25 Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) 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 the titled product as a white solid which was sufficiently pure for use in the next step.

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Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) 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<sub>3</sub>, and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder (85.8 g, 86% yield for two steps) which was sufficiently pure for use in the next reaction.

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

A solution of the product from Step B (85.8 g, 225 mmol) and  $\alpha$ -bromo-*p*-tolunitrile (50.1 g, 232 mmol) 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 (50.4 g, 67% yield, 89% purity by HPLC) which was used in the next step without further purification.

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

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide

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monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. NaHCO<sub>3</sub> and brine. The solution was then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to provide the title compound (26.2 g, 82% yield) as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

## EXAMPLE 2

### 10 4-CYANOBENZYL HISTAMINE

#### Step A: Preparation of 1-pivaloyloxymethyl-3-(4-cyanobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide

N<sup>+</sup>-Pivaloyloxymethyl-N<sup>α</sup>-phthaloylhistamine (4.55 g, 12.8 mmol; prepared as previously described (J. C. Emmett, F. H. Holloway, and J. L. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1341, (1979)) and α-bromo-p-tolunitrile (3.77 g, 19.2 mmol) were dissolved in acetonitrile (70 mL). The solution was heated at 55°C for 4 h, cooled to room temperature, and filtered to remove the white solid.

20 The acetonitrile (30 mL) was concentrated to 1/2 its volume under reduced pressure and the solution was heated at 55°C overnight. The solution was cooled and filtered to give a white solid. The volume of the filtrate was reduced to 10 mL, the solution was heated at 55°C for 1 hr, then cooled to room temperature, diluted with EtOAc (25 mL) and

25 filtered to obtain additional white solid. The solids were combined, dried, and used without further purification.

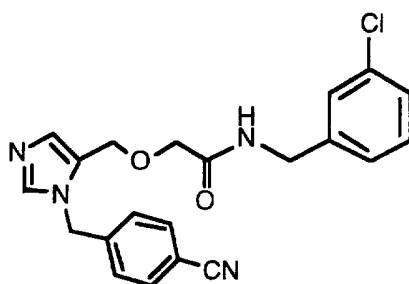
#### Step B: Preparation of 4-cyanobenzyl-N<sup>α</sup>-phthaloylhistamine

1-Pivaloyloxymethyl-3-(4-cyanobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide (6.13 g, 12.8 mmol) in methanol (100 mL) was saturated with ammonia gas while the temperature was maintained below 30°C. The solution was stirred for 1 hr, concentrated to dryness, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x200 mL), dried (MgSO<sub>4</sub>), concentrated, and chromatographed (silica gel, 10:90:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/NH<sub>4</sub>OH) to give 4-cyanobenzyl-N<sup>α</sup>-phthaloylhistamine.

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Step C: Preparation of 4-cyanobenzyl histamine

4-Cyanobenzyl-N $\alpha$ -phthaloylhistamine (1.64 g, 4.61 mmol), and hydrazine (1.46 mL, 46.1 mmol) were dissolved in absolute EtOH (70 mL). The solution was concentrated after 1 hr and filtered to remove a white precipitate which was washed several times with EtOH. The filtrate was concentrated and the residue was chromatographed (silica gel, 10:90:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/NH<sub>4</sub>OH) to give the title compound.

EXAMPLE 3

N-3-CHLOROBENZYL-2-{1-(4-CYANOBENZYL)IMIDAZOL-5-  
YLMETHOXY} ACETAMIDE

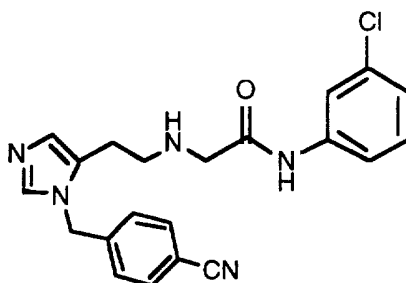
Step A: 2-{1-(4-Cyanobenzyl)imidazol-5-ylmethoxy} acetic acid

A solution of 2-bromoacetic acid in THF at room temperature is treated with excess sodium hydride for 15 minutes. To this mixture is added 1-(4-cyanobenzyl)-5-(hydroxymethyl)imidazole (Example 1) and the mixture is then heated. Upon cooling, the mixture is poured into H<sub>2</sub>O and EtOAc, extracted with EtOAc (3X), washed with brine, dried (MgSO<sub>4</sub>), filtered and evaporated to give the desired compound.

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Step B: N-3-Chlorobenzyl-2-{1-(4-cyanobenzyl)imidazol-5-ylmethoxy} acetamide

A solution of the acid from Step 1 in DMF is treated with EDC and HOBt followed by 3-chlorobenzylamine. After several hours, the mixture is poured into water and extracted with EtOAc. The organic layer is washed with water then brine, dried and evaporated to give the title compound.

EXAMPLE 4N-3-CHLOROPHENYL-2-{2-[1-(4-CYANOBENZYL)IMIDAZOL-5-YL]ETHYLAMINO} ACETAMIDE15 Step A. 2-Bromo-N-3-chlorophenylacetamide

A solution of 2-bromo acetyl bromide, 3-chloroaniline (1 equivalent) and Et<sub>3</sub>N (1.2 equivalents) in THF is stirred at room temperature for 1 h. The solution is poured into saturated NaHCO<sub>3</sub> solution, extracted with EtOAc (3X), washed with brine, dried (MgSO<sub>4</sub>) and the concentrated *in vacuo* to yield the title compound.

Step B. N-3-Chlorophenyl-2-{2-[1-(4-cyanobenzyl)imidazol-5-yl]ethylamino} acetamide

A solution of the bromo acetamide from Step A in DMF is treated with 4-cyanobenzyl histamine (1 equivalent) and Et<sub>3</sub>N (1.2 equivalents). The mixture is warmed for several hours, cooled and poured into water. After extraction with EtOAc, the organic layer is washed with water then brine, dried and concentrated to give the title compound.

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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<sup>+</sup>-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<sub>2</sub>, 5 mM dithiothreitol (DTT), 100 mM [<sup>3</sup>H]-farnesyl diphosphate ([<sup>3</sup>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 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 [<sup>3</sup>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<sub>2</sub> 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.

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

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

#### 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* 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* are seeded at a density of  $1 \times 10^4$  cells per plate (35 mm in diameter) in

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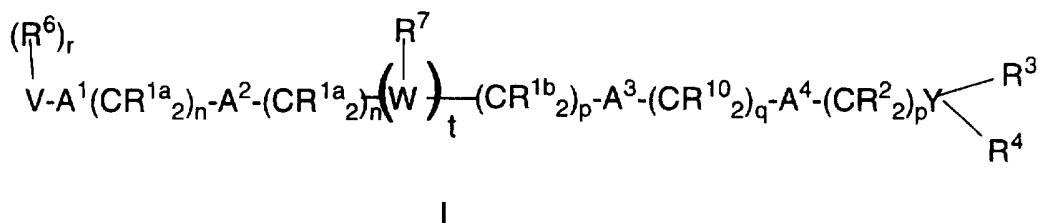
a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration 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.

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WHAT IS CLAIMED IS:

1. A compound of formula I:



5 or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup> and R<sup>10</sup> are independently selected from the group consisting of: hydrogen, aryl, substituted aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 10 R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>,  
 -N(R<sup>8</sup>)<sub>2</sub>, R<sup>9</sup>OC(O)NR<sup>8</sup>- and C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted or substituted with 1-3 groups selected from the group consisting of: halo, aryl, heterocyclyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-,  
 R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-,  
 15 N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub> and R<sup>9</sup>OC(O)NR<sup>8</sup>-;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of: H, F, Cl, Br, -N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 R<sup>8</sup>C(O)NH-, H<sub>2</sub>NC(NH)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, CN,  
 20 R<sup>9</sup>OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from the group consisting of: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>8</sup>-,  
 25 -NR<sup>8</sup>C(O)-, -O-, -N(R<sup>8</sup>)-, -S(O)<sub>2</sub>N(R<sup>8</sup>)-, -N(R<sup>8</sup>)S(O)<sub>2</sub>-, and S(O)<sub>m</sub>;

A<sup>3</sup> is selected from the group consisting of: -C(O)-, -O-, -S(O)<sub>m</sub>-, -OC(O)-, -C(O)O-, -NR<sup>5</sup>-, -NR<sup>5</sup>S(O)<sub>m</sub>- or S(O)<sub>m</sub>NR<sup>5</sup>-;

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A<sup>4</sup> is selected from -O-, -S(O)<sub>m</sub>-, -NR<sup>5</sup>-, -NR<sub>5</sub>C(O)-, -C(O)NR<sup>5</sup>-, -OC(O)-, -C(O)O-, -NR<sup>5</sup>S(O)<sub>m</sub>- and -S(O)<sub>m</sub>NR<sup>5</sup>-;

m represents 0, 1 or 2;

5

each R<sup>5</sup> is independently selected from the group consisting of: hydrogen, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, and C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1-3 members selected from the group consisting of: unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

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R<sup>6</sup> and R<sup>7</sup> are independently selected from the group consisting of: hydrogen, aryl, heterocyclyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1-6</sub> perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>9</sup>OC(O)NR<sup>8</sup>- and C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by 1-3 groups selected from: aryl, heterocyclyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>NC(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub> and R<sup>9</sup>OC(O)NR<sup>8</sup>-;

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each R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and aralkyl;

each R<sup>9</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

30

V is selected from the group consisting of: hydrogen, heterocyclyl, aryl, C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are

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replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub> alkenyl,  
provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

5

W represents heterocyclyl;

Y represents aryl;

10

each n and p independently represents 0, 1, 2, 3 or 4;  
q is 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.

15

2. A compound in accordance with claim 1 wherein R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup> and R<sup>10</sup> are independently selected from: hydrogen, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>C(O)NR<sup>8</sup>- or unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>O- and R<sup>8</sup>C(O)NR<sup>8</sup>-

20

3. A compound in accordance with claim 1 wherein R<sup>3</sup> and R<sup>4</sup> are selected from: hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl.

25

4. A compound in accordance with claim 1 wherein R<sup>6</sup> is selected from CN, NO<sub>2</sub> or R<sup>8</sup>O-.

5. A compound in accordance with claim 1 wherein R<sup>7</sup> represents hydrogen, unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl.

30

6. A compound in accordance with claim 1 wherein R<sup>8</sup> represents H or C<sub>1-6</sub> alkyl, and R<sup>9</sup> is C<sub>1-6</sub> alkyl.

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7. A compound in accordance with claim 1 wherein A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -C(O)NR<sup>8</sup>-, -NR<sup>8</sup>C(O)-, -O-, -N(R<sup>8</sup>)-, -S(O)<sub>2</sub>N(R<sup>8</sup>)- and -N(R<sup>8</sup>)S(O)<sub>2</sub>-.

5 8. A compound in accordance with claim 1 wherein A<sup>3</sup> represents O, S, NR<sup>5</sup> or NR<sup>5</sup>S(O)<sub>m</sub>, wherein m represents 2 and R<sup>5</sup> represents hydrogen.

10 9. A compound in accordance with claim 1 wherein A<sup>4</sup> represents -C(O)NR<sup>5</sup>- or -NR<sup>5</sup>C(O)-, with R<sup>5</sup> representing H.

10. A compound in accordance with claim 1 wherein V is selected from hydrogen, heterocyclyl and aryl.

15 11. A compound in accordance with claim 1 wherein V is phenyl.

20 12. A compound in accordance with claim 1 wherein W is heterocyclyl selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyrrolidinyl, thiazolyl and pyridyl.

13. A compound in accordance with claim 12 wherein W represents imidazolyl or pyridyl.

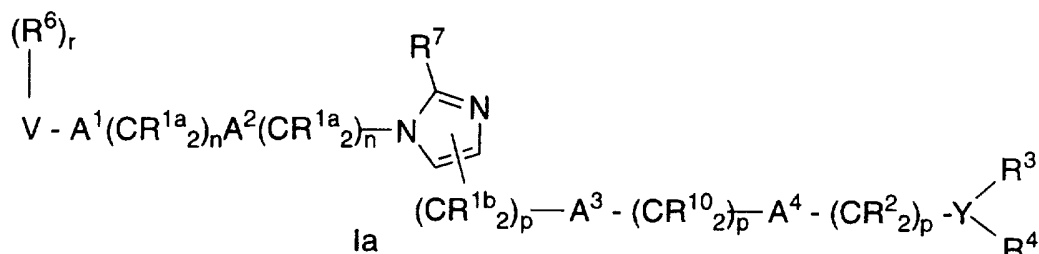
25 14. A compound in accordance with claim 1 wherein m is 0 or 2.

15. A compound in accordance with claim 1 wherein n and p are 0, 1, 2 or 3.

30 16. A compound in accordance with claim 1 wherein t is 1.

17. A subset of compounds of the invention is represented by formula Ia:

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wherein:

5  $R^3$ ,  $R^4$ ,  $A^3$ ,  $A^4$ ,  $Y$ ,  $R^8$ ,  $R^9$ ,  $m$ ,  $n$ ,  $p$  and  $r$  are as originally defined;

each  $R^{1a}$ ,  $R^{1b}$ ,  $R^2$  and  $R^{10}$  is independently selected from hydrogen and C1-C6 alkyl;

10  $R^5$  is selected from the group consisting of: hydrogen and C1-C6 alkyl, unsubstituted or substituted with 1-3 members selected from the group consisting of: unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C3-C10 cycloalkyl,  $-N(R^8)_2$ ,  $-CF_3$ ,  $-NO_2$ ,  $(R^8)O-$ ,  $(R^9)S(O)_m-$ ,  
 15  $(R^8)C(O)NH-$ ,  $H_2NC(NH)-$ ,  $(R^8)C(O)-$ ,  $(R^8)OC(O)-$ ,  $N_3$ ,  $CN$  and  $(R^9)OC(O)NR^8-$ ;

$R^6$  and  $R^7$  are independently selected from: hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $R^8O-$ ,  $R^8C(O)NR^8-$ ,  $CN$ ,  $NO_2$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  
 20  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$ , and C1-C6 alkyl substituted by C1-C6 perfluoroalkyl,  $R^8O-$ ,  $R^8C(O)NR^8-$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$  and  $R^9OC(O)NR^8-$ ;

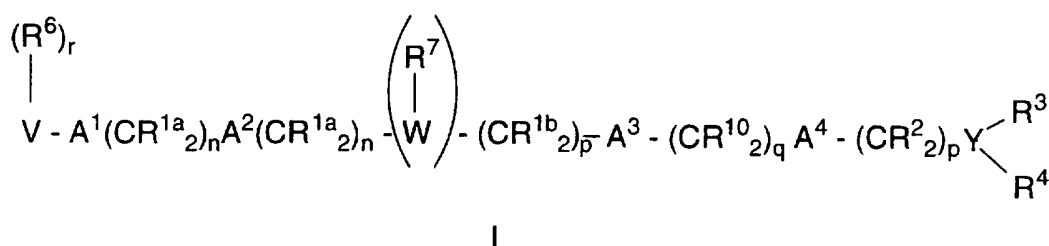
25  $A^1$  and  $A^2$  are independently selected from: a bond,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-C(O)-$ ,  $-C(O)NR^8-$ ,  $O$ ,  $-N(R^8)-$  and  $S(O)_m$ ;

and  $V$  is selected from: hydrogen; aryl; heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl,

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2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl and thienyl; C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub> alkenyl, provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond and A<sup>2</sup> is S(O)<sub>m</sub>.

18. A compound in accordance with claim 1 represented by formula I:



wherein:

R<sup>3</sup>, R<sup>4</sup>, A<sup>3</sup>, A<sup>4</sup>, Y, R<sup>8</sup>, R<sup>9</sup>, m, n, p and r are as originally defined;

each R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup> and R<sup>10</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>5</sup> is selected from the group consisting of: hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted or substituted with 1-3 members selected from the group consisting of: unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, -N(R<sup>8</sup>)<sub>2</sub>, -CF<sub>3</sub>, -NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>NC(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN and (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

R<sup>6</sup> and R<sup>7</sup> are independently selected from: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>8</sup>O-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-, and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub>

- 50 -

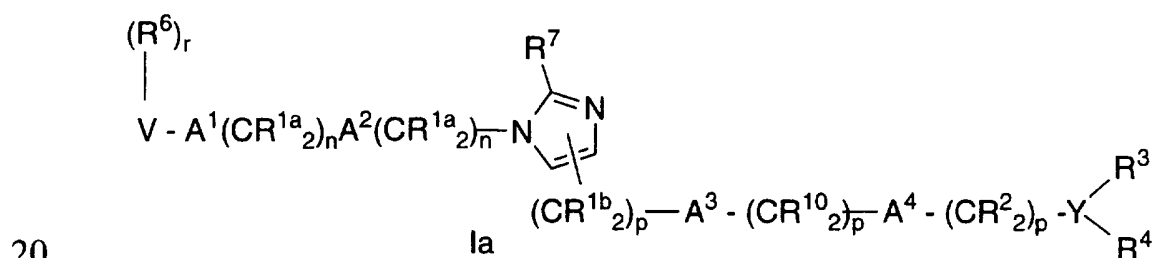
perfluoroalkyl,  $R^8O-$ ,  $R^8C(O)NR^8-$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$  and  $R^9OC(O)NR^8-$ ;

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

and  $V$  is selected from: hydrogen; aryl; heterocyclyl  
selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl,  
2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl and thienyl;  $C_1-C_{20}$   
10 alkyl wherein from 0 to 4 carbon atoms are replaced with a  
heteroatom selected from  $O$ ,  $S$ , and  $N$ , and  $C_2-C_{20}$  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 and  $A^2$  is  $S(O)_m$ ; and

$W$  represents heterocyclyl selected from pyrrolidinyl,  
15 pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl  
and isoquinolinyl.

19. A compound in accordance with claim 1 represented  
by formula Ia:



wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^2$ ,  $R^{10}$ ,  $A^1$ ,  $A^2$ ,  $A^4$ ,  $Y$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^8$ ,  $R^9$ ,  
 $m$ ,  $n$ ,  $p$ ,  $q$  and  $r$  are as originally defined;

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

$A^3$  represents  $-S-$ ;

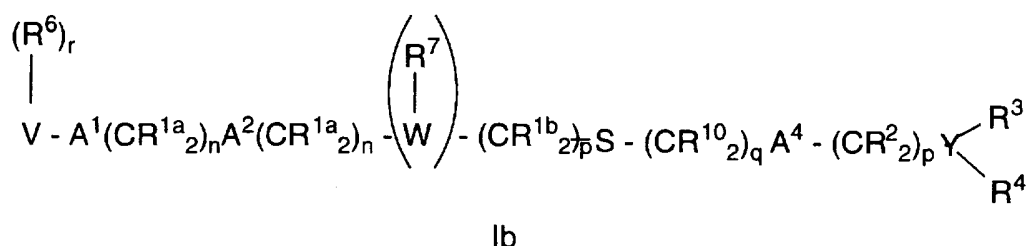
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V is selected from: hydrogen, heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, aryl, C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub> alkenyl,

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>; and

W represents heterocyclyl selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl and isoquinolinyl.

20. A compound in accordance with claim 1 represented by formula Ib:



wherein:

R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup>, R<sup>10</sup>, A<sup>1</sup>, A<sup>2</sup>, A<sup>4</sup>, Y, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup>, R<sup>9</sup>, m, n, p, q and r are as originally defined;

R<sup>7</sup> is selected from: hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

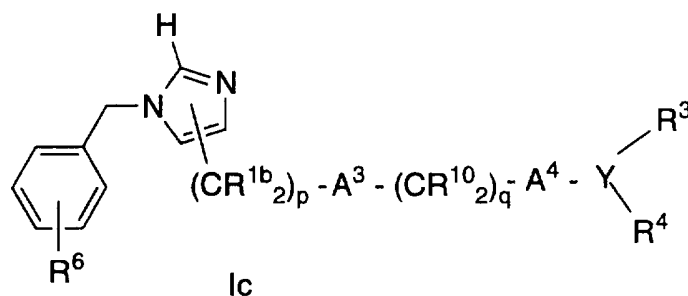
V is selected from: hydrogen, heterocyclyl selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, aryl, C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and C<sub>2</sub>-C<sub>20</sub> alkenyl,

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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  $S(O)_m$ ; and

W represents heterocyclyl selected from pyrrolidinyl,  
 5 pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl  
 and isoquinolinyl.

21. A compound in accordance with claim 1 represented  
 by formula Ic:  
 10



wherein:

each  $R^{1b}$  and  $R^{10}$  is independently selected from hydrogen  
 and C<sub>1</sub>-C<sub>6</sub> alkyl;  
 15

$R^3$ ,  $R^4$ ,  $R^8$ ,  $R^9$ , m, p, and q are as originally defined;

$A^3$  represents -O-, -S- or -NH-;

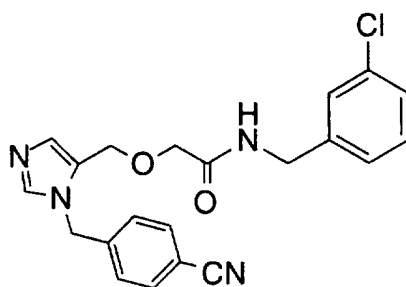
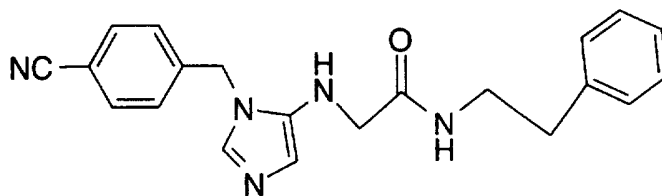
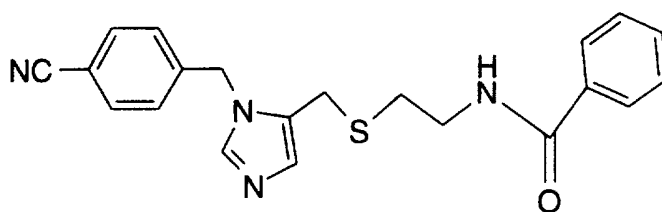
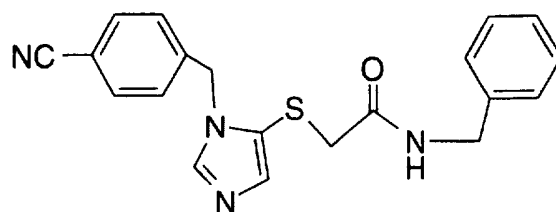
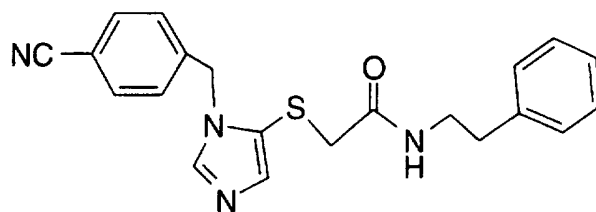
20  $A^4$  represents -C(O)NH- or -NHC(O)-;

and  $R^6$  is selected from the group consisting of: hydrogen,  
 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F,  
 Cl,  $R^8O$ -,  $R^8C(O)NR^8$ -, CN, NO<sub>2</sub>,  $(R^8)_2N-C(NR^8)$ -,  $R^8C(O)$ -,  
 25  $R^8OC(O)$ -,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8$ - and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by  
 C<sub>1</sub>-C<sub>6</sub> 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  $R^9OC(O)NR^8$ -.

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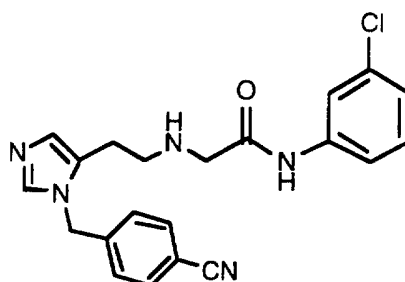
22. A compound in accordance with claim 1 having the structural formula:

- 54 -



or

- 55 -



or a pharmaceutically acceptable salt thereof.

5                    23. A pharmaceutical composition which is comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

10                   24. A method of treating cancer in a mammalian patient in need of such treatment, comprising administering to said patient an anti-cancer effective amount of a compound of claim 1.

15                   25. A method for inhibiting farnesyl-protein transferase in a mammalian patient in need of such treatment, which comprises administering to said mammal a farnesyl-protein transferase inhibiting amount of a compound of claim 1.

20                   26. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

25                   27. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

28. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

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29. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

5

30. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

10

31. A method for treating or preventing a disease selected from cancer, neurofibromin benign proliferative disorder, blindness related to retinal vascularization, infections from hepatitis delta and related viruses, restenosis and polycystic kidney disease, which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

15

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/05295

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07D 233/70, 233/66, 233/60; A61K 31/415

US CL : 548/325.1, 324.5, 326.5, 338; 514/398, 399

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/325.1, 324.5, 326.5, 338; 514/398, 399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
| A         | US 4,853,383 A (BALDWIN et al.) 01 August 1989, see entire document.               | 1-23                  |
| A,P       | US 5,534,537 A (CICCARONE et al.) 09 July 1996, see entire document.               | 1-23                  |
| A         | US 5,401,851 A (BOYD et al.) 28 March 1995, see entire document.                   | 1-23                  |
| A         | US 5,424,450 A (BOSWELL et al.) 13 June 1995, see entire document.                 | 1-23                  |

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

|                                                                                                                                                                         |                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
| *A* document defining the general state of the art which is not considered to be of particular relevance                                                                | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |
| *E* earlier document published on or after the international filing date                                                                                                | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family                                                                                                                                                                                                    |
| *O* document referring to an oral disclosure, use, exhibition or other means                                                                                            |                                                                                                                                                                                                                                                  |
| *P* document published prior to the international filing date but later than the priority date claimed                                                                  |                                                                                                                                                                                                                                                  |

Date of the actual completion of the international search

11 JULY 1997

Date of mailing of the international search report

20 AUG 1997

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/05295

## B. FIELDS SEARCHED

Documentation other than minimum documentation that are included in the fields searched:

CHEMICAL ABSTRACTS

INDEX CHemicus

CURRENT ABSTRACTS OF CHEMISTRY