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(54) Title: A METHOD OF TREATING CANCER

(57) Abstract

The present invention relates to methods of treating cancer using a combination of a compound which is an integrin antagonist and a compound which is an inhibitor of farnesyl–protein transferase, which methods comprise administering to said mammal, either sequentially in any order or simultaneously, amounts of at least two therapeutic agents selected from a group consisting of a compound which is an integrin antagonist and a compound which is an inhibitor of farnesyl–protein transferase. The invention also relates to methods of preparing such compositions.

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TITLE OF THE INVENTION
A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating cancer using a combination of a compound which is an integrin antagonist and a compound which is a inhibitor of farnesyl-protein transferase.

Osteoclasts are multinucleated cells of up to 400 μm in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate, in vertebrates. They are actively motile cells that migrate along the surface of bone. They can bind to bone, secrete necessary acids and proteases and thereby cause the actual resorption of mineralized tissue from the bone.

More specifically, osteoclasts are believed to exist in at least two physiological states. In the secretory state, osteoclasts are flat, attach to the bone matrix via a tight attachment zone (sealing zone), become highly polarized, form a ruffled border, and secrete lysosomal enzymes and acid to resorb bone. The adhesion of osteoclasts to bone surfaces is an important initial step in bone resorption. In the migratory or motile state, the osteoclasts migrate across bone matrix and do not take part in resorption until they attach again to bone.

Integrins are transmembrane, heterodimeric, glycoproteins which interact with extracellular matrix and are involved in osteoclast attachment, activation and migration. The most abundant integrin in osteoclasts (rat, chicken, mouse and human) is the vitronectin receptor, or $\alpha v\beta 3$, thought to interact in bone with matrix proteins that contain the RGD sequence. Antibodies to $\alpha v\beta 3$ block bone resorption in vitro indicating that this integrin plays a key role in the resorptive process. There is increasing evidence to suggest that $\alpha v\beta 3$ ligands can be used effectively to inhibit osteoclast mediated bone resoption in vivo in mammals.

A second integrin vitronectin receptor, αvβ5, has also been identified. A monoclonal antibody for αvβ5 has been shown to inhibit VEGF-induced angiogenesis in rabbit cornea and the chick chorioallantoic membrane model. *See* M.C. Friedlander, *et al.*, *Science 270*, 1500-1502, 1995, which is incorporated by reference herein in its entirety. Two collagen receptor integrins, α1β1 and α2β1, have also been proposed to mediate VEGF-induced mitogenesis in a mouse Matrigel implant model. *See* D.R. Senger, *et al, Proc. Natl. Acad. Sci 94*, 13612-13617, 1997, which is incorporated by reference herein in its entirety.

Additionally, αvβ3 ligands have been found to be useful in treating and/or inhibiting restenosis (recurrence of stenosis after corrective surgery on the heart valve), artherosclerosis, diabetic retinopathy, macular degeneration, and angiogenesis (formation of new blood vessels). Moreover, it has been postulated that the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models. (*See*, Harrison's Principles of Internal Medicine, 12th ed., 1991). αvβ3 antagonists, which inhibit angiogenesis, are therefore useful in the treatment of cancer for inhibiting tumor growth and metastasis. (*See e.g.*, Brooks et al., *Cell*, 79:1157-1164 (1994)).

Prenylation of proteins by intermediates of the isoprenoid biosynthetic pathway represents a class of post-translational modification (Glomset, J. A., Gelb, M. H., and Farnsworth, C. C. (1990). Trends Biochem. Sci. 15, 139-142; Maltese, W. A. (1990). FASEB J. 4, 3319-3328). This modification typically is required for the membrane localization and function of these proteins. Prenylated proteins share characteristic C-terminal sequences including CaaX (C, Cys; a, usually aliphatic amino acid; X, another amino acid), XXCC, or XCXC. Three post-translational processing steps have been described for proteins having a C-terminal CaaX sequence: addition of either a 15 carbon (farnesyl) or 20 carbon (geranylgeranyl) isoprenoid to the Cys residue, proteolytic cleavage of the last 3 amino acids, and methylation

of the new C-terminal carboxylate (Cox, A. D. and Der, C. J. (1992a). *Critical Rev. Oncogenesis* 3:365-400; Newman, C. M. H. and Magee, A. I. (1993). *Biochim. Biophys. Acta* 1155:79-96). Some proteins may also have a fourth modification: palmitoylation of one or two Cys residues N-terminal to the farnesylated Cys. While some mammalian cell proteins terminating in XCXC are carboxymethylated, it is not clear whether carboxy methylation follows prenylation of proteins terminating with a XXCC motif (Clarke, S. (1992). Annu. Rev. Biochem. 61, 355-386). For all of the prenylated proteins, addition of the isoprenoid is the first step and is required for the subsequent steps (Cox, A. D. and Der, C. J. (1992a). *Critical Rev. Oncogenesis* 3:365-400; Cox, A. D. and Der, C. J. (1992b) *Current Opinion Cell Biol.* 4:1008-1016).

Three enzymes have been described that catalyze protein prenylation: farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). These enzymes are found in both yeast and mammalian cells (Clarke, 1992; Schafer, W. R. and Rine, J. (1992) *Annu. Rev. Genet.* 30:209-237). Each of these enzymes selectively uses farnesyl diphosphate or geranylgeranyl diphosphate as the isoprenoid donor and selectively recognizes the protein substrate. FPTase farnesylates CaaX-containing proteins that end with Ser, Met, Cys, Gln or Ala. For FPTase, CaaX tetrapeptides comprise the minimum region required for interaction of the protein substrate with the enzyme. The enzymological characterization of these three enzymes has demonstrated that it is possible to selectively inhibit one with little inhibitory effect on the others (Moores, S. L., Schaber, M. D., Mosser, S. D., Rands, E., O'Hara, M. B., Garsky, V. M., Marshall, M. S., Pompliano, D. L., and Gibbs, J. B., *J. Biol. Chem.*, 266:17438 (1991), U.S. Pat. No. 5,470,832).

The prenylation reactions have been shown genetically to be essential for the function of a variety of proteins (Clarke, 1992; Cox and Der, 1992a; Gibbs, J. B. (1991). *Cell* 65: 1-4; Newman and Magee, 1993; Schafer and Rine, 1992). This requirement often is demonstrated by mutating the CaaX Cys acceptors so that the proteins can no longer

be prenylated. The resulting proteins are devoid of their central biological activity. These studies provide a genetic "proof of principle" indicating that inhibitors of prenylation can alter the physiological responses regulated by prenylated proteins.

The Ras protein is 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)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, Science *271*:810-812).

Mutated *ras* genes 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.

The Ras protein is one of several proteins that are known to undergo post-translational modification. 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)).

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)). 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.

Other farnesylated proteins include the Ras-related GTP-binding proteins such as RhoB, 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.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to 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)).

Mammalian cells express four types of Ras proteins (H-, N-, K4A-, and K4B-Ras) among which K-Ras4B is the most frequently mutated form of Ras in human cancers. Inhibition of farnesyl-protein transferase has been shown to block the growth of H-*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 H-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 H-*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 H-*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. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells.

A pharmaceutically effective combination of an integrin antagonist and a farnesyl-protein transferase inhibitor are used in the present invention to treat cancer, such as in tumor cells that are less susceptable to treatment by an integrin antagonist or a farnesyl-protein transferase inhibitor when administered alone.

SUMMARY OF THE INVENTION

A method of treating cancer is disclosed which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a combination of an integrin antagonist and a farnesyl protein transferase inhibitor. Preferably a selective integrin antagonist and a selective farnesyl protein transferase inhibitor are used in such a combination.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating cancer which is comprised of admininstering to a mammalian patient in need

of such treatment an effective amount of a combination of an integrin antagonist and a farnesyl-protein transferase inhibitor. The present method of treating cancer by simultaneously inhibiting farnesyl-protein transferase and binding to either or both of the αvβ3 integrin and αvβ5 integrin offers advantages over previously disclosed methods which utilize a prenyl-protein transferase inhibitor or an integrin antagonist alone, in that the inhibitory activity of the instant combination of inhibitors against FPTase or integrin activity can be varied by formulation depending on the nature of the cancer cells to be treated. Any compound which acts as an integrin antagonist and any compound which inhibits farnesyl protein transferase can be used in the instant method. Preferably the compounds utilized in the instant combination are a selective integrin antagonist and a selective farnesyl-protein transferase inhibitor. When practicing the present method the integrin antagonist and the inhibitor of farnesyl-protein transferase may be administered either sequentially in any order or simultaneously.

It is anticipated that the therapeutic effect of the instant compositions may be achieved with smaller amounts of either or both of the integrin antagonist and farnesyl-protein transferase inhibitor than would be required if such an integrin antagonist and a selective farnesyl-protein transferase inhibitor were administered alone, thereby avoiding any non-mechanism-based adverse toxicity effects which might result from administration of an amount of the integrin antagonist or farnesyl-protein transferase inhibitor sufficient to achieve the same therapeutic effect. It is also anticipated that the instant compositions will achieve a synergistic therapeutic effect or will exhibit unexpected therapeutic advantage over the effect of either of the component compounds if administered alone.

As used herein the term an integrin antagonist refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ3 integrin, which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, which antagonize, inhibit or counteract binding of a physiological ligand to both the αvβ3 integrin and the αvβ5 integrin, or

which antagonize, inhibit or counteract the activity of the particular integrin or integrins expressed on capillary endothelial cells. The term also refers to a combination of a selective antagonist of the αvβ3 integrin and a selective antagonist of the αvβ5 integrin. The term also refers to antagonists of the α1β1 and α2β1 integrins.

The term farnesyl protein transferase (FPTase) inhibiting compound likewise refers to compounds which antagonize, inhibit or counteract the activity of the gene coding farnesyl-protein transferase or the protein produced in response thereto.

The terms selective and selectively as used herein refer to the antagonistic activity of the particular compound against either an integrin or integrins or the inhibitory activity of the compound against FPTase activity. Preferably, a selective compound exhibits at least 20 times greater activity against either an single integrin, a group of integrins or all of the integrins which have been demonstrated as being important for angiogenesis when comparing its activity against other integrins. Such integrins which have been demonstrated as being important for angiogenesis include, but are not limited to, αvβ3, αvβ5, α1β1 and α2β1 integrins. More preferably the selectivity is at least 100 times or more. As used herein, a selective FPTase inhibitor may also be an inhibitor of geranylgeranyl-protein transferase.

The extent of selectivity of the two or more inhibitors that comprise the method of the instant invention effects the advantages that the method of treatment claimed herein offers over previously disclosed methods of using a single integrin antagonist or FPTase inhibitor for the treatment of cancer. In particular, use of two independent pharmaceutically active components that have complementary, essentially non-overlapping activities allows the person utilizing the instant method of treatment to independently and accurately vary the inhibitory activity of the combination without having to synthesize a single drug having a particular pharmaceutical activity profile.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of this invention is greater than the sum of the effects that result from methods and compositions

comprising the FPTase inhibitor and integrin antagonist separately and in the amounts employed in the methods and compositions hereof.

The preferred therapeutic effect provided by the instant composition is the treatment of cancer and specifically the inhibition of cancerous tumor growth and/or the regression of cancerous tumors. Cancers which are treatable in accordance with the invention described herein include cancers of the brain, breast, colon, genitourinary tract, lymphatic system, pancreas, rectum, stomach, larynx, liver and lung. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, small cell lung cancers and neurological tumors.

Other therapeutic effects provided by the instant composition include inhibiting: bone resorption mediated by osteoclast cells, restenosis, artherosclerosis, diabetic retinopathy, macular degeneration and angiogenesis in animals, preferably mammals, especially humans.

The instant composition may also be useful for preventing or treating osteoporosis.

Additional illustrations of the invention are methods of treating hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

The composition of this invention is 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 instant composition to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The composition of the instant invention is 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 composition 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 pharmaceutical composition 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 combination according to this invention, the selected combination or compounds 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 ingredients are 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.

The combinations 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 combinations may be useful in combination with other known anti-cancer and cytotoxic agents.

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

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the combinations 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 blood-stream by local bolus injection.

When a combination 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 an integrin antagonist(s) and a farnesyl-protein transferase inhibitor are administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of each type of inhibitor of 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. A particular therapeutic dosage that comprises the instant composition includes from about 0.01mg to about 500mg of an integrin antagonist and from about 0.01mg to about 500mg of a farnesyl-protein transferase inhibitor. Preferably, the dosage comprises from about 1mg to about 100mg of an

integrin antagonist and from about 1mg to about 100mg of a farnesyl-protein transferase inhibitor.

The integrin antagonist component of the instant invention may be selected from the following:

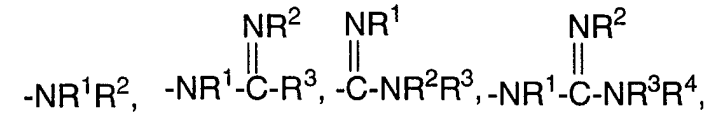
(a) a compound of the formula I-a:

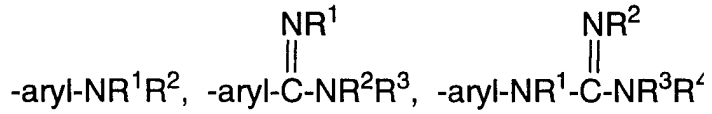
X-Y-Z-Aryl-A-B

wherein:

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms and either unsubstituted or substituted with R^8 and R^9;

X is selected from





a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1, R^2, R^3 and R^4, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1, R^2, R^3 and R^4 ;

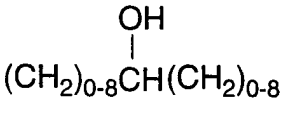
Y is selected from

C_{0-8} alkylene,

C_{3-10} cycloalkyl,

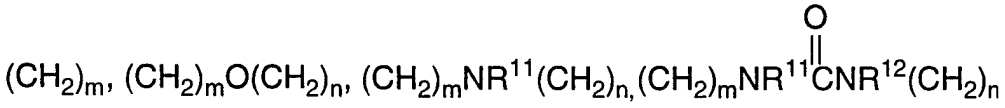
C_{0-8} alkylene-NR^{10}-CO-C_{0-8} alkylene,

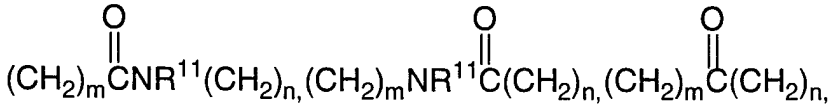
C_{0-8} alkylene-$CONR^{10}$-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^{10}-C_{0-8} alkylene,
C_{0-8} alkylene-$S(O)_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^{10}-C_{0-8} alkylene,
C_{0-8} alkylene-NR^{10}-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NR^{10}-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl$NR^{10}CO(CH_2)_{0-6}$, or

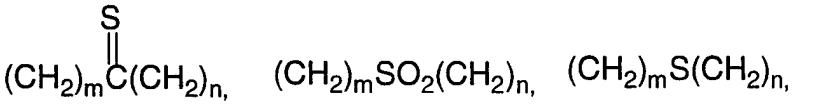


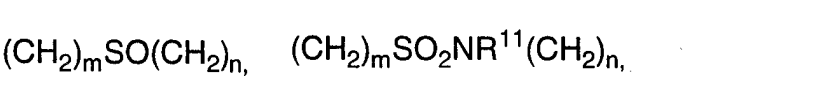
;

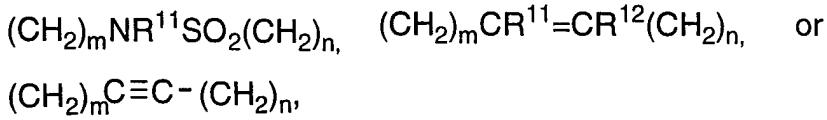
Z and A are each independently selected from

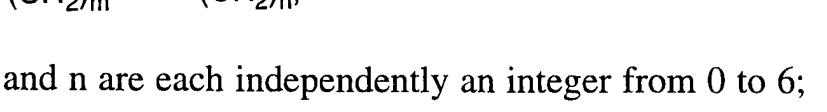






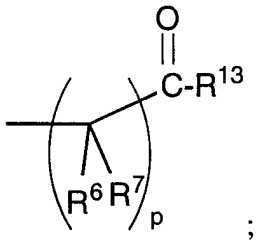






where m and n are each independently an integer from 0 to 6;

B is



;

where p is an integer from 1 to 3;

R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11} and R^{12} are each independently selected from

hydrogen,
halogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
hydroxycarbonyl C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
hydroxycarbonyl C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl or
hydroxy C_{0-6} alkyl;

R^6 is selected from

hydrogen,
fluorine,
C_{1-8} alkyl,
hydroxyl,

hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylcarbonyl,
aryl C_{0-6} alkylcarbonyl,
C_{1-6} alkylcarbonyloxy,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-6} alkylaminocarbonyloxy,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, or
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl;
wherein the alkyl or N atoms may be unsubstituted or substituted with R^5;

R^7 is selected from
hydrogen,
C_{0-6} alkylamino C_{0-6} alkyl,

C_{0-6} dialkylamino C_{0-6} alkyl,
aryl C_{0-6} alkyloxycarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl and
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylsulfonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylcarbonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl or
C_{7-20} polycyclyl C_{0-8} alkyloxycarbonylamino C_{0-6} alkyl;

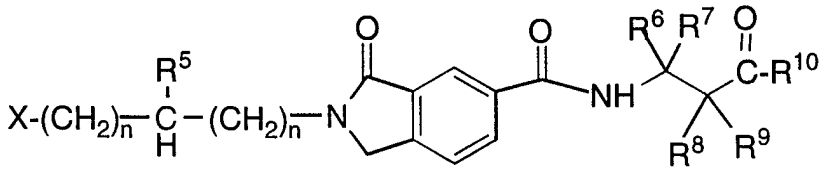
wherein the polycyclyl may be unsubstituted or substituted with R^{14}, R^{15}, R^{16} and R^{17}; and wherein any of the alkyl groups may be unsubstituted or subsituted with R^{14} and R^{15};

R^{13} is selected from
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
C_{1-6} dialkylaminocarbonylmethyloxy,
aryl C_{1-6} dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{14}, R^{15}, R^{16} and R^{17} are each independently selected from
hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, oxo, aryl,
aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl,
C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-

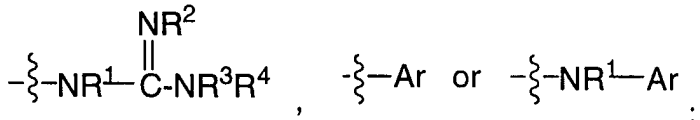
C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy, C_{1-8} alkyl-$S(O)_q$, C_{1-8} alkylaminocarbonyl, C_{1-8} dialkylaminocarbonyl, C_{1-8} alkyloxycarbonylamino, C_{1-8} alkylaminocarbonyloxy or C_{1-8}alkylsulfonylamino;

(b) a compound of the formula I-b:



I-b

wherein X is selected from



;

Ar is a 4- to 10-membered mono- or polycyclic aromatic or non-aromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S and wherein the mono- or polycyclic aromatic or non-aromatic ring system is either unsubstituted or substituted with R^1, R^2, R^3 and R^4;

R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, hydroxyl, C_{1-8} alkyl, halogen, aryl C_{0-8} alkyl, oxo, thio, amino-C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl, C_{1-6} alkylamino C_{0-8} alkyl, C_{1-6} dialkylamino C_{0-8} alkyl, aryl C_{0-6} alkylamino C_{0-6} alkyl, C_{1-4} alkoxyamino C_{0-8} alkyl, hydroxy C_{1-6} alkylamino C_{0-8} alkyl, C_{1-4} alkoxy C_{0-8} alkyl, carboxy C_{0-8} alkyl, C_{1-4} alkoxycarbonyl-C_{0-8} alkyl, carboxy C_{0-8} alkoxy, hydroxy C_{0-8} alkyl or C_{3-8} cycloalkyl C_{0-6} alkyl;

R^5 is selected from hydrogen, C_{1-6} alkyl, C_{0-6} alkylaryl, aryl or

C_{3-8} cycloalkyl C_{0-6} alkyl;

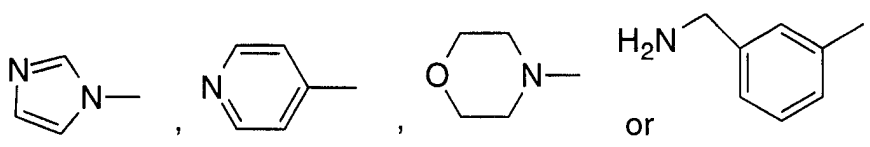
R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, fluorine, C_{1-8} alkyl, hydroxyl, hydroxy C_{1-6} alkyl, carboxy-C_{0-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylaminocarbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, C_{1-8} alkylsulfonylamino-C_{0-6} alkyl, aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl, C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, aryl C_{0-8} alkoxycarbonylamino C_{0-8} alkyl, aryl-C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkylcarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino-C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, C_{0-8} alkylamino-sulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino-C_{0-6} alkyl, C_{1-6} alkylsulfonyl C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl-C_{0-6} alkyl, C_{1-6} alkylcarbonyl C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl-C_{0-6} alkyl, C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkyl-thiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino C_{0-6} akyl, C_{3-8} cycloalkyl-C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonyloxy or C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

R^{10} is selected from hydroxyl, C_{1-8} alkoxy, aryl C_{0-6} alkoxy, C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy, aryl C_{1-8} alkylcarbonyloxy-C_{1-4} alkoxy, C_{1-6} dialkylaminocarbonylmethoxy, aryl C_{1-6} dialkylaminocarbonylmethoxy or an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of the amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

each n is independently an integer from 0 to three;

provided that when R^5 is hydrogen and X is Ar and Ar is a 6-membered monocyclic non-aromatic ring system containing one nitrogen atom and R^6 and R^7 are each hydrogen, and R^8 is selected from hydrogen or C_{1-6} alkyl, and R^{10} is selected from hydroxyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy or an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of the amino acid is as the free acid or is esterified with C_{1-6} alkyl, then R^9 is selected from fluorine, hydroxyl, hydroxy C_{1-6} alkyl, carboxy-C_{0-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylamino-carbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, aryl C_{0-8} alkoxycarbonyl-amino C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkyl-carbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylamino-carbonylamino C_{0-6} alkyl, C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl, C_{1-6} alkylsulfonyl-C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl, C_{1-6} alkylcarbonyl-C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl, C_{1-6} alkylthiocarbonyl-amino C_{0-6} alkyl, aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino-C_{0-6} akyl, C_{3-8} cycloalkyl C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl-C_{0-6} alkylaminocarbonyloxy or C_{3-8} cycloalkyl C_{0-6} alkylamino-carbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

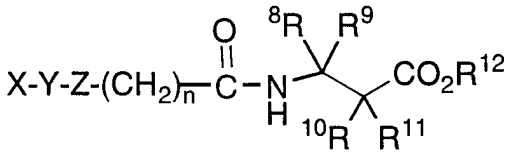
and provided further that when R^5 is hydrogen and X is Ar and Ar is



and R^6, R^7 and R^8 are each hydrogen, and R^{10} is selected from hydroxyl and C_{1-8} alkoxy, then R^9 is selected from fluorine, C_{1-8} alkyl, hydroxyl, hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl,

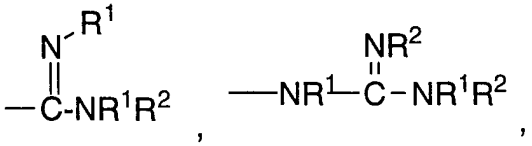
C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylamino-carbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, C_{1-8} alkylsulfonylamino-C_{0-6} alkyl, C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, aryl C_{0-8} alkoxycarbonyl-amino C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkylcarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino-C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, C_{0-8} alkylamino-sulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino-C_{0-6} alkyl, C_{1-6} alkylsulfonyl C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl-C_{0-6} alkyl, C_{1-6} alkylcarbonyl C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl-C_{0-6} alkyl, C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkyl-thiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino C_{0-6} akyl, C_{3-8} cycloalkyl-C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonyloxy orC_{3-8} cycloalkyl C_{0-6} alkylaminocarbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

(c) a compound of the formula I-c:



I-c

wherein
X is selected from

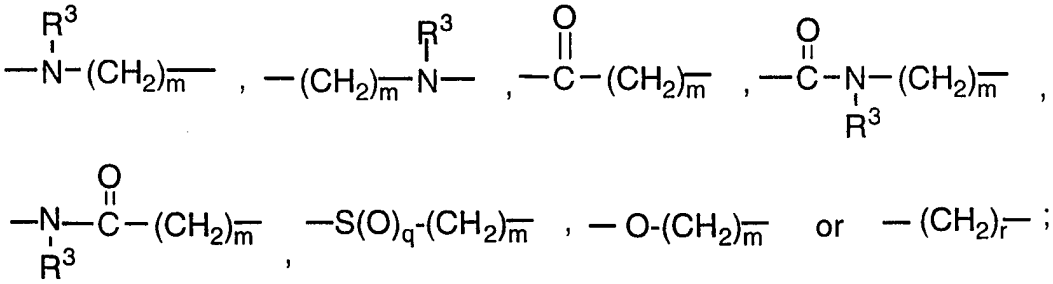


a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from

N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 and R^2;

Y is selected from



Z is

a 5-11 membered aromatic or nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^4, R^5, R^6 and R^7; provided that Z is not a 6-membered monocyclic aromatic ring system; preferably, Z is a 5-11 membered nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^4, R^5, R^6 and R^7;

R^1, R^2, R^4, R^5, R^{13} and R^{14} are each independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl,

aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy, C_{1-8} alkyl-$S(O)_q$, C_{1-8} aminocarbonyl, C_{1-8} dialkylaminocarbonyl, C_{1-8} alkyloxycarbonylamino, C_{1-8} alkylaminocarbonyloxy or C_{1-8} alkylsulfonylamino;

R^3 is selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
hydroxyl,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{3-8} cycloalkyl,
amino C_{1-6} alkyl,
arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino C_{1-6} alkyl,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-8} alkylsulfonyl,
C_{1-8} alkoxycarbonyl,
aryloxycarbonyl,
aryl C_{1-8} alkoxycarbonyl,
C_{1-8} alkylcarbonyl,

arylcarbonyl,
aryl C_{1-6} alkylcarbonyl,
C_{1-8} alkylaminocarbonyl,
aminosulfonyl,
C_{1-8} alkylaminosulfonyl,
arylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonyl,
C_{1-6} alkylsulfonyl,
arylsulfonyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylcarbonyl,
C_{1-6} alkylthiocarbonyl,
arylthiocarbonyl, or
aryl C_{1-6} alkylthiocarbonyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{13} and R^{14};

R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
halogen,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
oxo,
amino,
C_{1-6} alkylamino,
amino C_{1-6} alkyl,

arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylaminocarbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or hydroxycarbonyl C_{1-5} alkyl,
$-(CH_2)_S$ C≡CH,
$-(CH_2)_S$ C≡C-C_{1-6} alkyl,
$-(CH_2)_S$ C≡C-C_{3-7} cycloalkyl,
$-(CH_2)_S$ C≡C-aryl,
$-(CH_2)_S$ C≡C-C_{1-6} alkylaryl,
$-(CH_2)_S$ CH=CH_2,
$-(CH_2)_S$ CH=CH C_{1-6} alkyl,
$-(CH_2)_S$ CH=CH-C_{3-7} cycloalkyl,
$-(CH_2)_S$ CH=CH aryl,
$-(CH_2)_S$ CH=CH C_{1-6} alkylaryl,
$-(CH_2)_S$ SO_2C_{1-6} alkyl,
$-(CH_2)_S$ SO_2C_{1-6} alkylaryl,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,
arylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino,

aryl C_{1-6} alkylamino C_{1-6} alkyl,
arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,
aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
C_{1-6} alkylsulfonyl,

C_{1-6} alkylsulfonyl C_{1-6} alkyl,
arylsulfonyl C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl, or
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{13} and R^{14}; and provided that the carbon atom to which R^8 and R^9 are attached is itself attached to no more than one heteroatom; and provided further that the carbon atom to which R^{10} and R^{11} are attached is itself attached to no more than one heteroatom;

R^{12} is selected from
hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-8} alkyl,
hydroxy,
C_{1-8} alkoxy,
aryloxy,
aryl C_{1-6} alkoxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy,

aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy,
C_{1-8} alkylaminocarbonylmethyleneoxy, or
C_{1-8} dialkylaminocarbonylmethyleneoxy;

m is an integer from 0 to 3;
n is an integer from 1 to 3;
p is an integer from 1 to 4;
q is an integer from 0 to 2;
r is an integer from 0 to 6; and
s is an integer from 0 to 3;

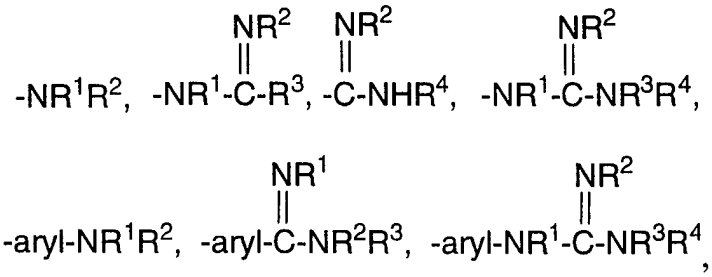
(d) a compound of the formula I-d:

X-Y-Z-Ring-A-B
I-d

wherein:

Ring is a 4- to 10-membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, and either unsubstituted or substituted with R^{27} and R^{28};

X is selected from

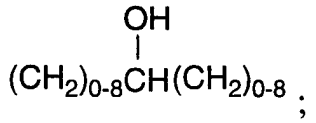


or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted

with R^{13}, R^{14}, R^{15} or R^{16};

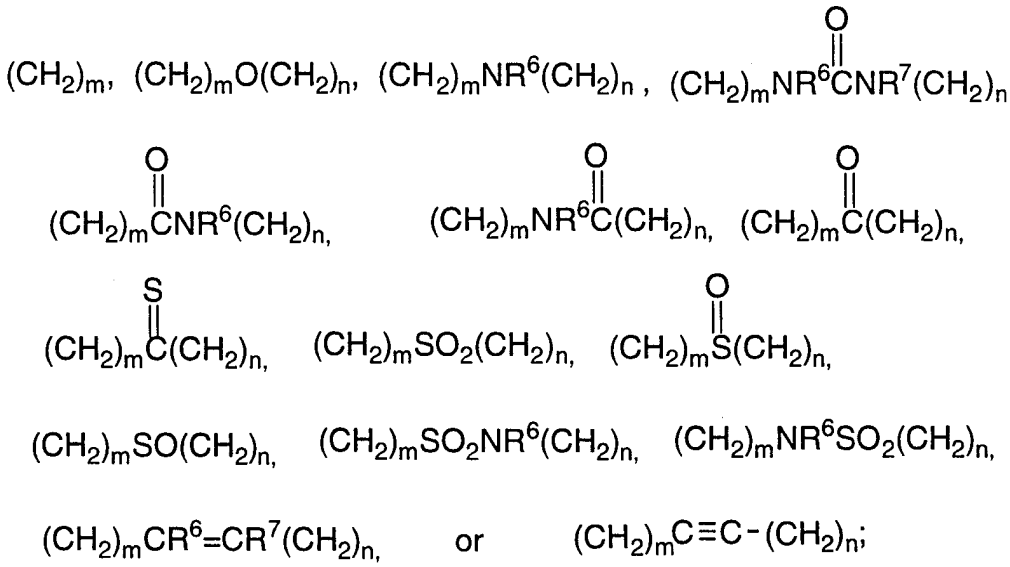
Y is selected from

C_{0-8} alkylene,
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-CONR^5-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-S(O)$_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NR^5-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-NR^5-CO-$(CH_2)_{0-6}$, or



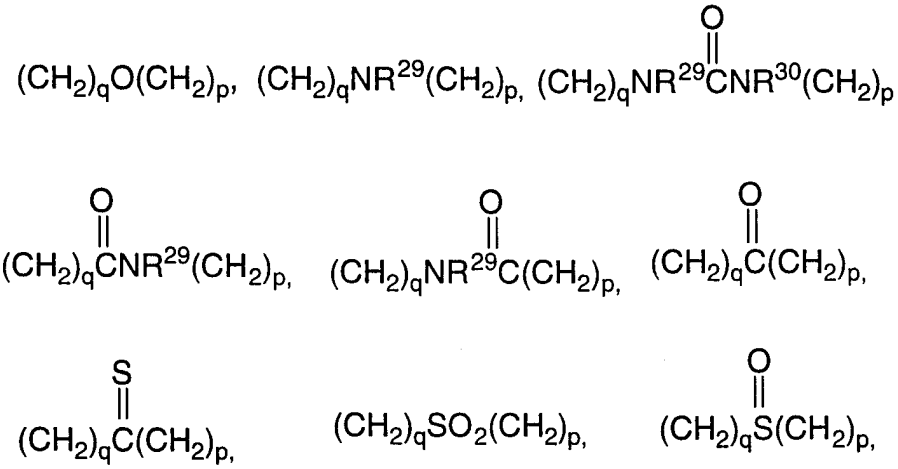
;

Z is selected from



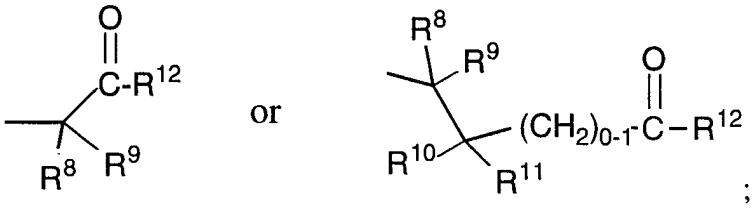
where m and n are each independently an integer from 0 to 6;

A is selected from



where p and q are each independently an integer from 0 to 6;

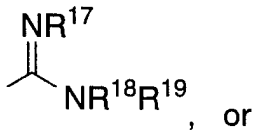
B is selected from



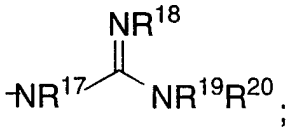
;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29} and R^{30} are each independently selected from

hydrogen,
halogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,



, or



;

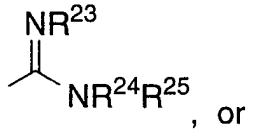
R^8, R^9, R^{10}, and R^{11} are each independently selected from

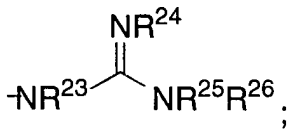
hydrogen,
fluorine,
C_{1-8} alkyl,
hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylcarbonyl,
aryl C_{0-6} alkylcarbonyl,
C_{1-6} alkylcarbonyloxy,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-6} alkylaminocarbonyloxy,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, or
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl
wherein the alkyl or N atoms may be unsubstituted or substituted with one or more substituents selected from R^{21} and

R^{22} (e.g., any amino group such as -NH- can be substituted with R^{21} to be -NR^{21}-);

R^{12} is selected from
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{0-8} alkylcarbonyloxy C_{1-4} alkyloxy,
C_{1-6} dialkylaminocarbonylmethyloxy,
aryl C_{1-6} dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

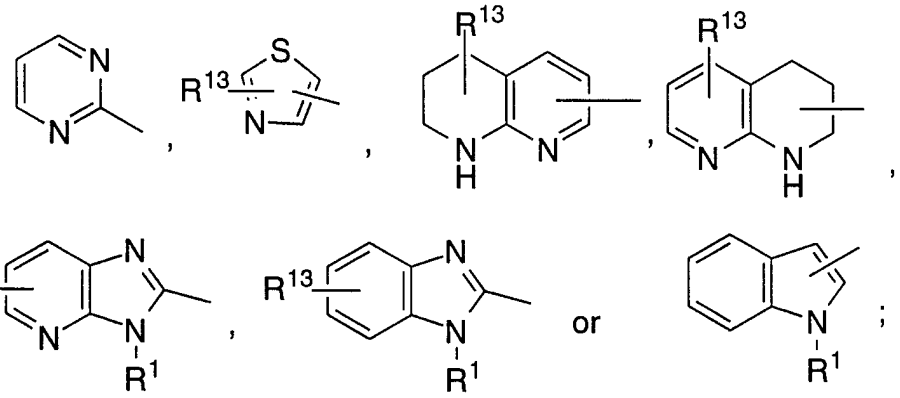
R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from
hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,


, or

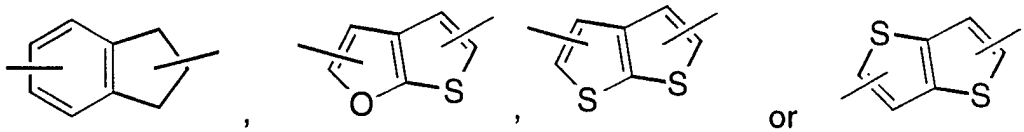

;

provided that Ring is not a 6-membered monocyclic aromatic ring;

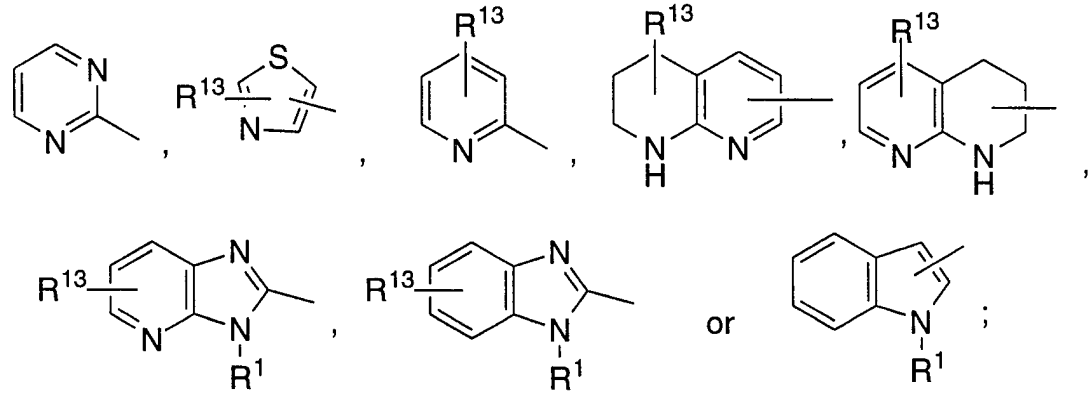
provided further that when Ring is thiophene, then X is selected from


;

provided further that when Ring is selected from isoxazole, isoxazoline, imidazole, imidazoline, benzofuran, benzothiophene, benzimidazole, indole, benzothiazole, benzoxazole,


;

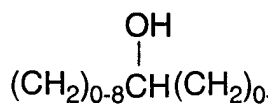
then X is selected from



and the pharmaceutically acceptable salts thereof.

In one embodiment of the invention is the compound wherein Y is selected from

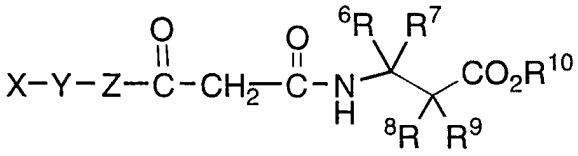
C_{0-8} alkylene,
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-CONR^5-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-S(O)$_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NH-$(CH_2)_{0-6}$, or



;

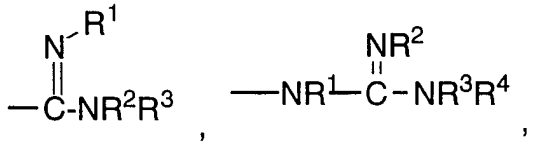
Z is $(CH_2)_m$ where m is an integer from 0 to 3; preferably, m is zero; and all other variables are as defined above;

(e) a compound of the formula I-e:



I-e

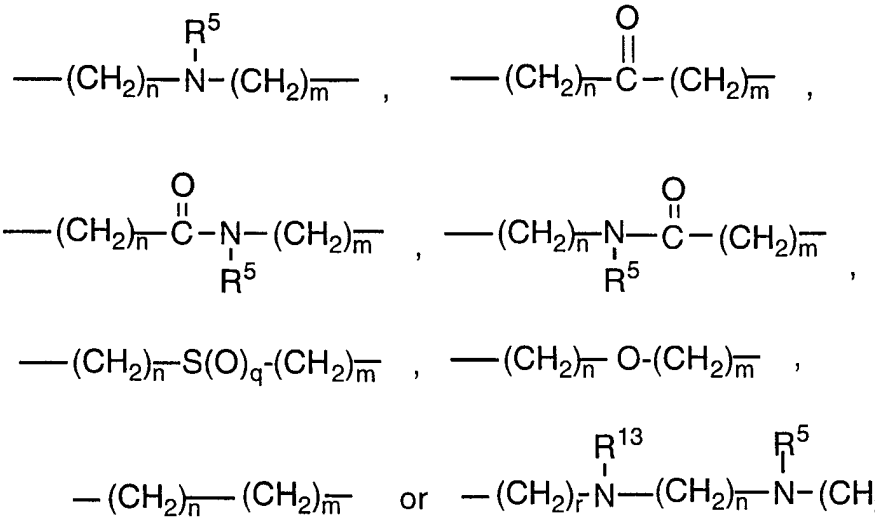
wherein X is selected from



a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2;

Y is selected from



Z is absent or is a 4- to 11-membered aromatic or nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^{14}, R^{15}, R^{16} and R^{17}; preferably, Z is not a 6-membered monocyclic aromatic ring system;

R^1, R^2, R^3, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{16} and R^{17} are each independently selected from
hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy or hydroxy C_{1-6} alkyl;

R^6, R^7, R^8, R^9, R^{14} and R^{15} are each independently selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
oxo,
amino,
C_{1-6} alkylamino,

amino C_{1-6} alkyl,
arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylaminocarbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or hydroxycarbonyl C_{1-5} alkyl,
$-(CH_2)_r C{\equiv}CH$,
$-(CH_2)_r C{\equiv}C\text{-}C_{1-6}$ alkyl,
$-(CH_2)_r C{\equiv}C\text{-}C_{3-7}$ cycloalkyl,
$-(CH_2)_r C{\equiv}C$-aryl,
$-(CH_2)_r C{\equiv}C\text{-}C_{1-6}$ alkylaryl,
$-(CH_2)_r CH{=}CH_2$,
$-(CH_2)_r CH{=}CH\ C_{1-6}$ alkyl,
$-(CH_2)_r CH{=}CH\text{-}C_{3-7}$ cycloalkyl,
$-(CH_2)_r CH{=}CH$ aryl,
$-(CH_2)_r CH{=}CH\ C_{1-6}$ alkylaryl,
$-(CH_2)_r SO_2C_{1-6}$ alkyl,
$-(CH_2)_r SO_2C_{1-6}$ alkylaryl,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,
arylamino C_{1-6} alkyl,

aryl C_{1-6} alkylamino,
aryl C_{1-6} alkylamino C_{1-6} alkyl,
arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,
aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,

C_{1-6} alkylsulfonyl,
C_{1-6} alkylsulfonyl C_{1-6} alkyl,
arylsulfonyl C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl, or
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{11} and R^{12}; and provided that the carbon atom to which R^6 and R^7 are attached is itself attached to no more than one heteroatom; and provided further that the carbon atom to which R^8 and R^9 are attached is itself attached to no more than one heteroatom;

R^{10} is selected from
hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-8} alkyl,
aryl C_{1-6} alkoxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyl,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyl,
C_{1-8} alkylaminocarbonylmethylene, or

C_{1-8} dialkylaminocarbonylmethylene;

m, n and r are each independently an integer from 0 to 3;
p is an integer from 1 to 4; and
q is an integer from 0 to 2;

or a pharmaceutically acceptable salt thereof.

Specific examples of compounds that are integrin antagonists include the following:

4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-benzyloxycarbonylamino-β-alanine,

4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-phenylsulfonylamino-β-alanine,

2(S)-Phenylsulfonylamino-3-[4-(4-guanidobutyloxy)phenyl]-propionic acid,

2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-propionic acid,

4-(3-Guanidinopropyloxy)benzoyl-2-(S)-phenylsulfonylamino-β-alanine,

4-(3-Formamidinopropyloxy)benzoyl-2-(S)-phenylsulfonylamino-β-alanine,

3-Methoxy-4-(3-guanidinopropyloxy)benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

3-Methoxy-4-(3-aminopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

3-(3-Guanidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid,

4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxybenzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate,

2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy)phenyl]-propionic acid,

2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-butyloxy)phenyl]propionic acid,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenylsulfonylamino-β-alanine,

4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino-β-alanine t-butyl ester,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine methyl ester,

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(1H-Imidazo[4,5-6]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine t-butyl ester,

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,

4-[2-(1,8-Naphthyidin-7-yl)ethenyl)benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butylester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β-alanine,

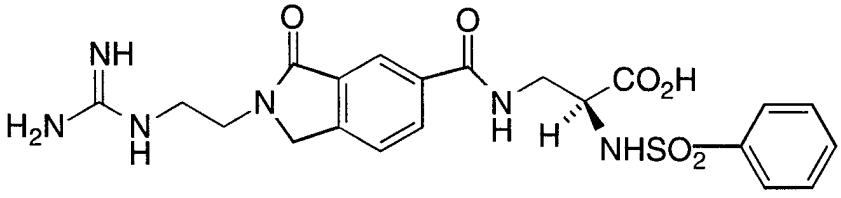
4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-β-alanine ethyl ester,

4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate,

4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate,

4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester, and

4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine.



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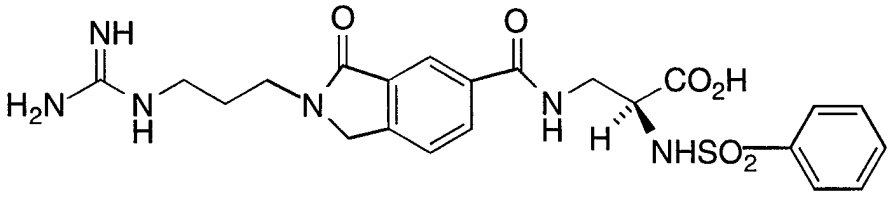

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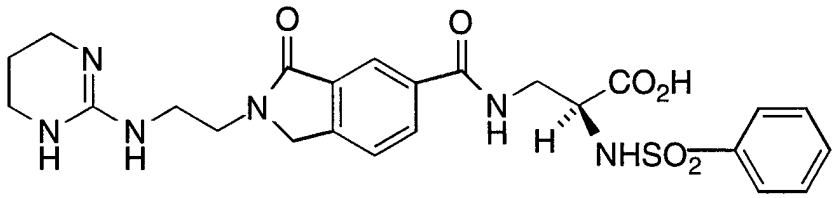

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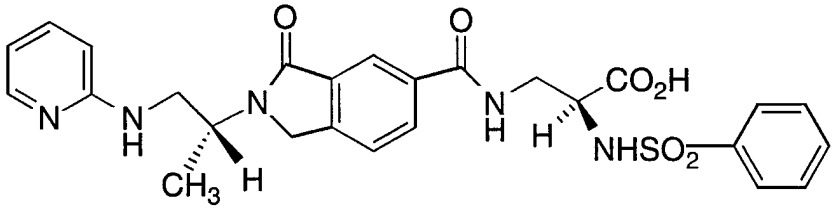

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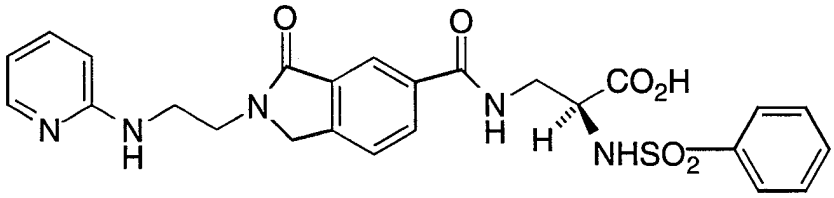

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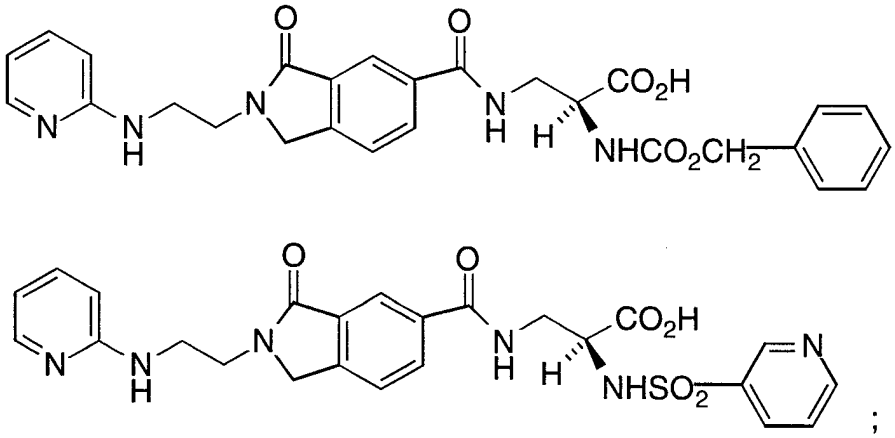


2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]piperidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]piperin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine trifluoroacetate;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine ethyl ester;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]-pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine ethyl ester;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]-pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]-tetrahydropyrimidin-l-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl}ethyl]-tetrahydropyrimidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]imidazolidin-l-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl}ethyl]-imidazolidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]pyrrolidin-l-yl)acetyl-3(R)-(2-ethylindol-3-yl)-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]pyrrolidin-l-yl)acetyl-3(R)-(2-ethylindol-3-yl)-β-alanine;

Ethyl 3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-pyridin-3-yl-propionic acid;

3-(S)-(2-{2-Oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]pyrrolidin-1-yl}-acetylamino)-3-(S)-pyridin-3-yl-propionic acid;

3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-quinolin-3-yl-propionic acid;

3-{2-[6-Oxo-1-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-hexahydro-(3aS, 6aS)pyrrolo[3,4-b]pyrrol-5-yl]-acetylamino}-3-(S)-pyridin-3-yl-propionic acid;

3-{2-[6-Oxo-1-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-hexahydro-(3aR, 6aR)pyrrolo[3,4-b]pyrrol-5-yl]-acetylamino}-3-(S)-pyridin-3-yl-propionic acid;

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine ethyl ester;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine;

6-[(1,4,5,6-Tetrahydropyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

Ethyl 3(S)-pyridin-3-yl-3-{2-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)propylcarbamoyl]acetylamino}propionate;

3(S)-pyridin-3-yl-3-{2-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)propylcarbamoyl]acetylamino}propionic acid;

3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester; or

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;
or the pharmaceutically acceptable salts and optical isomers thereof.

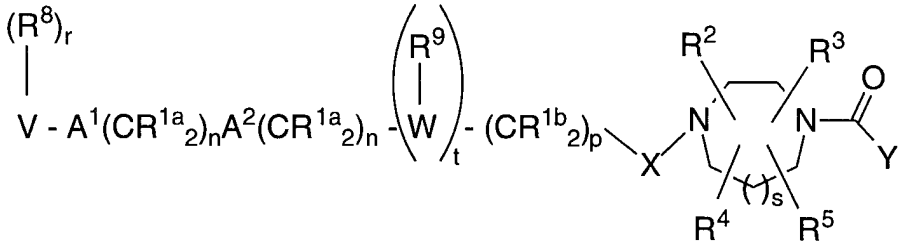
Compounds which are described as antagonists of the αvβ3 receptor and may therefore be useful in the present invention, and methods of synthesis thereof, can be found in the following pending applications and publications, which are herein incorporated by reference:

PCT Patent Pub. Nos. WO96/00574; WO 96/00730; WO 96/26190; WO 96/37492; EPO Patent Publication Nos. EP 0,578,083; EP 0,711,770; EP 0,727,425; EP 0,546,548.

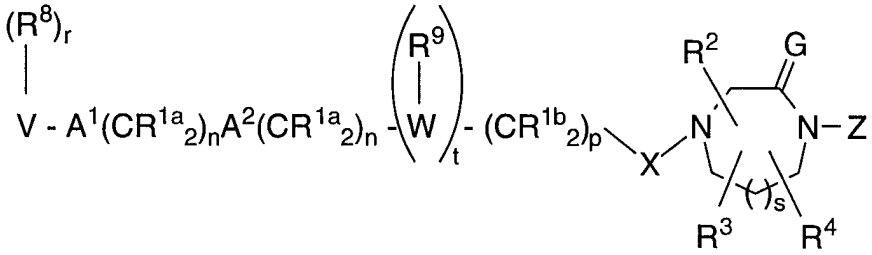
Compounds which are antagonists of the $\alpha v\beta 3$ receptor and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following pending publications, which is herein incorporated by reference:
PCT Patent Pub. Nos. WO95/32710.

Examples of farnesyl protein transferase inhibiting compounds and in particular selective farnesyl protein transferase inhibiting compounds include the following:

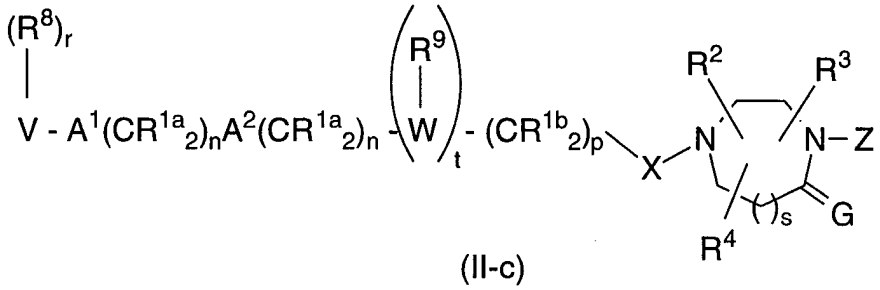
(a) a compound represented by formula (II-a) through (II-c):



(II-a)

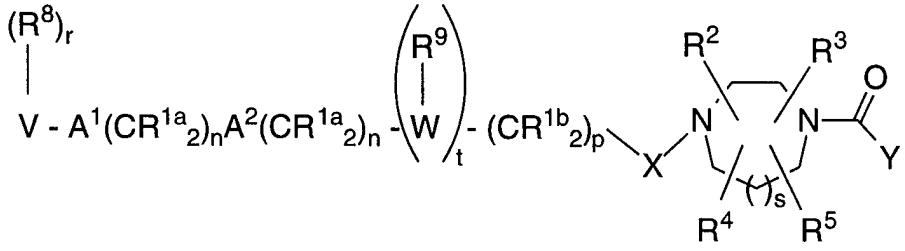


(II-b)



(II-c)

wherein with respect to formula (II-a):



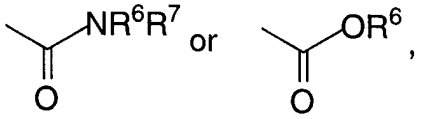
(II-a)

or a pharmaceutically acceptable salt thereof,

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

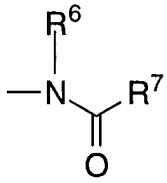
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



wherein the substituted group is substituted with one or more of:
1) aryl or heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkyl,
b) $(CH_2)_pOR^6$,
c) $(CH_2)_pNR^6R^7$,
d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^6, $S(O)R^6$, SO_2R^6,

5)  ,

6)  ,

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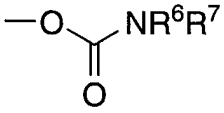
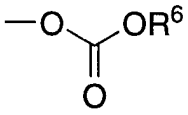
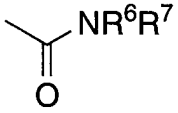
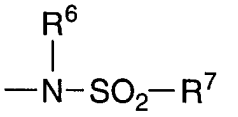
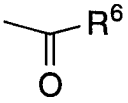
8)  ,

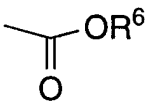
9)  ,

10)  ,

11)  ,

12)  ,

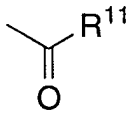
13)  , or

14)  ; or

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

R^4 and R^5 are independently selected from H and CH_3; and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

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

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

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

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

R^8 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, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-C(NH)-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

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

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

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

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

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;

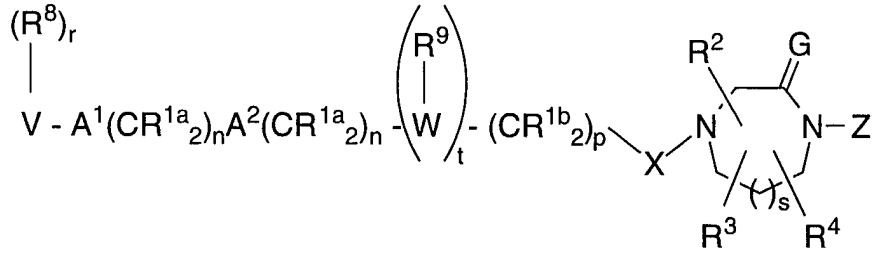
X is $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

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

with respect to formula (II-b):



(II-b)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, R^{7a}, u, R^8, A^1, A^2, V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

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

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

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

G is H_2 or O;

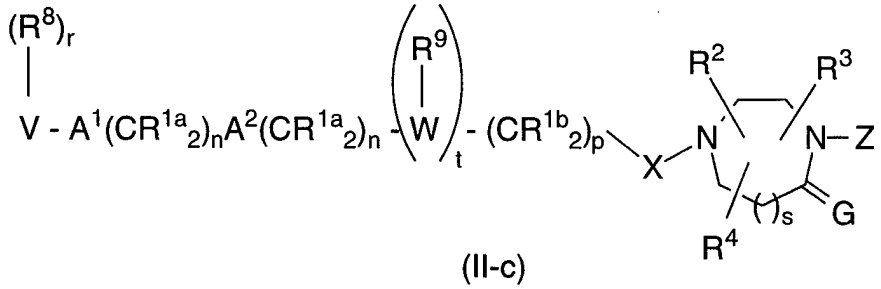
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$,

2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

with respect to formula (II-c):



(II-c)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, u, R^{7a}, R^8, A^1, A^2, V, W, X, n, r and t are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

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

G is O;

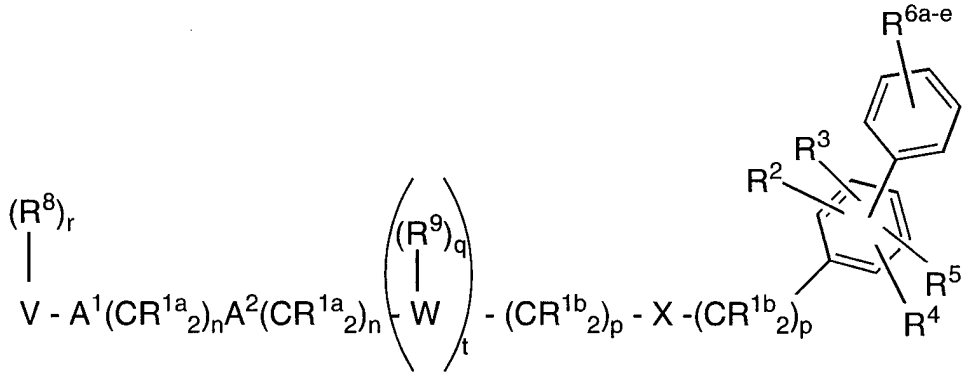
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

and

s is 1;

(b) a compound represented by formula (II-d):



II-d

wherein:

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

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^2, R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-,

$R^{10}{}_2N$-C(NR^{10})-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-C(NR^{10})-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

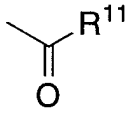
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-C(NR^{10})-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-C(NR^{10})-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

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

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$,
g) $N(R^{10})_2$ or
h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-,

$(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

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

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$- or $S(O)_m$;

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,

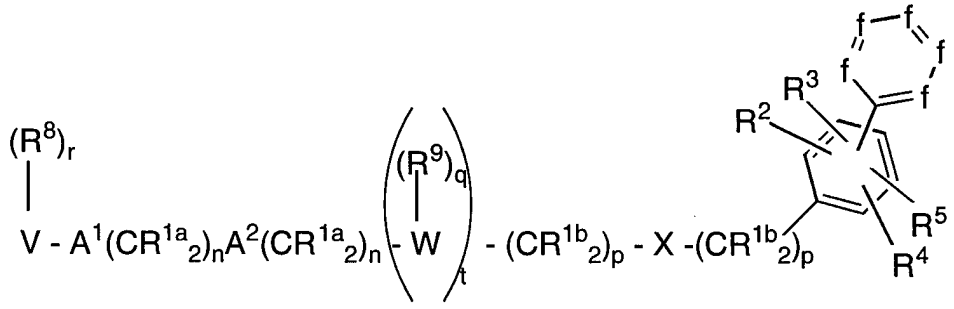
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^{7}C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{7}C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

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

(c) a compound represented by formula (II-e):



II-e

wherein:

R^{1a}, R^{1b}, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-3 of f(s) are independently N, and the remaining f's are independently CR^6; and

each R^6 is independently selected from:

a) hydrogen,

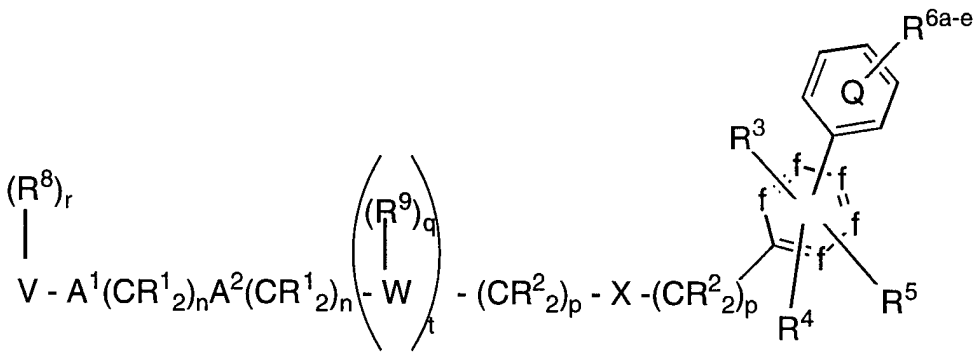
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

(d) a compound represented by formula (II-f):



II-f

wherein:

R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-2 of f(s) are independently N, and the remaining f's are independently CH; and

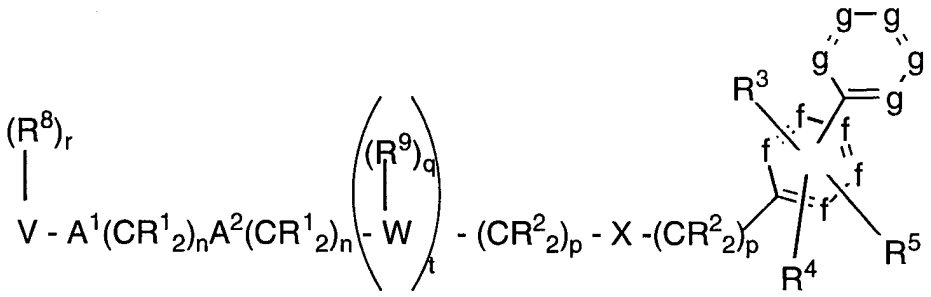
R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

(f) a compound represented by formula (II-g):



II-g

wherein:

R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-2 of f(s) are independently N, and the remaining f's are independently CH;

from 1-3 of g(s) are independently N, and the remaining g's are independently CR^6;

R^1 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, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; and

each R^6 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

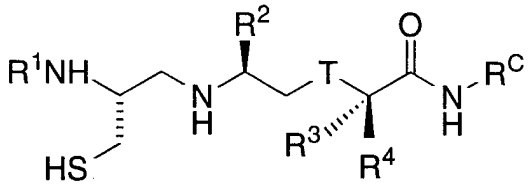
c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or

substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

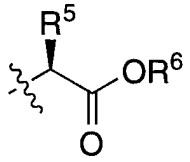
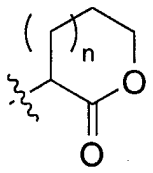
any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

(g) a compound represented by formula (II-h):



II-h

wherein
R^C is selected from:


and

;

R^1 is hydrogen, an alkyl group, an aralkyl group, an acyl group, an aracyl group, an aroyl group, an alkylsulfonyl group, aralkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

R^2 and R^3 are
the side chains of naturally occurring amino acids, including their oxidized forms which may be methionine sulfoxide or methionine

sulfone, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substitutents may be substituted with an aromatic or heteroaromatic ring;

R^4 is hydrogen or an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

R^5 is selected from:

a) a side chain of naturally occurring amino acids,

b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,

c) substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl, or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituent is optionally substituted with an aromatic or heteroaromatic ring, and

d) $-CH_2CH_2OH$ or $-CH_2CH_2CH_2OH$;

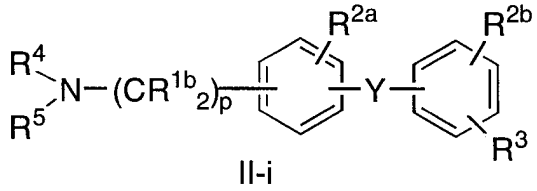
R^6 is a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;

T is O or $S(O)_m$;

m is 0, 1 or 2;

n is 0, 1 or 2;

(h) a compound represented by formula (II-i):



II-i

wherein:

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

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_6 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 unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_6 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^{2a}, R^{2b} and R^3 are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

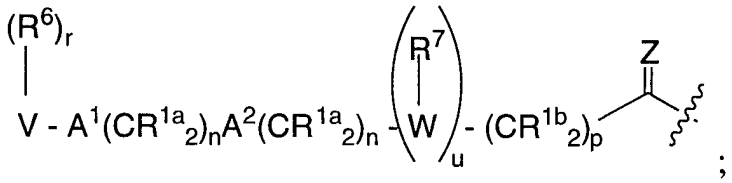
c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, halogen or $R^9OC(O)NR^8$-, and

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

R^4 and R^5 are independently selected from:

a) hydrogen, and

b)



;

R^6 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 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 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 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, C_1-C_6 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 C_1-C_6 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, substituted or unsubstituted C_1-C_6 aralkyl and substituted or unsubstituted aryl;

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

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 aralkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, $-NR^8C(O)$-, O, $-N(R^8)$-, $-S(O)_2N(R^8)$-, $-N(R^8)S(O)_2$-, or $S(O)_m$;

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 $S(O)_m$;

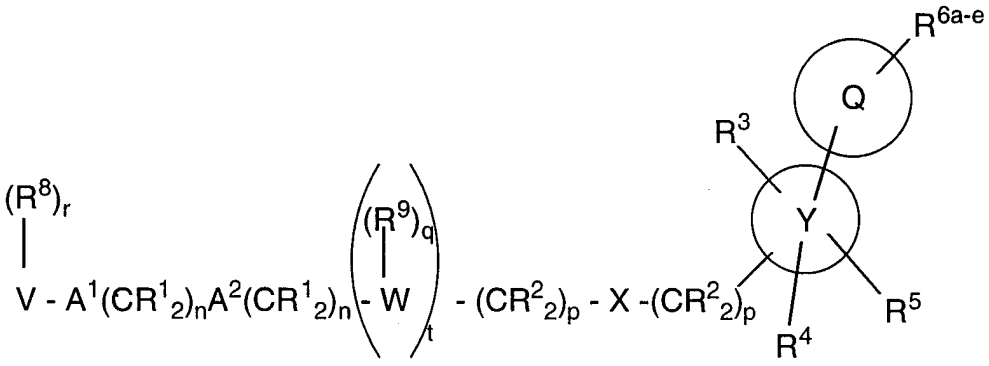
W is a heterocycle;

Y is selected from: a bond, -C(R10)=C(R10)-, -C≡C-, -C(O)-, -C(R10)-2-, -C(OR10)R10-, -CN(R10)2R10-, -OC(R10)2-, -NR10C(R10)2-, -C(R10)2O-, -C(R10)2NR10-, -C(O)NR10-, -NR10C(O)-, O, -NC(O)R10-, -NC(O)OR10-, -S(O)2N(R10)-, -N(R10)S(O)2-, or S(O)m;

Z is H2 or O;

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

(e) a compound represented by formula (II-m):



II-m

wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR13)- or sulfonyl moiety adjacent to the nitrogen atom attached to Y;

Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R^1 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, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

$R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

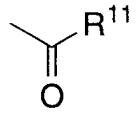
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

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

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

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

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

R^{13} is selected from hydrogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkylsulfonyl and C_1-C_6 acyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

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 heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

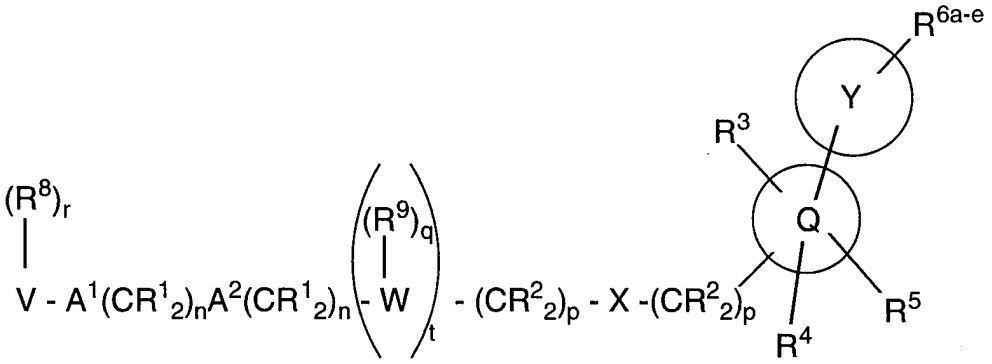
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^{7}C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{7}C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

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

(f) a compound represented by formula (II-n):



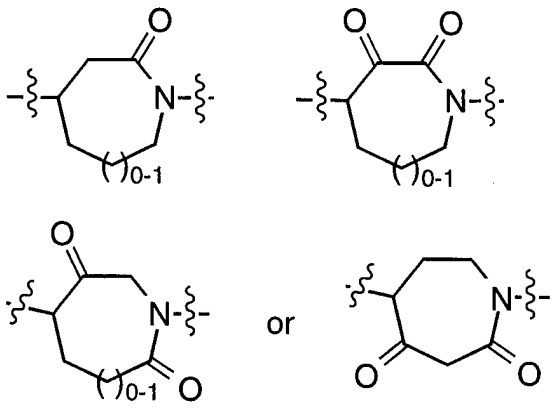
II-n

wherein:

R^1, R^2, R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-m);

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or

sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

or a pharmaceutically acceptable salt or disulfide thereof.

Examples of compounds which selectively inhibit farnesyl protein transferase include the following:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[*N*-ethyl-2-acetamido]-2-piperazinone;

(±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one;

4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)piperazin-2-one;

5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one;

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one;

4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)-piperazin-2-one;

4-[5-(4-Cyanobenzyl)-1-imidazolylethyl]-1-(3-chlorophenyl)piperazin-2-one;

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methy1-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto)propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]pentyloxypentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5-pentyloxy-4-methylpentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-methylpentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercaptolpropylamino-3(S)-methyllpentyloxy-3-methylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester (Compound 5),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound 6),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyt-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyI-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyllpentyloxy-3-methybutanoyl-methionine methyl ester.

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methybutanoyl-methionine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyI-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester

1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-methylimidazole

1-(4-Biphenylmethyl)-5-(4-cyanophenyloxy)-imidazole

5-(4-Cyanophenyloxy)-1-(2'-methyl-4-biphenylmethyl)-imidazole

5-(4-Biphenyloxy)-1-(4-cyanobenzyl)-imidazole

5-(2'-Methyl-4-biphenoxy)-1-(4-cyanobenzyl)-imidazole

5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl) methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl) methylimidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-methoxy-1-(4-cyanophenyl)-methylimidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)-imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl-imidazole

5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

1-(4-Biphenylmethyl)-5-(4-bromophenyloxy)-imidazole

1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl}-5-(pyrid-2-yl)-2-amino-pyrimidine
N,N-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene

N-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-[1-(4-Cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

4-{3-[4-(-2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-3-Methyl-2-oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-(-2-Oxo-piperidin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

(4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

Compounds which are described as inhibitors of farnesyl-protein transferase and may therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

WO 95/32987 published on 7 December 1995;
U. S. Pat. No. 5,420,245;
European Pat. Publ. 0 618 221 ;
European Pat. Publ. 0 675 112 ;
WO 95/08542 ;
WO 95/11917;
WO 95/12612;
WO 95/12572;

WO 95/10514;
WO 95/10515;
WO 95/10516;
WO 95/24612;
WO 95/34535;
WO 96/22278;
WO 96/24611;
WO 96/24612;
WO 96/05168;
WO 96/05169;
WO 96/00736 and U.S. Pat. No. 5,571,792 granted on November 5, 1996;
WO 96/17861;
WO 96/33159;
WO 96/34850;
WO 96/34851;
WO 96/30017;
WO 96/30018;
WO 96/30362;
WO 96/30363;
WO 96/31111;
WO 96/31477;
WO 96/31478;
WO 96/31501; and
U. S. Pat. No. 5,532,359 granted on July 2, 1996.

Compounds which are inhibitors of farnesyl-protein transferase and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

U. S. Pat. No. 5,238,922 granted on August 24, 1993;

U. S. Pat. No. 5,340,828 granted on August 23, 1994;

U. S. Pat. No. 5,480,893 granted on January 2, 1996;

U. S. Pat. No. 5,352,705 granted on October 4, 1994;

U. S. Pat. No. 5,504,115 granted on April 2, 1996;

U. S. Pat. No. 5,536,750 granted on July 16, 1996;

U. S. Pat. No. 5,504,212 granted on April 2, 1996;

U. S. Pat. No. 5,439,918 granted on August 8, 1995;

WO 94/10138 (May 11, 1994); USSN 08/968,025 filed on October 29, 1992 and USSN 08/143,943 filed on October 27, 1993 ;

WO 95/00497 (January 5, 1995); USSN 08/080,028 filed on June 18, 1993 and USSN 08/237,586 filed on May 11, 1994 ;

U. S. Pat. No. 5,576,293 granted on November 19, 1996

U. S. Pat. No. 5,468,733 granted on November 21, 1995

WO 96/06609 (March 3, 1996) and USSN 08/298,478 filed on August 24, 1994 ;

U. S. Pat. No. 5,585,359 granted on December 17, 1996

U. S. Pat. No. 5,523,456 granted on June 4, 1996;

WO 96/10035 (April 4, 1996); USSN 08/315,161 filed on September 29, 1994; USSN 08/399,282 filed on March 6, 1995; USSN 472,077 filed on June 6, 1995 and USSN 08/527,972 filed on September 14, 1995

U. S. Pat. No. 5,571,835 granted on November 5, 1996;

U. S. Pat. No. 5,491,164 granted on February 13, 1996;

WO 96/10034 (April 4, 1996); USSN 08/314,974 filed on September 29, 1994; USSN 08/526,244 filed on September 21, 1995

WO 96/30014 (October 3, 1996); USSN 08/412,621 filed on March 29, 1995 and USSN 08/448,865 filed on May 24, 1995 ;

U. S. Pat. No. 5,578,629 granted on November 26, 1996;

WO 96/34010 (October 31, 1996); USSN 08/412,828 filed on March 29, 1995; USSN 08/600,794 filed on February 13, 1996

WO 96/30343 (October 3, 1996); USSN 08/412,829 filed on March 29, 1995; and USSN 08/470,690 filed on June 6, 1995; and USSN 08/600,728 filed on February 28, 1996;

WO 96/31525 (October 10, 1996); USSN 08/412,626 filed on March 29, 1995; USSN 08/600,792 filed on February 13, 1996;

U. S. Pat. No. 5,534,537 granted on July 9, 1996;

WO 96/37204 (November 28, 1996); USSN 08/449,038 filed on May 24, 1995; USSN 08/648,330 filed on May 15, 1996;

WO 96/39137 (December 12, 1996); USSN 08/468,160 filed on June 6, 1995; USSN 08/652,055 filed on May 23, 1996;

USSN 08/729,265 filed on October 10, 1996;

USSN 08/749,254 filed on November 15, 1996;

USSN 60/010,798 filed on January 30, 1996; USSN 08/ , filed on January 21, 1997;

USSN 60/010,799 filed on January 30, 1996; USSN 08/ , filed on January 21, 1997;

USSN 60/010,860 filed on January 30, 1996; USSN 08/ , filed on January 21, 1997;

USSN 60/011,081 filed on January 30, 1996; USSN 08/ , filed on January 21, 1997;

USSN 60/010,798 filed on January 30, 1996; USSN 08/ , filed on January 21, 1997;

USSN 60/014,587 filed on April 3, 1996;

USSN 60/014,589 filed on April 3, 1996;

USSN 60/014,592 filed on April 3, 1996;

USSN 60/014,593 filed on April 3, 1996;

USSN 60/014,594 filed on April 3, 1996;

USSN 60/014,668 filed on April 3, 1996;

USSN 60/014,775 filed on April 3, 1996;

USSN 60/014,776 filed on April 3, 1996;

USSN 60/014,777 filed on April 3, 1996;

USSN 60/014,791 filed on April 3, 1996;

USSN 60/014,792 filed on April 3, 1996;

USSN 60/014,793 filed on April 3, 1996;

USSN 60/014,794 filed on April 3, 1996;

USSN 60/014,798 filed on April 3, 1996;

USSN 60/014,774 filed on April 3, 1996;

USSN 60/022,332 filed on July 24, 1996;

USSN 60/022,340 filed on July 24, 1996;

USSN 60/022,341 filed on July 24, 1996;

USSN 60/022,342 filed on July 24, 1996;

USSN 60/022,558 filed on July 24, 1996;

USSN 60/022,582 filed on July 24, 1996;

USSN 60/022,586 filed on July 24, 1996;

USSN 60/022,587 filed on July 24, 1996;

USSN 60/022,647 filed on July 24, 1996;

USSN 60/032,126 filed on December 5, 1996;

USSN 60/032,428 filed on December 5, 1996;

USSN 60/032,578 filed on December 5, 1996;

USSN 60/032,579 filed on December 5, 1996;

USSN 60/ 033,990, filed on December 30, 1996; and

USSN 60/033,991, filed on December 30, 1996;

All patents, publications and pending patent applications identified are hereby incorporated by reference.

With respect to the compounds of formulas I-a through I-e the following definitions apply:

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "alkenyl" shall mean straight or branched chain alkenes of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes of two to ten total carbon atoms, or any number within this range.

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-5} alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

The term "aryl," as used herein, refers to a mono- or polycyclic system composed of 5- and 6-membered aromatic rings containing 0, 1, 2, 3 or 4 heteroatoms chosen from N, O or S and either unsubstituted or substituted with one or more groups selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-5} alkoxycarbonyl,

C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, cyano, trifluoromethyl or C_{1-5} alkylcarbonyloxy. Examples of aryl include, but are not limited to, phenyl, naphthyl, pyridyl, pyrimidinyl, imidazolyl, benzimidazolyl, indolyl, thienyl, oxazolyl, isoxazolyl and thiazolyl, which are either unsubstituted or substituted with one or more groups selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-5} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, cyano, trifluoromethyl or C_{1-5} alkylcarbonyloxy. Preferably, the aryl group is unsubstituted, mono-, di-, tri- or tetra-substituted with one to four of the above-named substituents; more preferably, the aryl group is unsubstituted, mono-, di- or tri-substituted with one to three of the above-named substituents; most preferably, the aryl group is unsubstituted, mono- or di-substituted with one to two of the above-named substituents.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C_{0-8} alkyl) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{0-m} or C_{1-m} designation where m may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl

include, but are not limited to, toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine and butylpyridine.

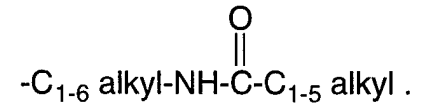
When substituent Y, B, R^1 to R^{28} includes the definition C_0 (e.g., aryl C_{0-8} alkyl), the group modified by C_0 is not present in the substituent. Similarly, when any of the variables m, q, r or s is zero, then the group modified by the variable is not present; for example, when s is zero, the group "-$(CH_2)_S$ C≡CH" is "-C≡CH".

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" shall mean =O.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

Under standard nonmenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to



With respect to the compounds of formulas II-a through II-n the following definitions apply:

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

Heteroalkyl refers to an alkyl group having from 2-15 carbon atoms, and interrupted by from 1-4 heteroatoms selected from O, S and N.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include vinyl, allyl, iso-propenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl.

Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups. With regard to the farnesyl transferase inhibitors, "aryl" is intended to include any stable monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine, pyrazine and triazine. Examples of partially aromatic groups are tetrahydro-imidazo[4,5-c]pyridine, phthalidyl and saccharinyl, as defined below.

With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl,

benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydro-benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolinyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

With regard to the farnesyl transferase inhibitors, 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.

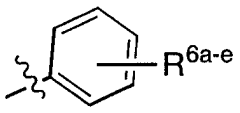
In the present method, amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Asparagine or Aspartic acid	Asx	B
Cysteine	Cys	C
Glutamine	Gln	Q

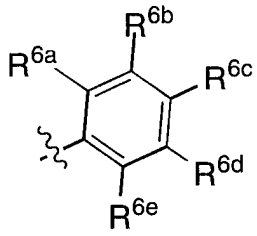
Glutamic acid	Glu	E
Glutamine or Glutamic acid	Glx	Z
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

The compounds used in the present method 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. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration

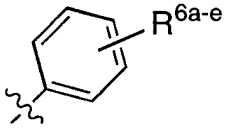
With respect to the farnesyl-protein transferase inhibitors of the formulas II-d and II-f,the substituent illustrated by the structure



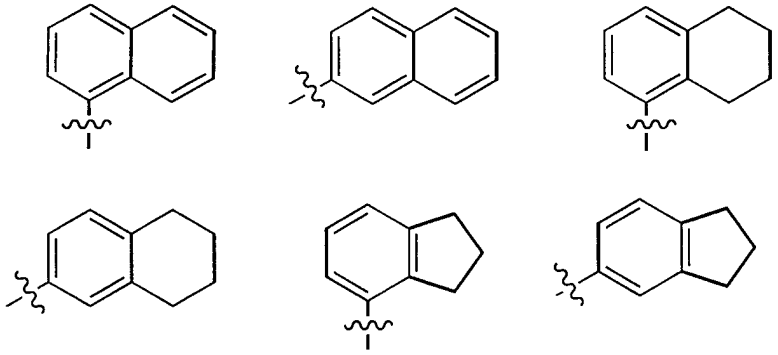
is a simplified representation of a phenyl ring having five (5) substituents (hydrogens and/or non-hydrogens) and may also be represented by the structure



With respect to the farnesyl-protein transferase inhibitors of the formulas II-d and II-f, the moiety described as



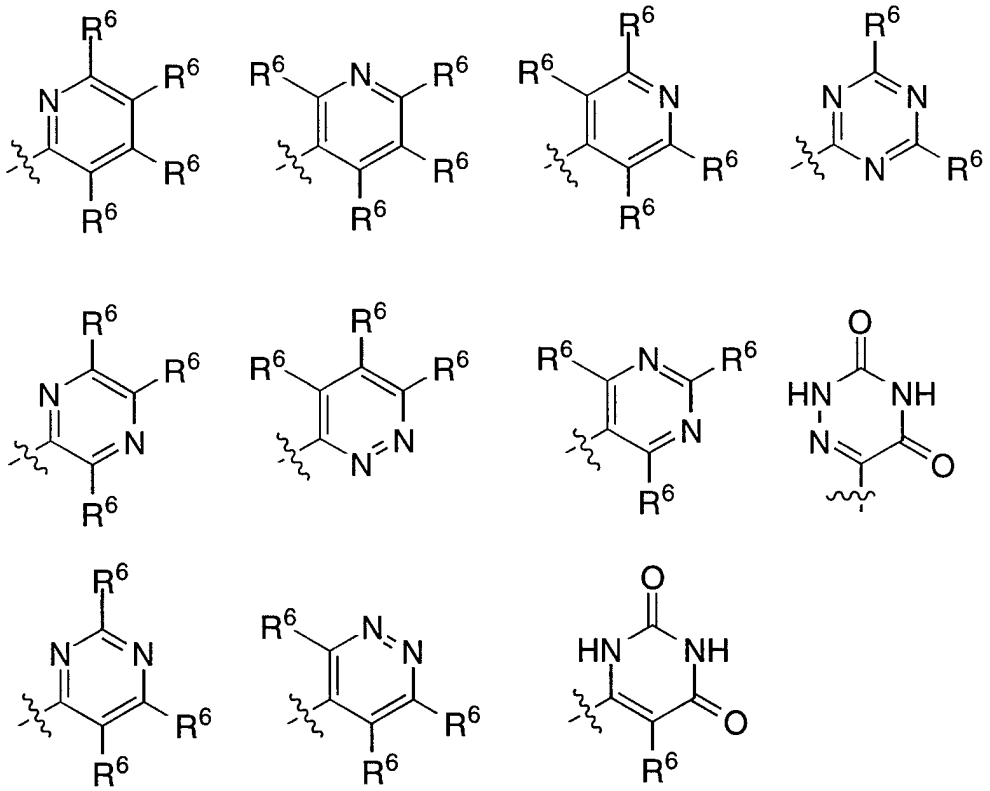
where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, $-(CH_2)_4-$ and $-(CH_2)_4-$ includes the following structures:



It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors of the formulas II-e and II-g, the moieties designated by the following structures

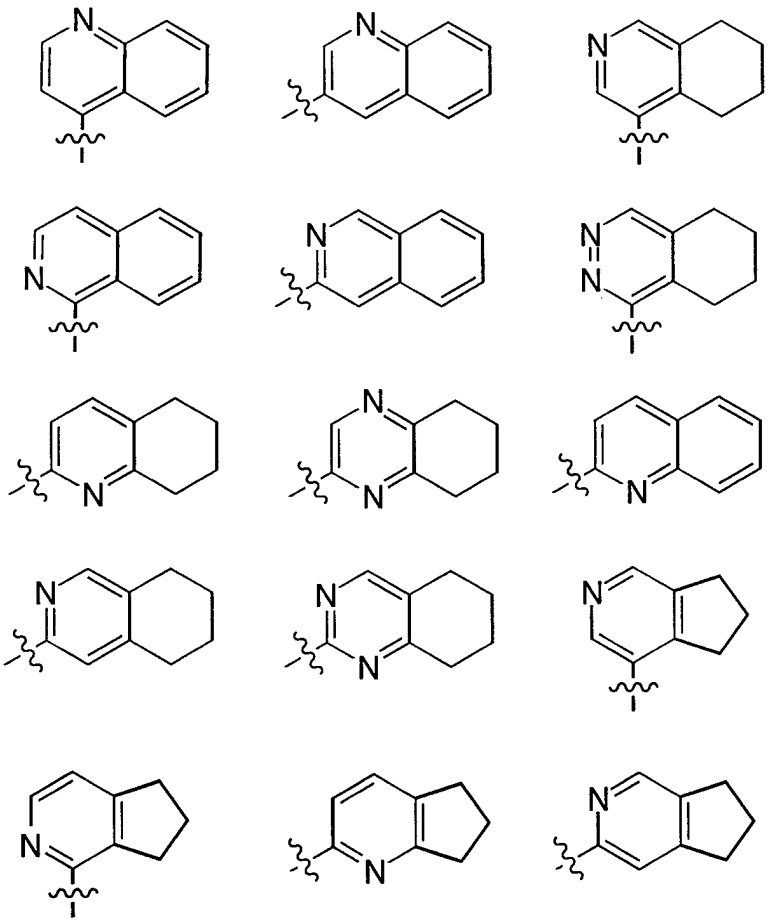
represent an aromatic 6-membered heterocyclic ring and includes the following ring systems:



wherein R^6 is as defined hereinabove.

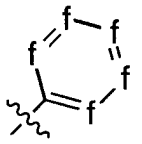
With respect to the farnesyl-protein transferase inhibitors of the formulas II-e and II-g, the moieties designated by the following structures

where any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH-, $-(CH_2)_4-$ and $-(CH_2)_4-$ include, but are not limited to the following structures:

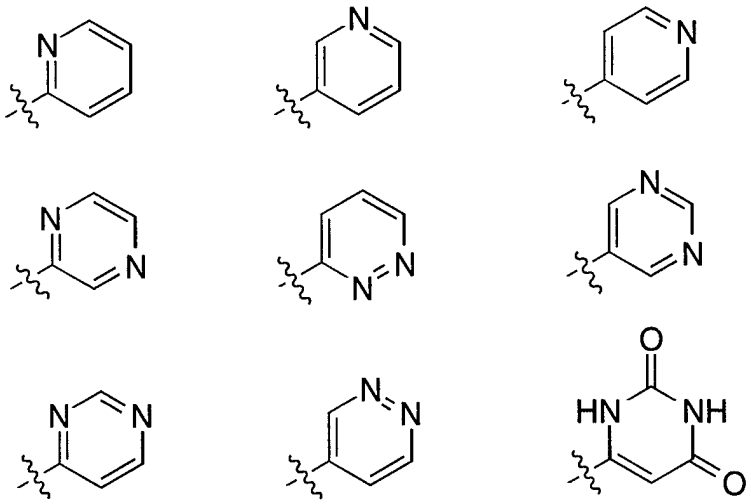


It is understood that such fused ring moieties may be further substituted by the remaining R^6s as defined hereinabove.

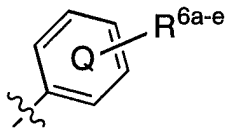
With respect to the farnesyl-protein transferase inhibitors of the formulas II-f and II-g, the moiety designated by the following structure



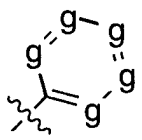
represents an aromatic 6-membered heterocyclic ring and includes the following ring systems:



wherein it is understood that one of the ring carbon atoms is substituted with

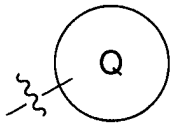


or

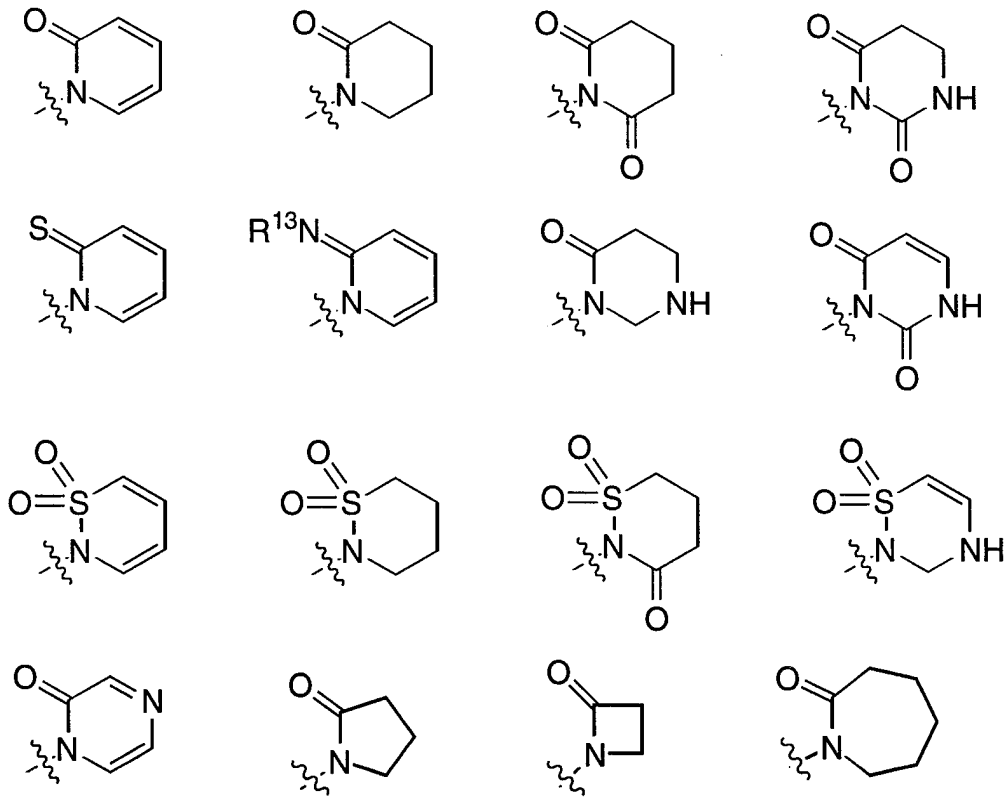


respectively.

With respect to the farnesyl-protein transferase inhibitors of the formula II-m, the substituent illustrated by the structure

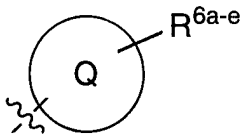


represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

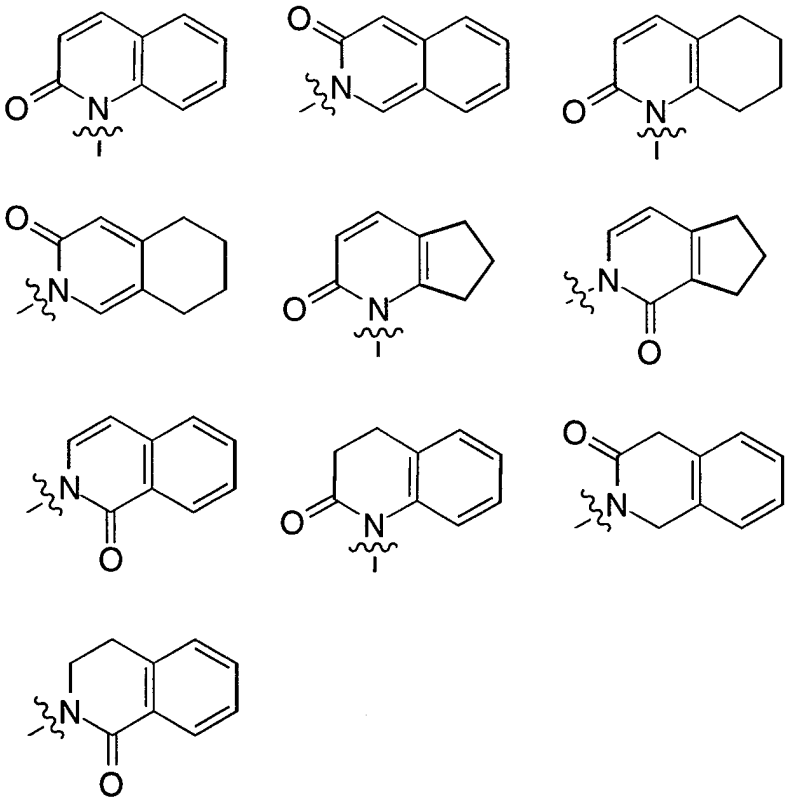


It is understood that such rings may be substituted by R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors of the formula II-m, the moiety described as

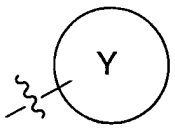


where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, $-(CH_2)_4-$ and $-(CH_2)_4-$ includes, but is not limited to, the following structures:

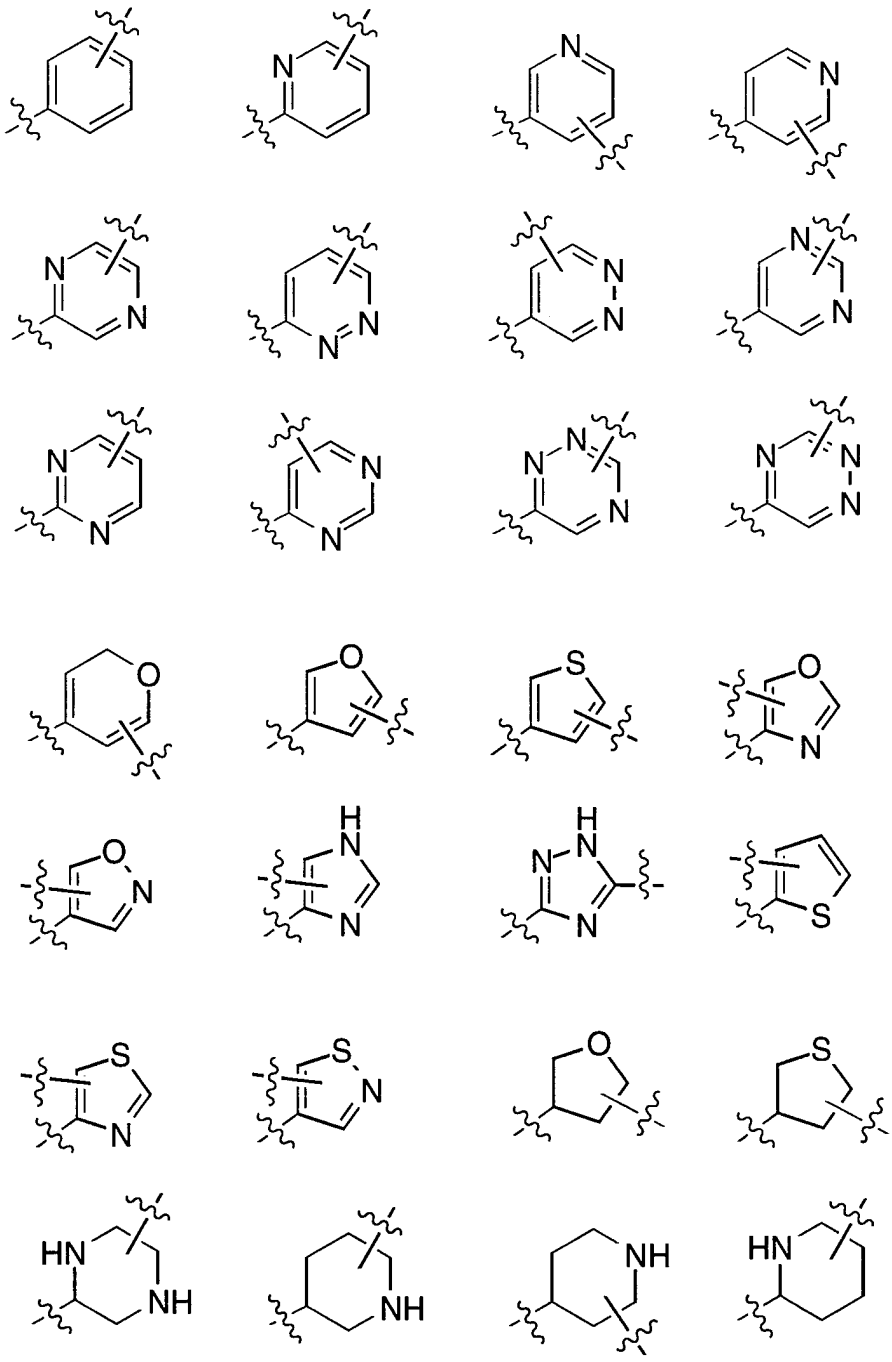


It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

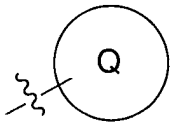
With respect to the farnesyl-protein transferase inhibitors of the formula II-m, the substituent illustrated by the structure



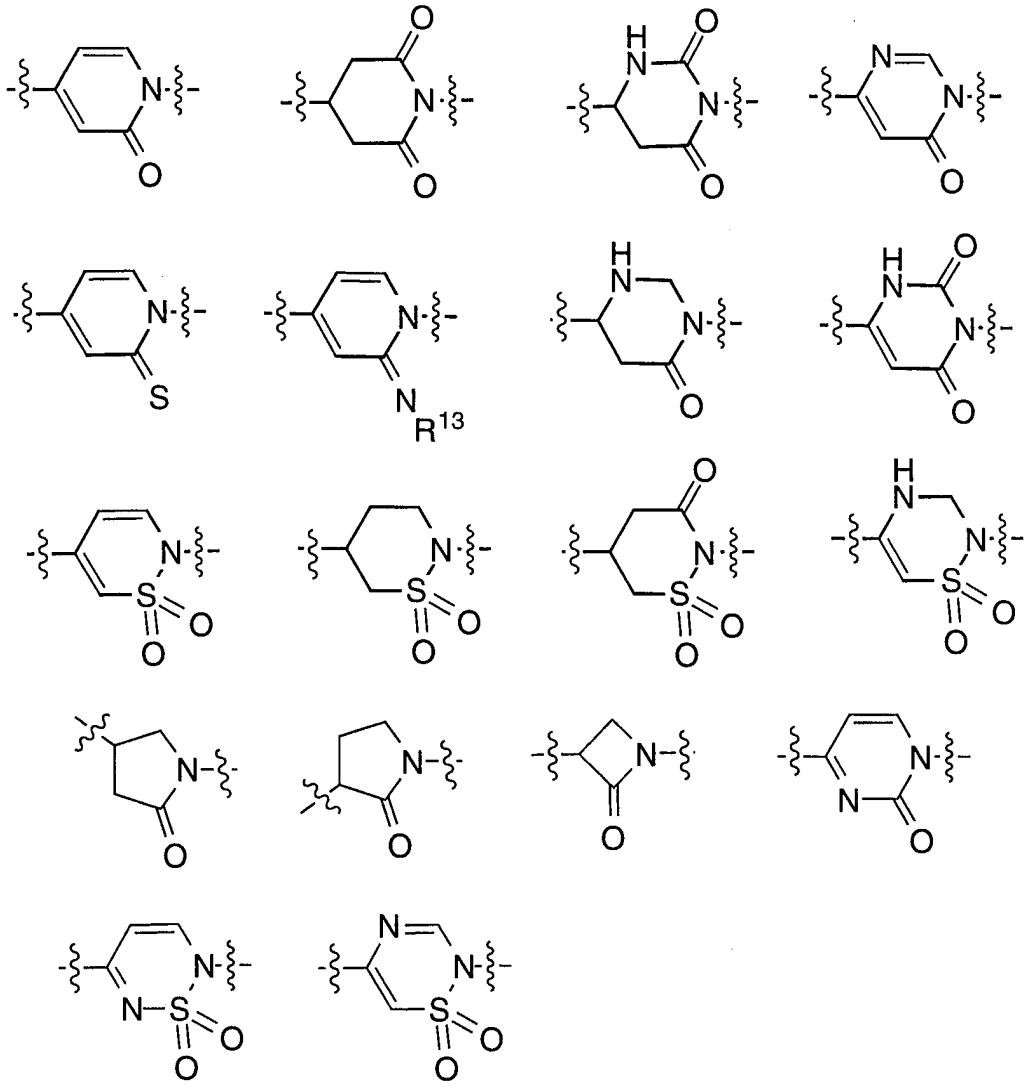
represents a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:



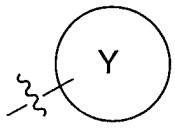
With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the substituent illustrated by the structure



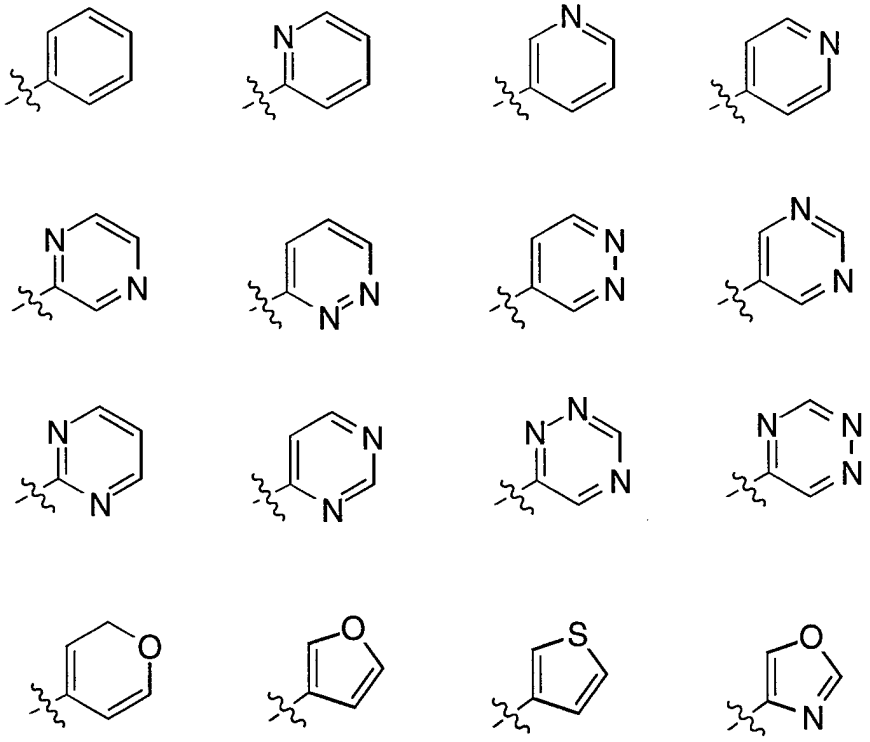
represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

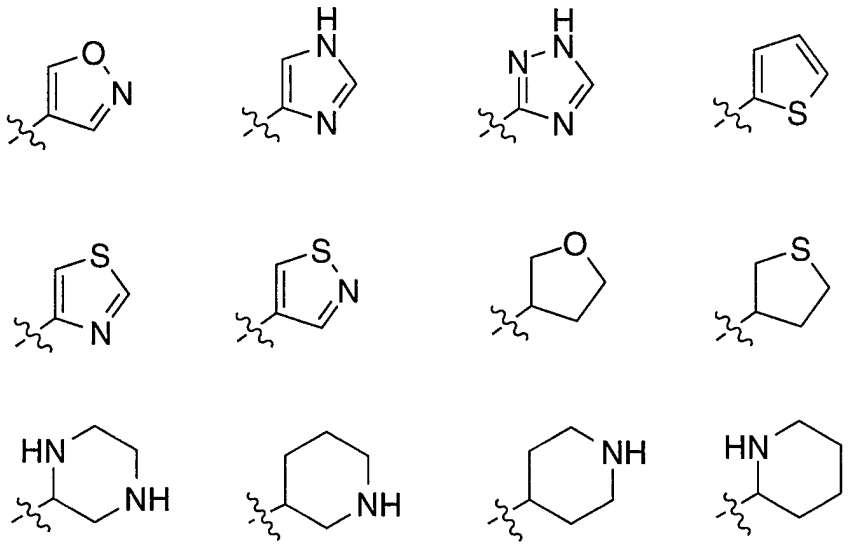


With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the substituent illustrated by the structure

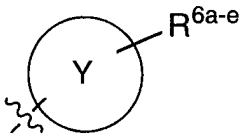


represents a 5-, 6- or 7-membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:

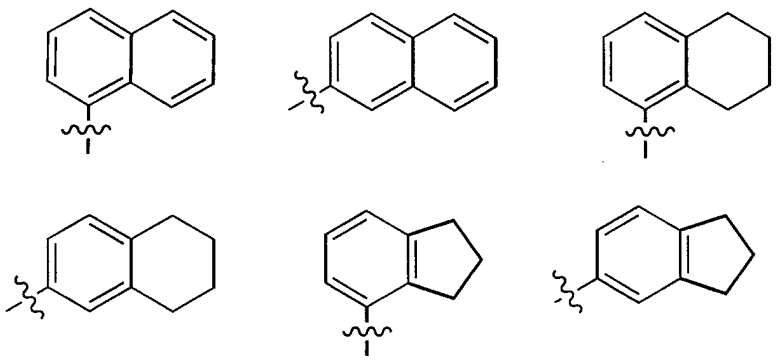


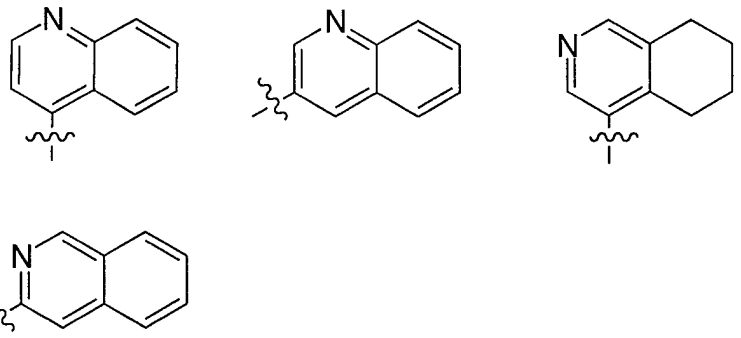


With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the moiety described as



where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, $-(CH_2)_4-$ and $-(CH_2)_4-$ includes, but is not limited to, the following structures:

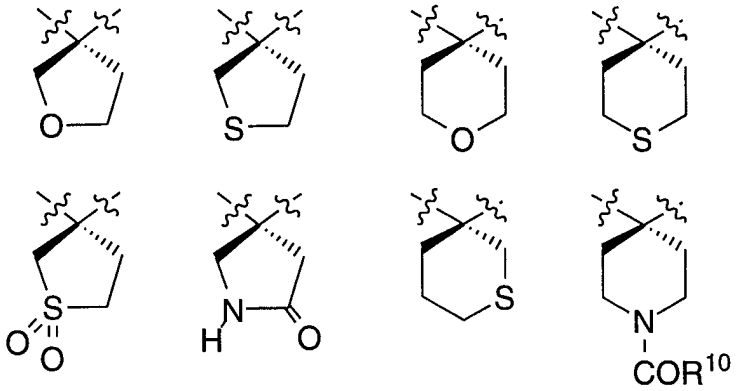




It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

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

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



When R^6 and R^7, R^7 and R^{7a}, or are combined to form -$(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

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, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

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

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 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.

The utility of a compound as an $\alpha v\beta 3$ antagonist may be demonstrated by the methodology known in the art, such as the assays described in WO95/32710, published 7 December 1995.

The compounds of formula (II-h) can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, *"The Peptides"*, Vol. I, Academic Press 1965, or Bodanszky *et al.*, *"Peptide Synthesis"*, Interscience Publishers, 1966, or McOmie (ed.) *"Protective Groups in Organic Chemistry"*, Plenum Press, 1973, or Barany *et al.*, *"The Peptides: Analysis, Synthesis, Biology" 2*, Chapter 1, Academic Press, 1980, or Stewart *et al.*, *"Solid Phase Peptide Synthesis"*, Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al. Tetrahedron,* 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β-acetylamino)alanine residue at the C-terminus, use of the commercially available $N\alpha$-Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred.

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

Ac_2O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
HOBT	1-Hydroxybenzotriazole hydrate;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
MCPBA	m-Chloroperoxybenzoic acid;
MsCl	Methanesulfonyl chloride;
NaHMDS	Sodium bis(trimethylsilyl)amide;
Py	Pyridine;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. 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, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The farnesyl transferase inhibitors of formula (II-a) through (II-c) can be synthesized in accordance with Schemes 1-22, 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, R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

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

Synopsis of Schemes 1-22:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., **1990**, *22*, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can

be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride , chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be treated with an acid chloride, or a carboxylic acid under standard dehydrating conditions to furnish the carboxamides VII; a final acid deprotection as previously described gives the intermediate VIII (Scheme 2). The intermediate VIII can be reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

Alternatively, the protected piperazine intermediate VII can be reductively alkylated with other aldehydes such as 1-trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give

products such as XVI (Scheme 4). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). 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 XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

The Boc protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXXII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

In addition, the piperazine VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XL.

Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated into the piperazine. For example when I is the Boc-protected β-benzyl ester of aspartic acid, the intermediate diketopiperazine XLII where n=1 and R=benzyl is obtained, as shown in Scheme 10. Subsequent lithium aluminum hydride reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XLIV can then be carried on to final products as described in Schemes 3-9.

N-Aryl piperazines can be prepared as described in Scheme 11. An aryl amine XLV is reacted with *bis* -chloroethyl amine hydrochloride (XLVI) in refluxing *n* -butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of Boc-protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide to give LI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated

LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as described in Schemes 3-9.

Access to alternatively substituted piperazines is described in Scheme 14. Following deprotection with trifluoroacetic acid, the N-benzyl piperazine V can be acylated with an aryl carboxylic acid. The resulting N-benzyl aryl carboxamide LIX can be hydrogenated in the presence of a catalyst to give the piperazine carboxamide LX which can then be carried on to final products as described in Schemes 3-9.

Reaction Scheme 15 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^2 and R^3 are combined to form - $(CH_2)_u$ -. For example, 1-aminocyclohexane-1-carboxylic acid LXI can be converted to the spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXIX can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the substituent Y which is 2-(naphthyl) and the imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an aniline as shown in Scheme 16. The product LXXI can be converted to a piperazinone by acylation with chloroacetyl chloride to give LXXII, followed by base-induced cyclization to LXXIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXV, which can be alkylation with an arylmethylhalide to give the imidazolium salt LXXVI. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product LXXVII.

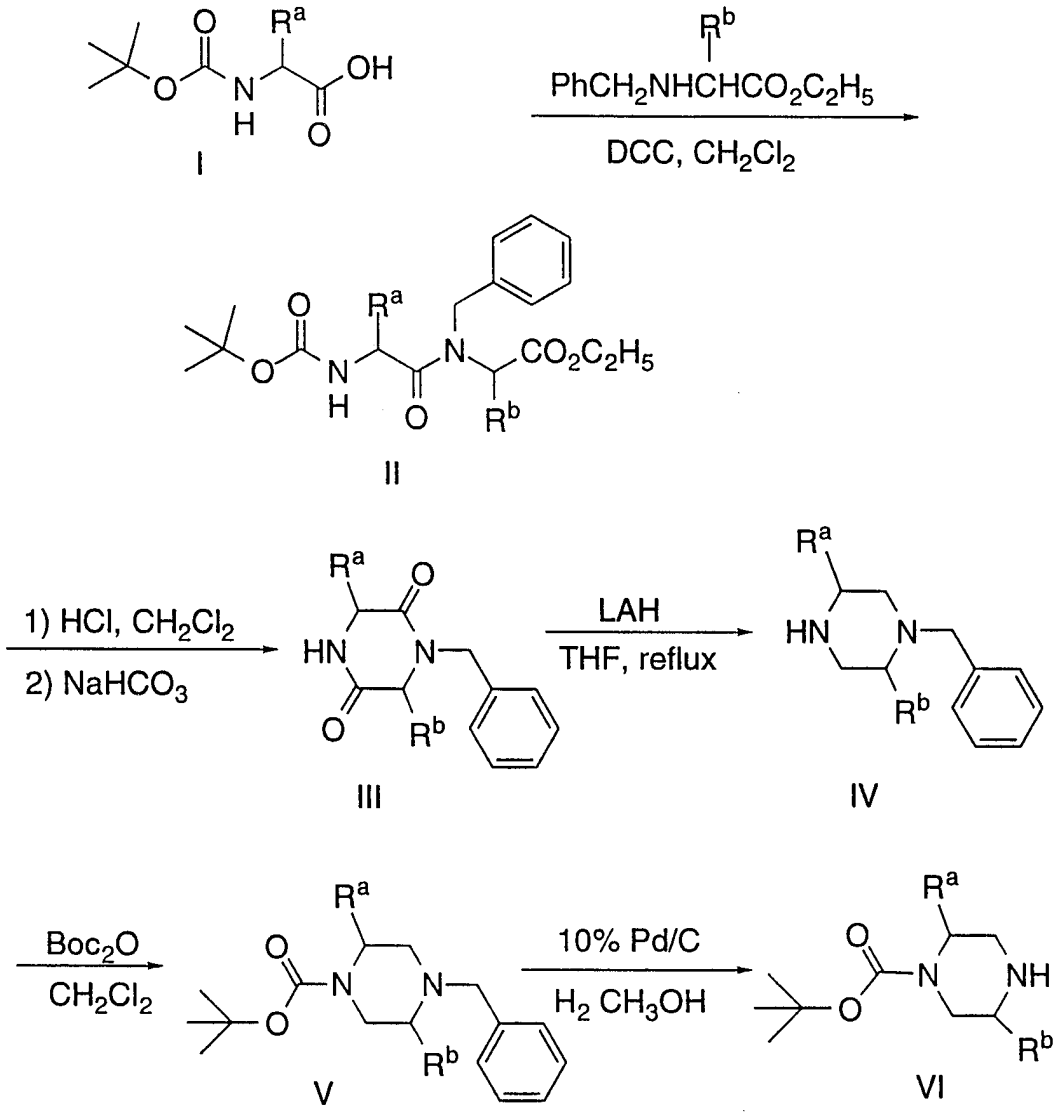
Scheme 17 illustrates the use of an optionally substituted homoserine lactone LXXIX to prepare a Boc-protected piperazinone LXXXII. Intermediate LXXXII may be deprotected and reductively

alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of intermediate LXXXII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate LXXXIII. Intermediate LXXXII may also be oxidized to provide the carboxylic acid on intermediate LXXXIV, which can be utilized form an ester or amide moiety.

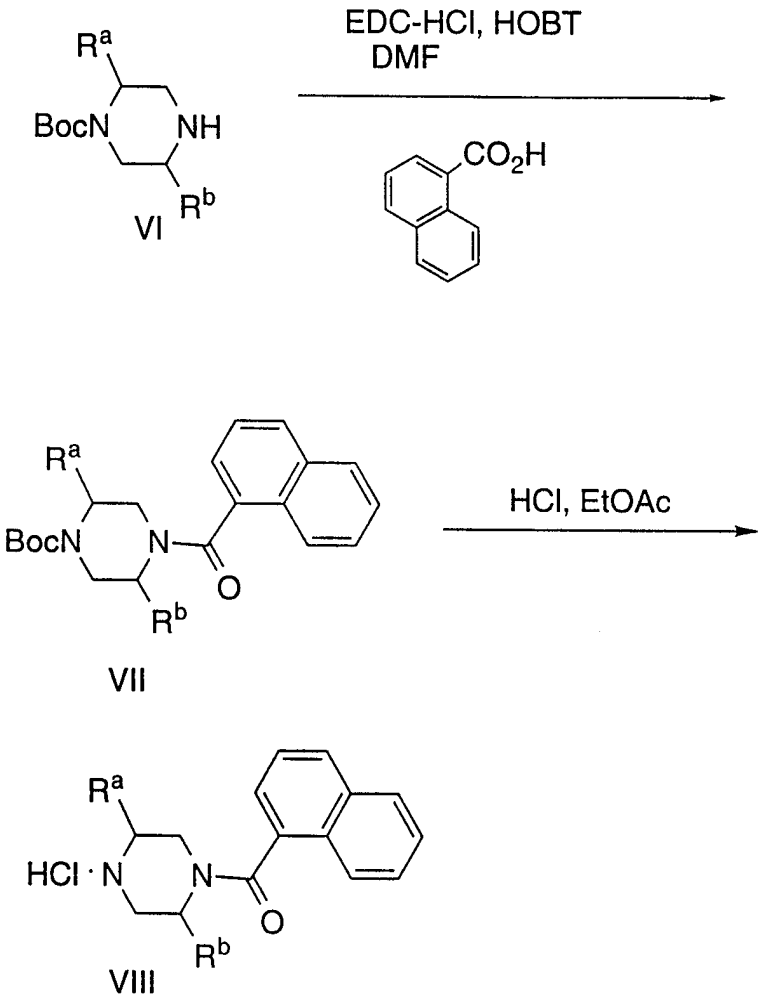
Amino acids of the general formula LXXXVI which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 18 starting with the readily prepared imine LXXXV.

Schemes 19-22 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.

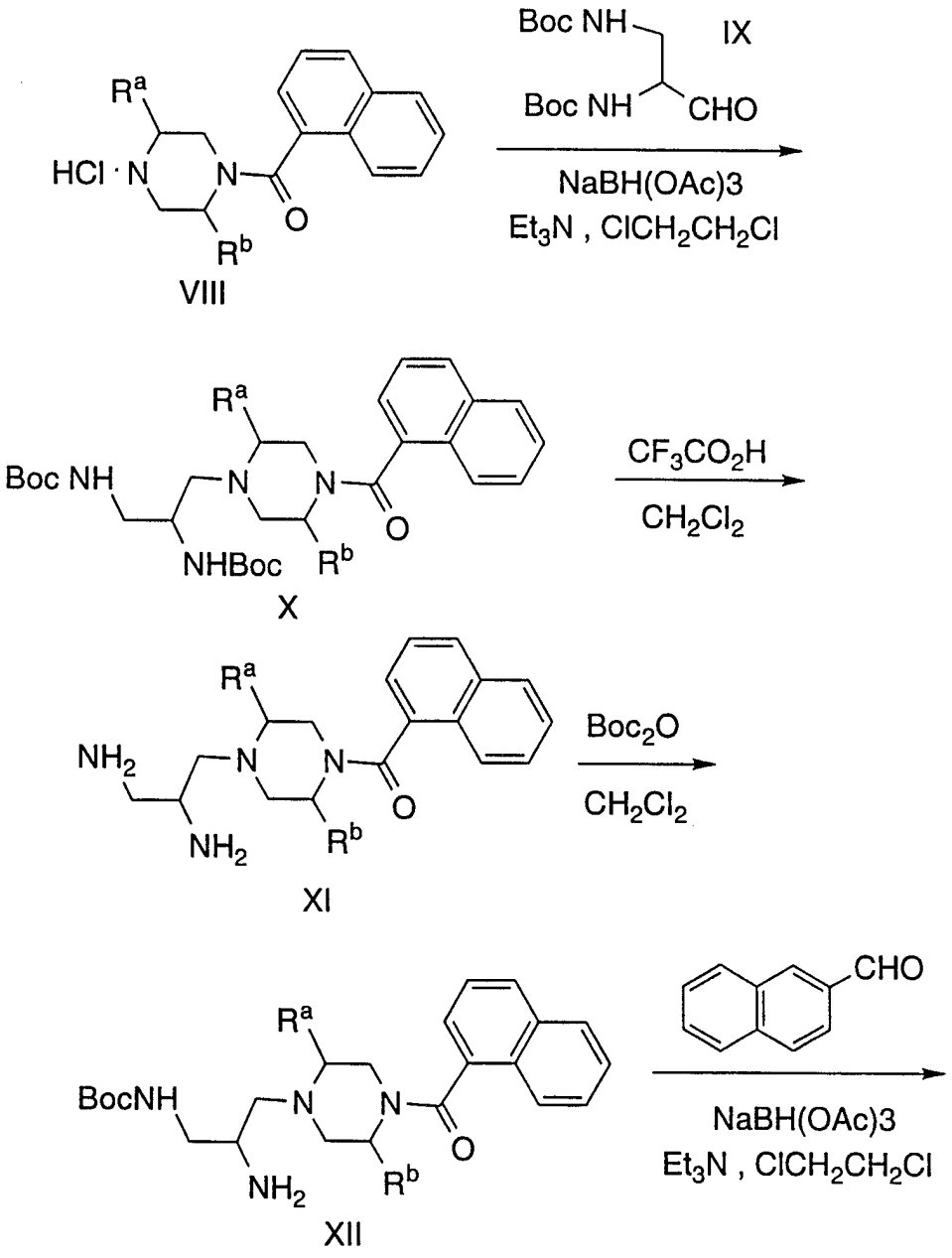
SCHEME 1


PhCH2NHCHCO2C2H5
DCC, CH2Cl2
I
II
1) HCl, CH2Cl2
2) NaHCO3
III
LAH
THF, reflux
IV
Boc2O
CH2Cl2
V
10% Pd/C
H2 CH3OH
VI

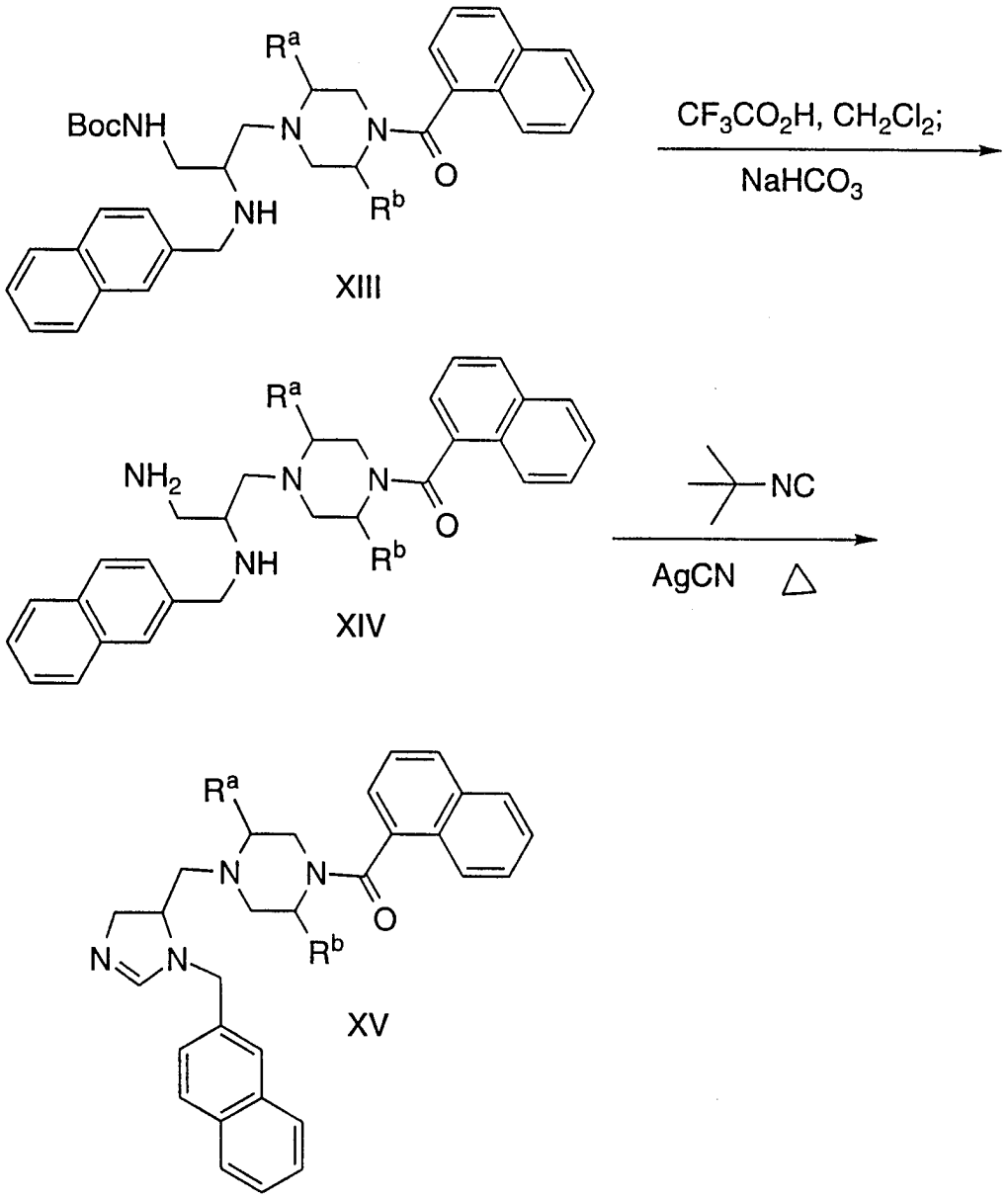
SCHEME 2


EDC-HCl, HOBT
DMF
R^a
BocN
NH
R^b
VI
CO_2H
R^a
BocN
N
O
R^b
VII
HCl, EtOAc
R^a
HCl · N
N
O
R^b
VIII

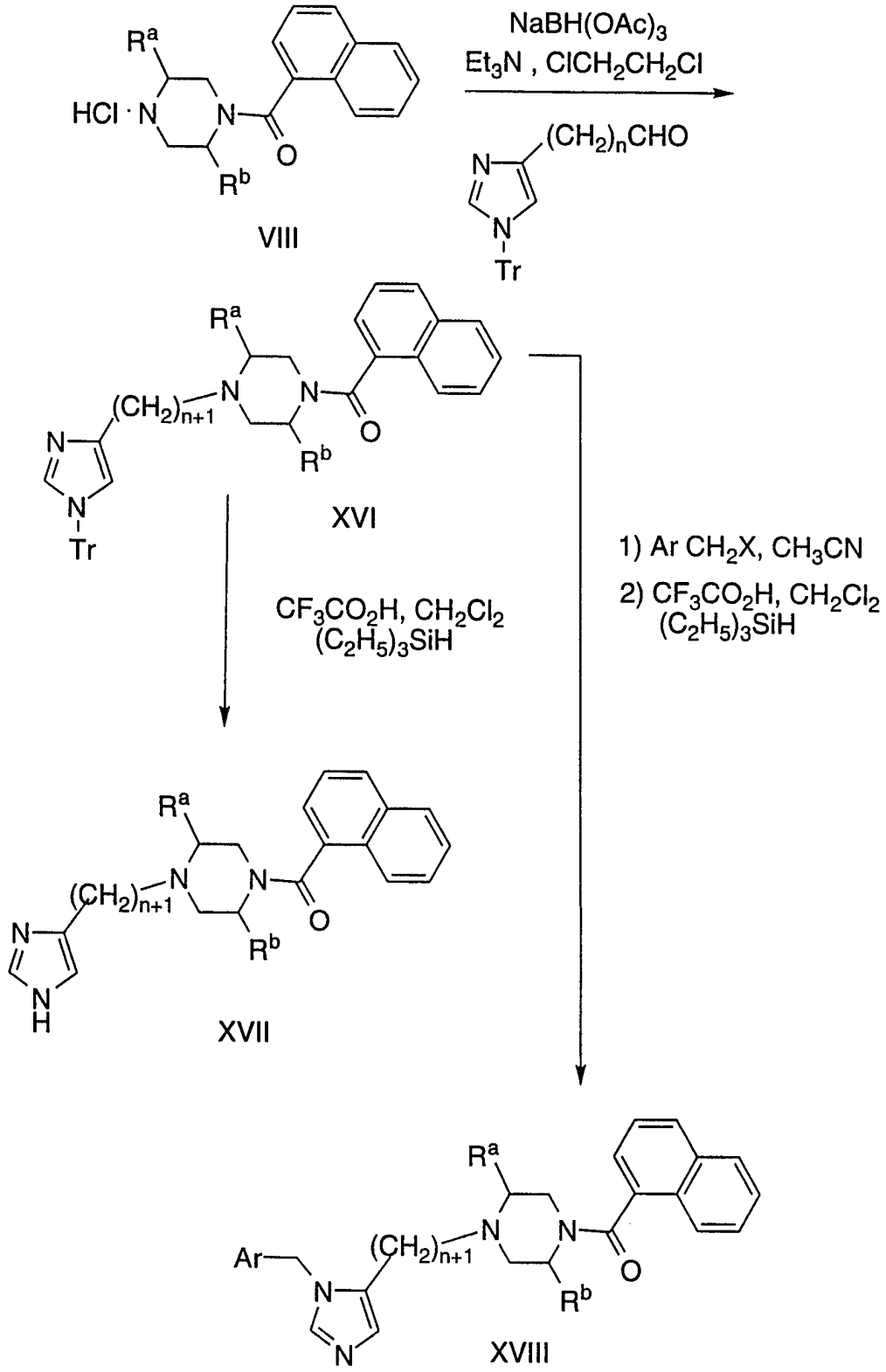
SCHEME 3


Boc NH
IX
Boc NH
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl
HCl · N
N
O
Ra
Rb
VIII
Boc NH
NHBoc
X
CF3CO2H
CH2Cl2
NH2
NH2
XI
Boc2O
CH2Cl2
BocNH
NH2
XII
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl

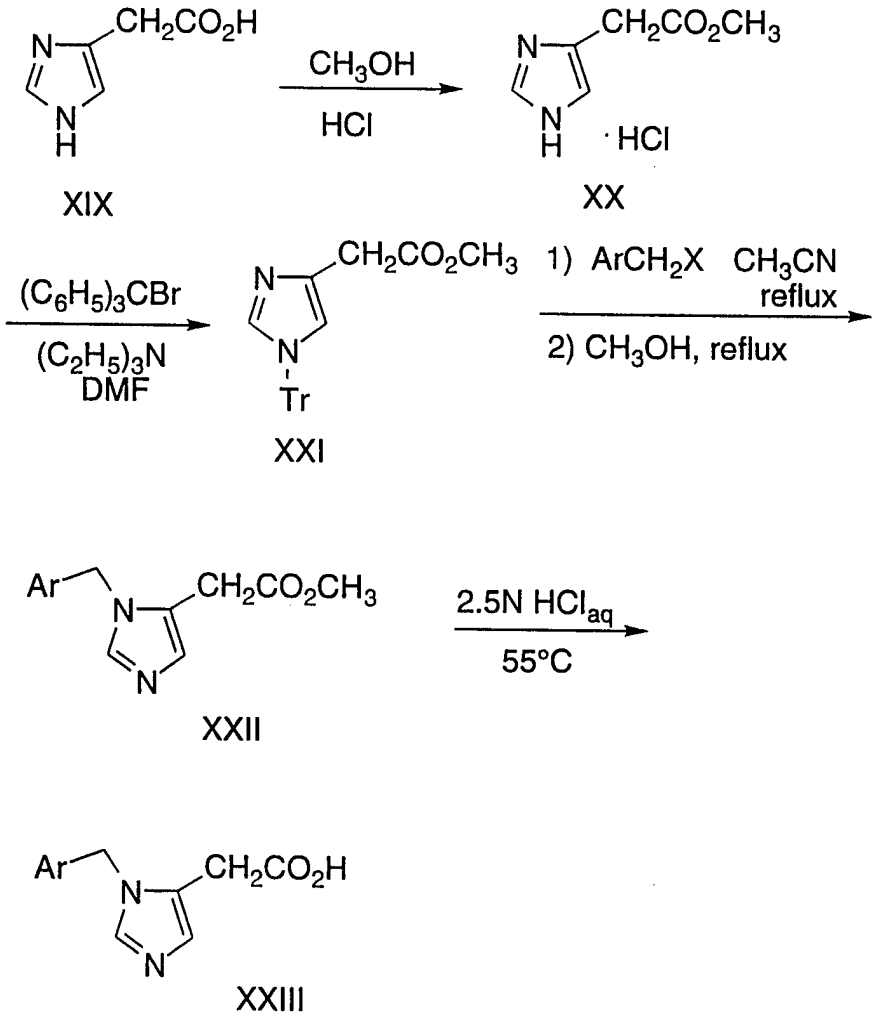
SCHEME 3 (continued)



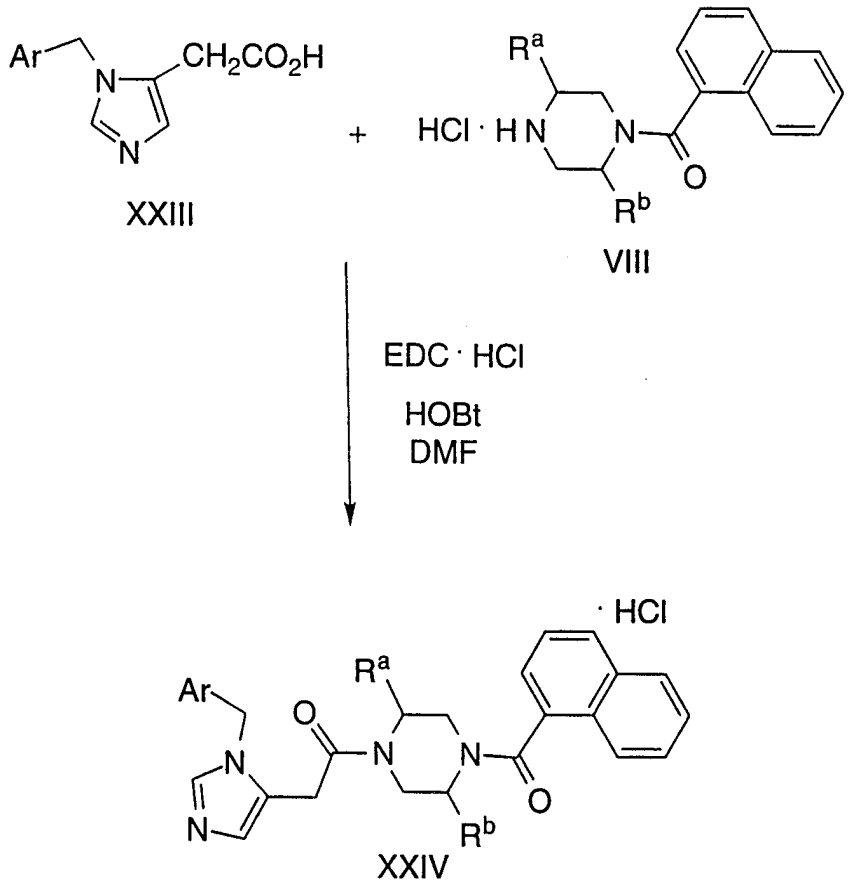
SCHEME 4


NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
Tr
VIII
XVI
CF3CO2H, CH2Cl2
(C2H5)3SiH
1) Ar CH2X, CH3CN
2) CF3CO2H, CH2Cl2
(C2H5)3SiH
XVII
XVIII

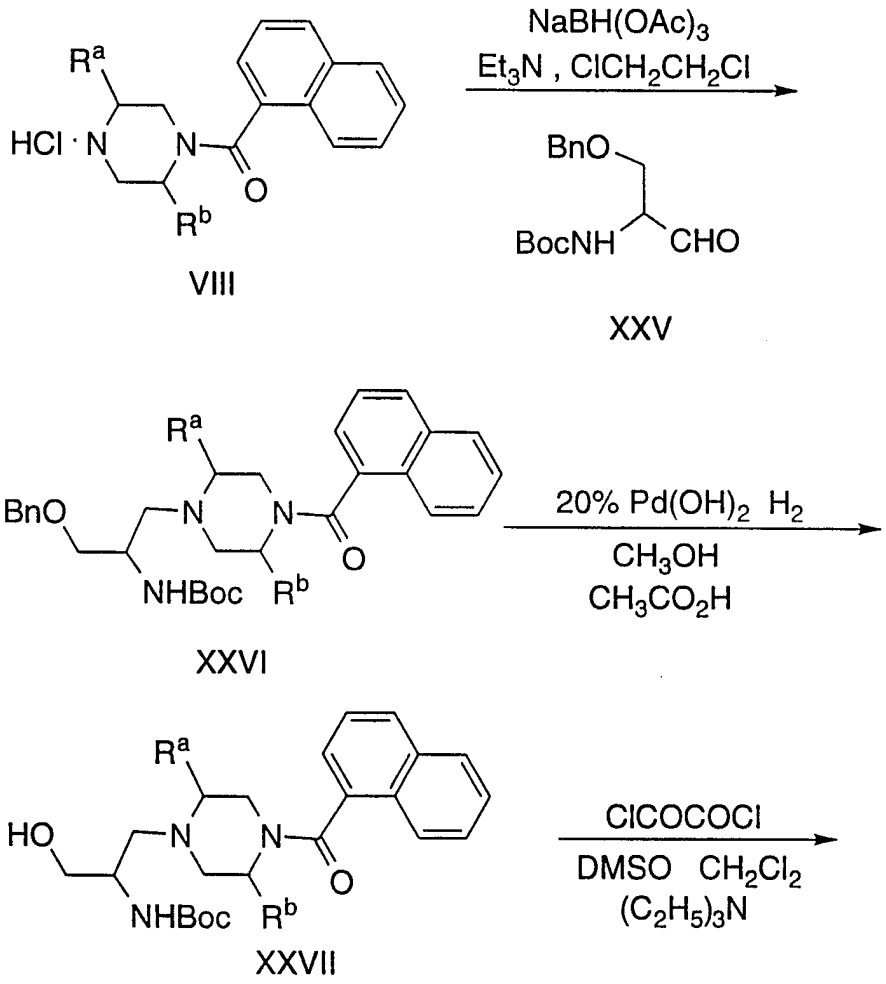
SCHEME 5


CH2CO2H
N
N
H
XIX
CH3OH
HCl
CH2CO2CH3
N
N
H
·HCl
XX
(C6H5)3CBr
(C2H5)3N
DMF
CH2CO2CH3
N
N
Tr
XXI
1) ArCH2X CH3CN
reflux
2) CH3OH, reflux
Ar
CH2CO2CH3
N
N
XXII
2.5N HClaq
55°C
Ar
CH2CO2H
N
N
XXIII

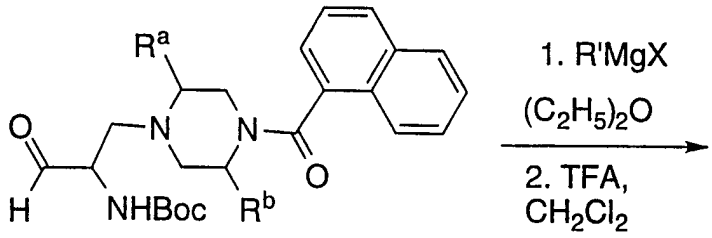
SCHEME 5 (continued)



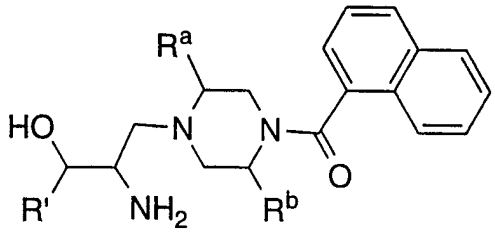
SCHEME 6


NaBH(OAc)3
Et3N , ClCH2CH2Cl
BnO
BocNH
CHO
HCl · N
N
O
Ra
Rb
VIII
XXV
20% Pd(OH)2 H2
CH3OH
CH3CO2H
BnO
NHBoc
XXVI
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
HO
XXVII

SCHEME 6 (CONTINUED)

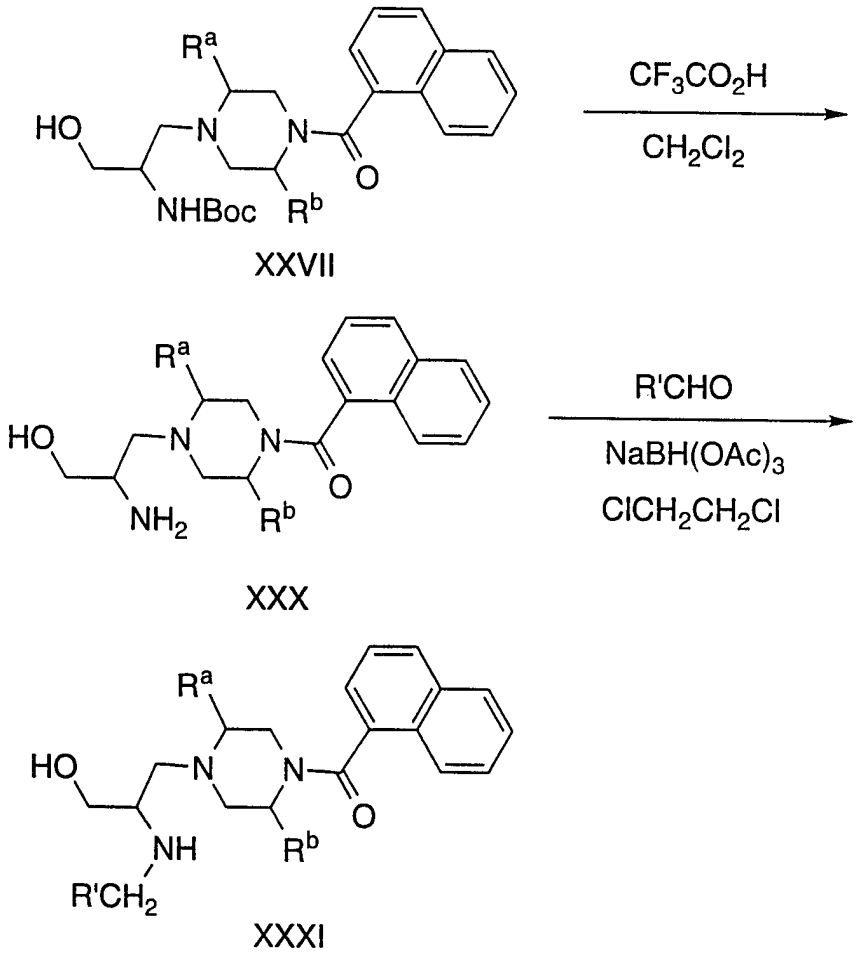


XXVIII

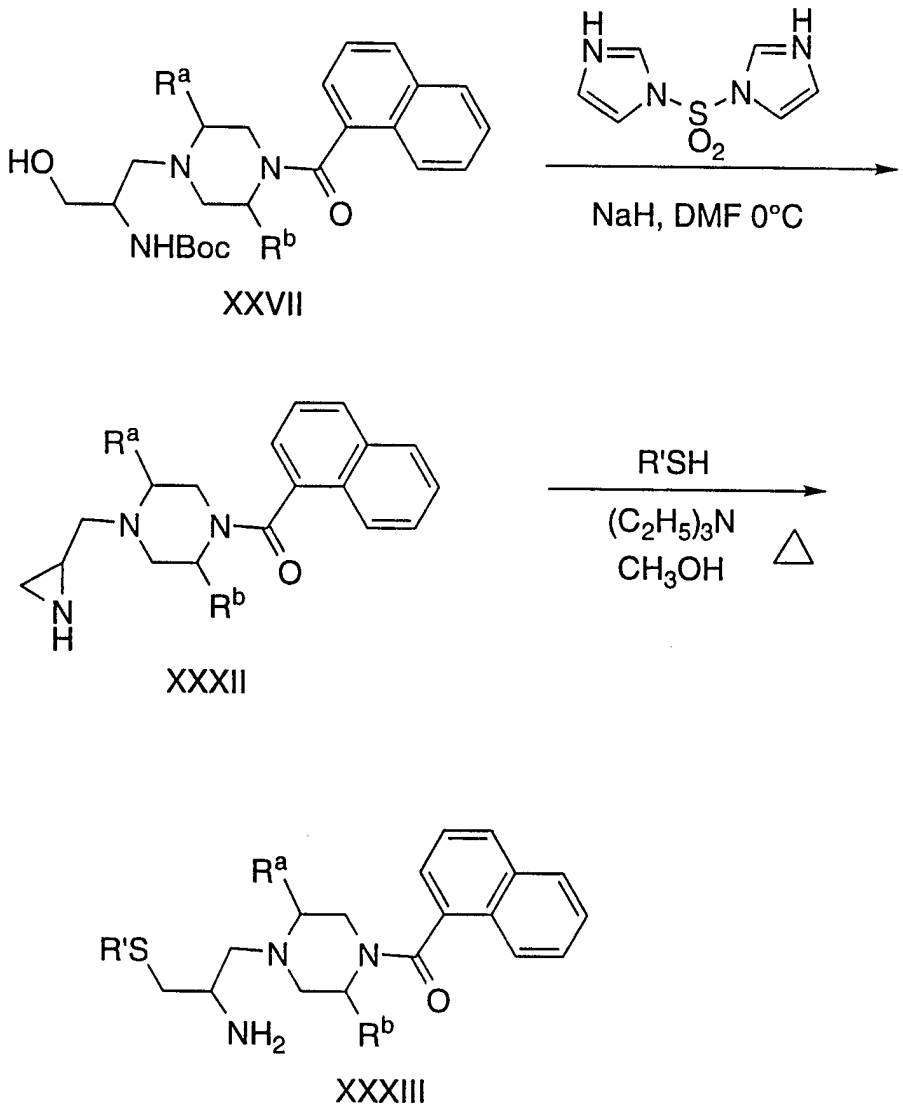


XXIX

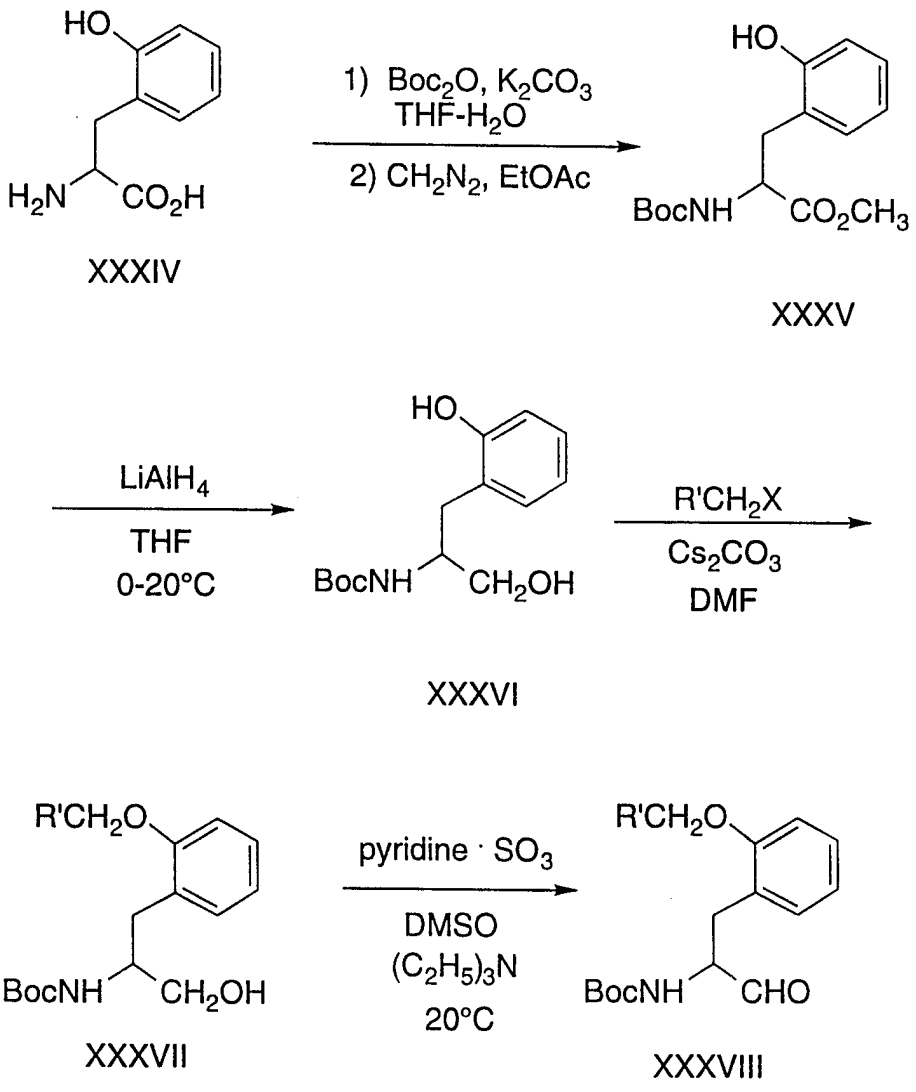
SCHEME 7


Ra
HO
N
N
O
NHBoc
Rb
CF3CO2H
CH2Cl2
XXVII
Ra
HO
N
N
O
NH2
Rb
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
XXX
Ra
HO
N
N
O
NH
R'CH2
Rb
XXXI

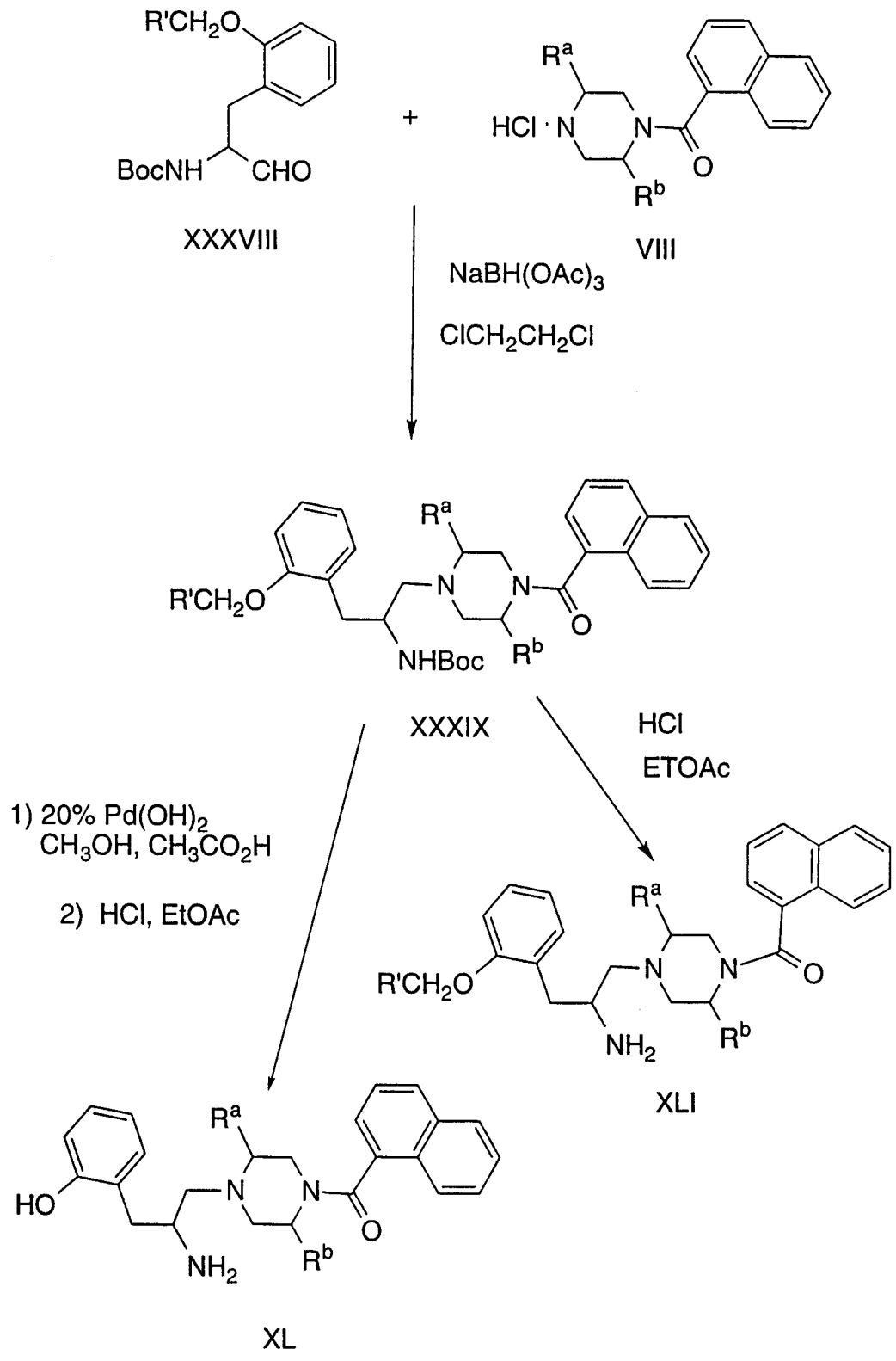
SCHEME 8


HO
NHBoc
O
NaH, DMF 0°C
XXVII
R'SH
$(C_2H_5)_3N$
CH_3OH
XXXII
R'S
NH_2
XXXIII

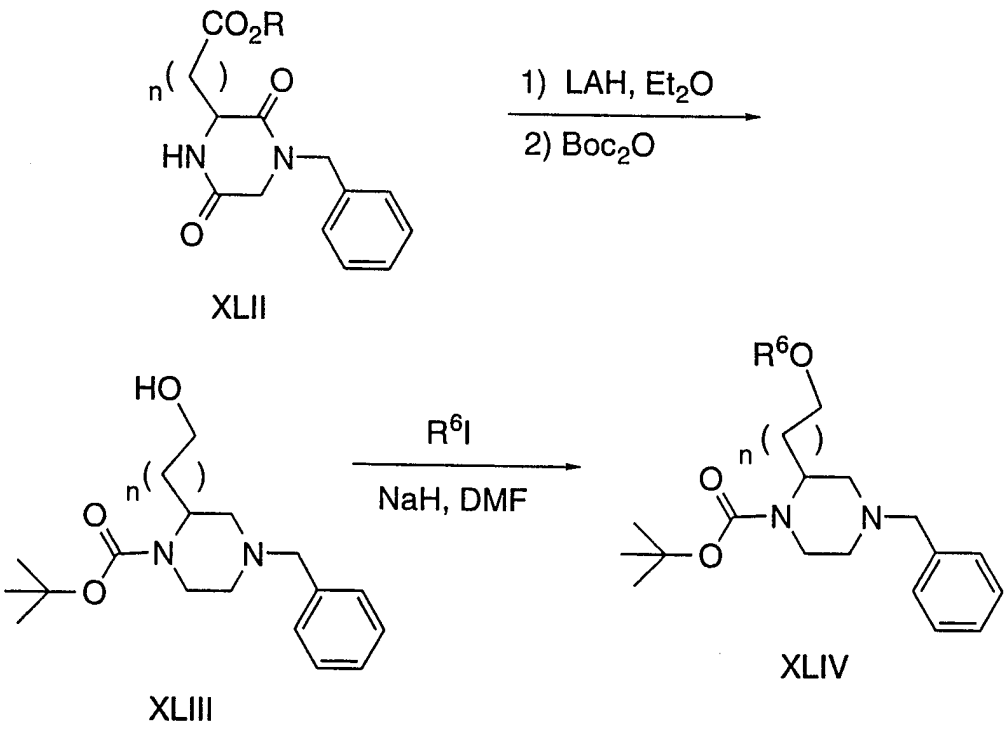
SCHEME 9


HO
H2N
CO2H
XXXIV
1) Boc2O, K2CO3
THF-H2O
2) CH2N2, EtOAc
HO
BocNH
CO2CH3
XXXV
LiAlH4
THF
0-20°C
HO
BocNH
CH2OH
XXXVI
R'CH2X
Cs2CO3
DMF
R'CH2O
BocNH
CH2OH
XXXVII
pyridine · SO3
DMSO
(C2H5)3N
20°C
R'CH2O
BocNH
CHO
XXXVIII

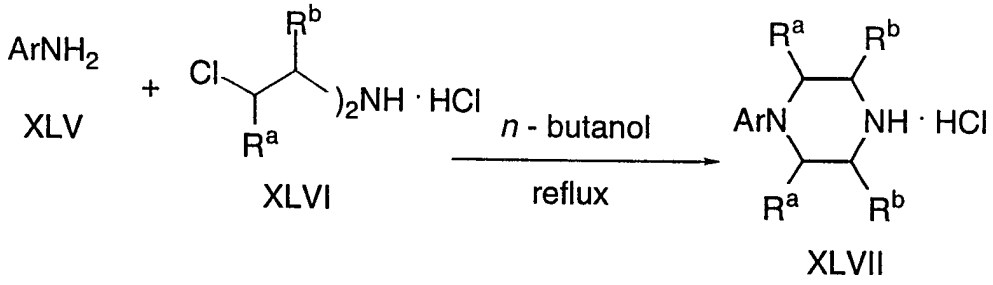
SCHEME 9 (continued)



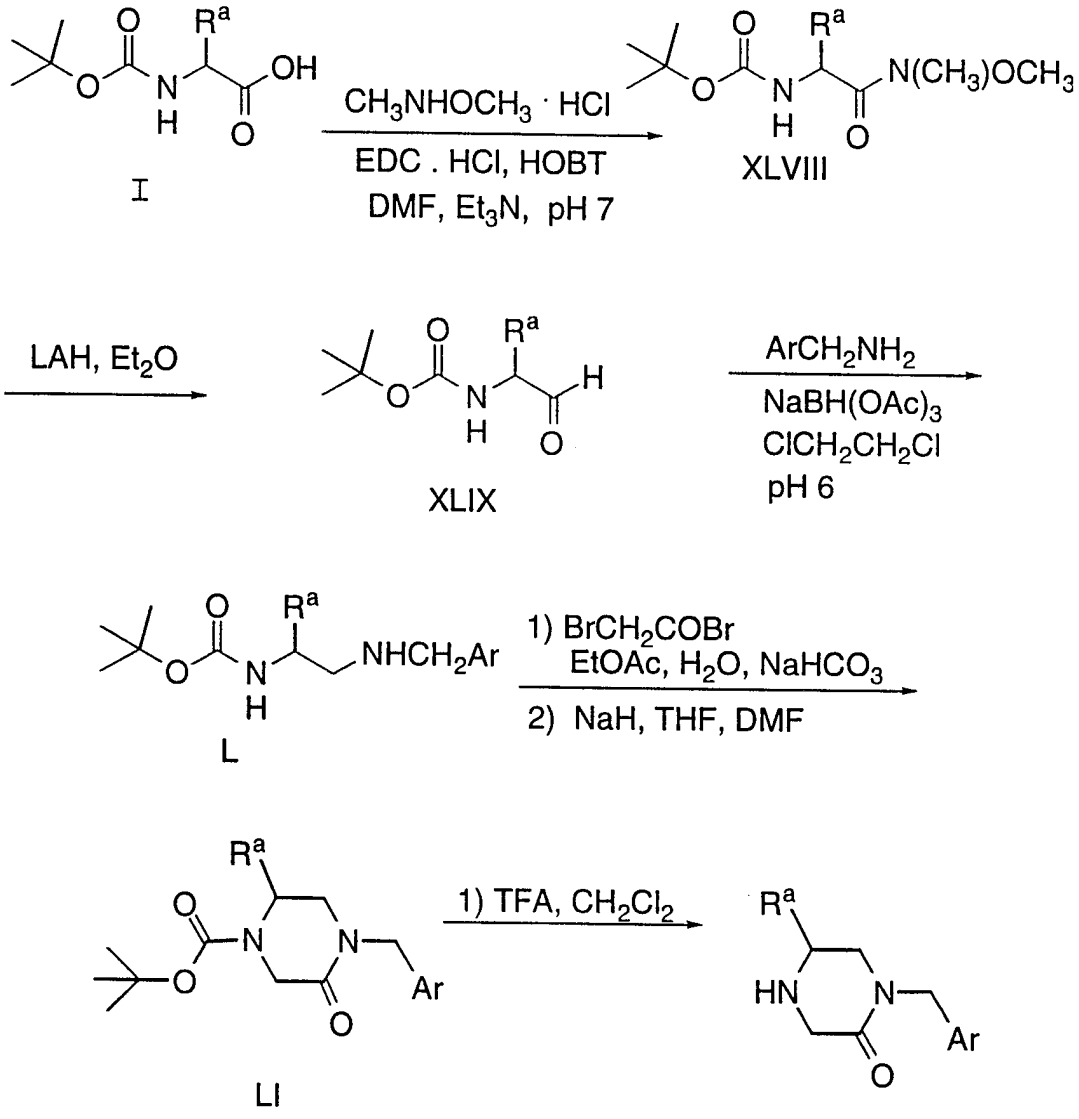
SCHEME 10



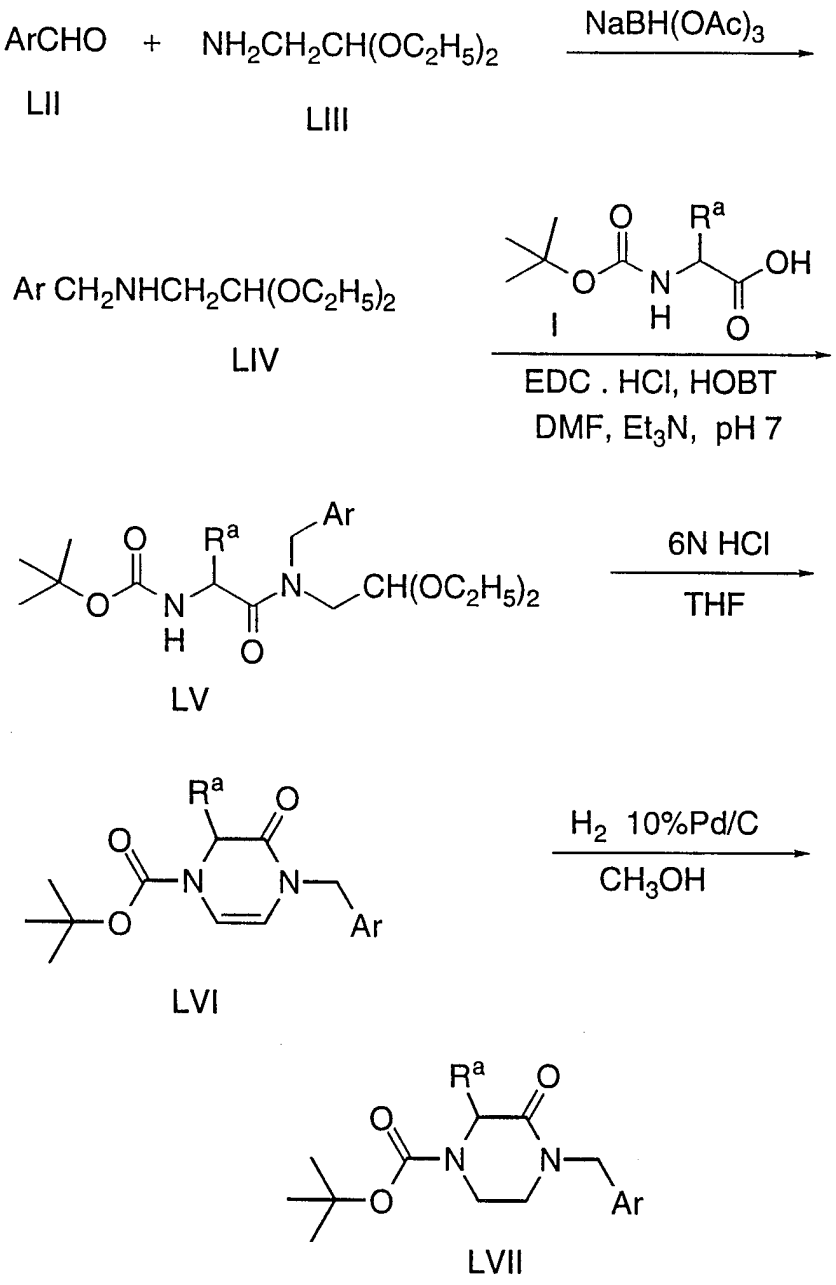
SCHEME 11



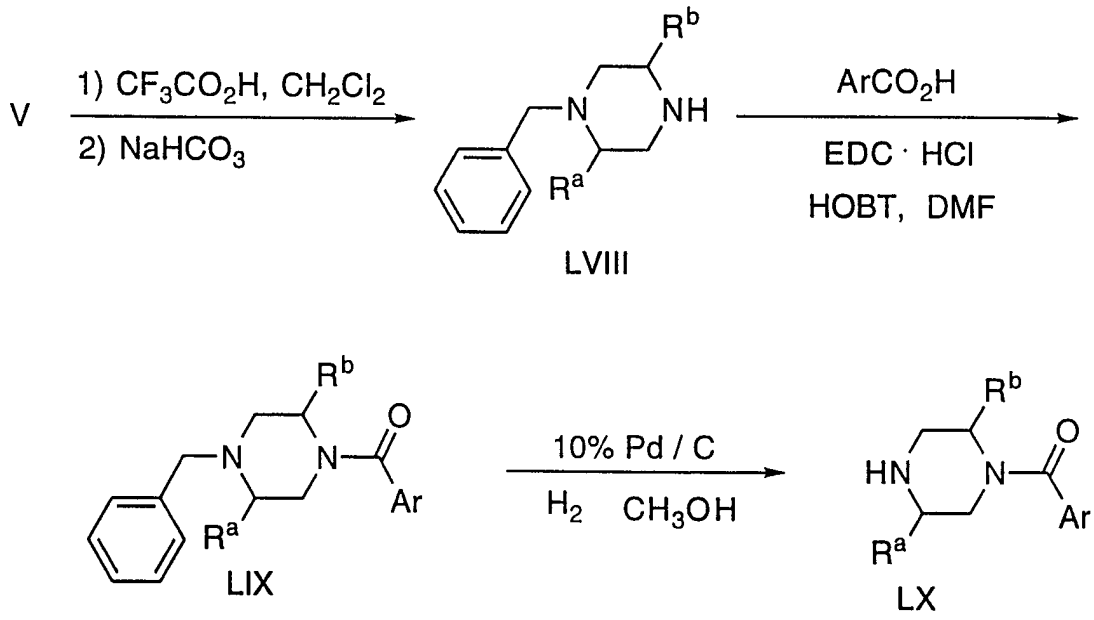
SCHEME 12


Ra
O
N
H
OH
I
CH3NHOCH3 · HCl
EDC . HCl, HOBT
DMF, Et3N, pH 7
N(CH3)OCH3
XLVIII
LAH, Et2O
H
XLIX
ArCH2NH2
NaBH(OAc)3
ClCH2CH2Cl
pH 6
NHCH2Ar
L
1) BrCH2COBr
EtOAc, H2O, NaHCO3
2) NaH, THF, DMF
Ar
LI
1) TFA, CH2Cl2
HN

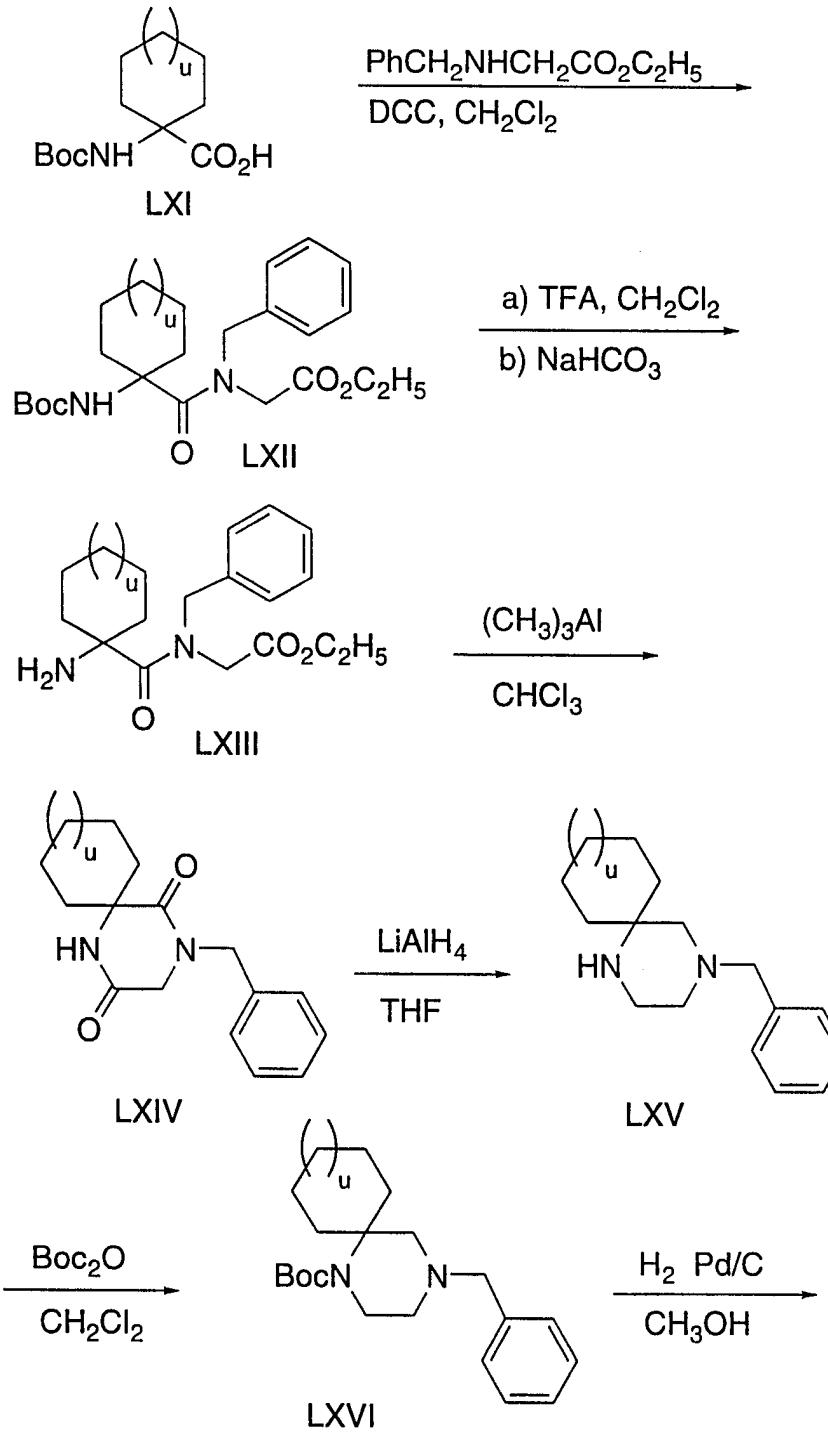
SCHEME 13


ArCHO
+
NH2CH2CH(OC2H5)2
NaBH(OAc)3
LII
LIII
Ar CH2NHCH2CH(OC2H5)2
LIV
I
EDC . HCl, HOBT
DMF, Et3N, pH 7
LV
6N HCl
THF
LVI
H2 10%Pd/C
CH3OH
LVII

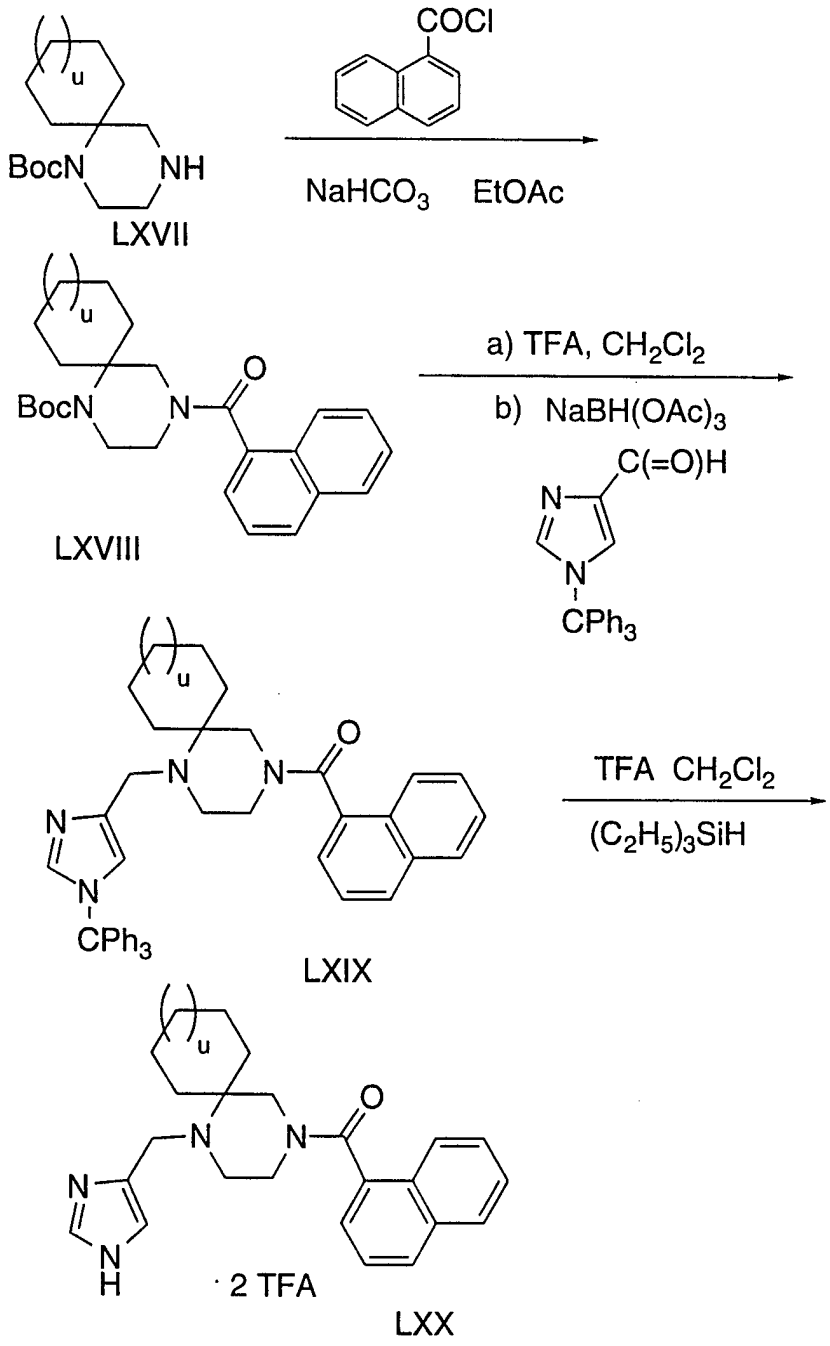
SCHEME 14


V
1) CF_3CO_2H, CH_2Cl_2
2) $NaHCO_3$
R^b
N
NH
R^a
LVIII
$ArCO_2H$
EDC · HCl
HOBT, DMF
R^b
N
N
O
Ar
R^a
LIX
10% Pd / C
H_2 CH_3OH
R^b
HN
N
O
Ar
R^a
LX

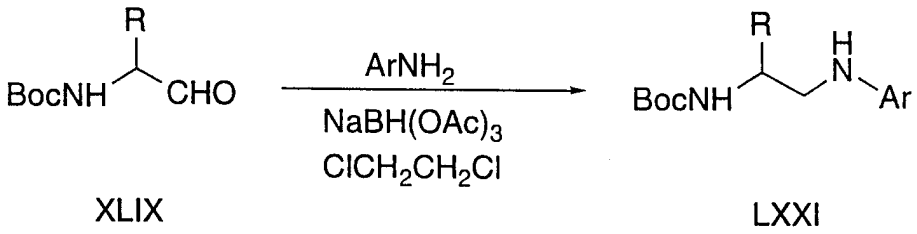
SCHEME 15


PhCH2NHCH2CO2C2H5
DCC, CH2Cl2
BocNH
CO2H
LXI
a) TFA, CH2Cl2
b) NaHCO3
CO2C2H5
LXII
(CH3)3Al
CHCl3
H2N
LXIII
LiAlH4
THF
HN
LXIV
LXV
Boc2O
CH2Cl2
BocN
H2 Pd/C
CH3OH
LXVI

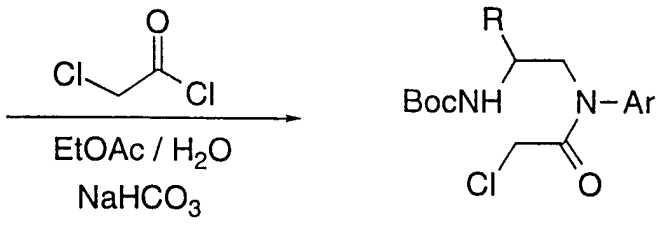
SCHEME 15 (continued)



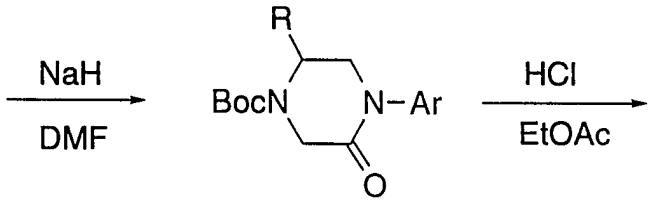
SCHEME 16



XLIX LXXI

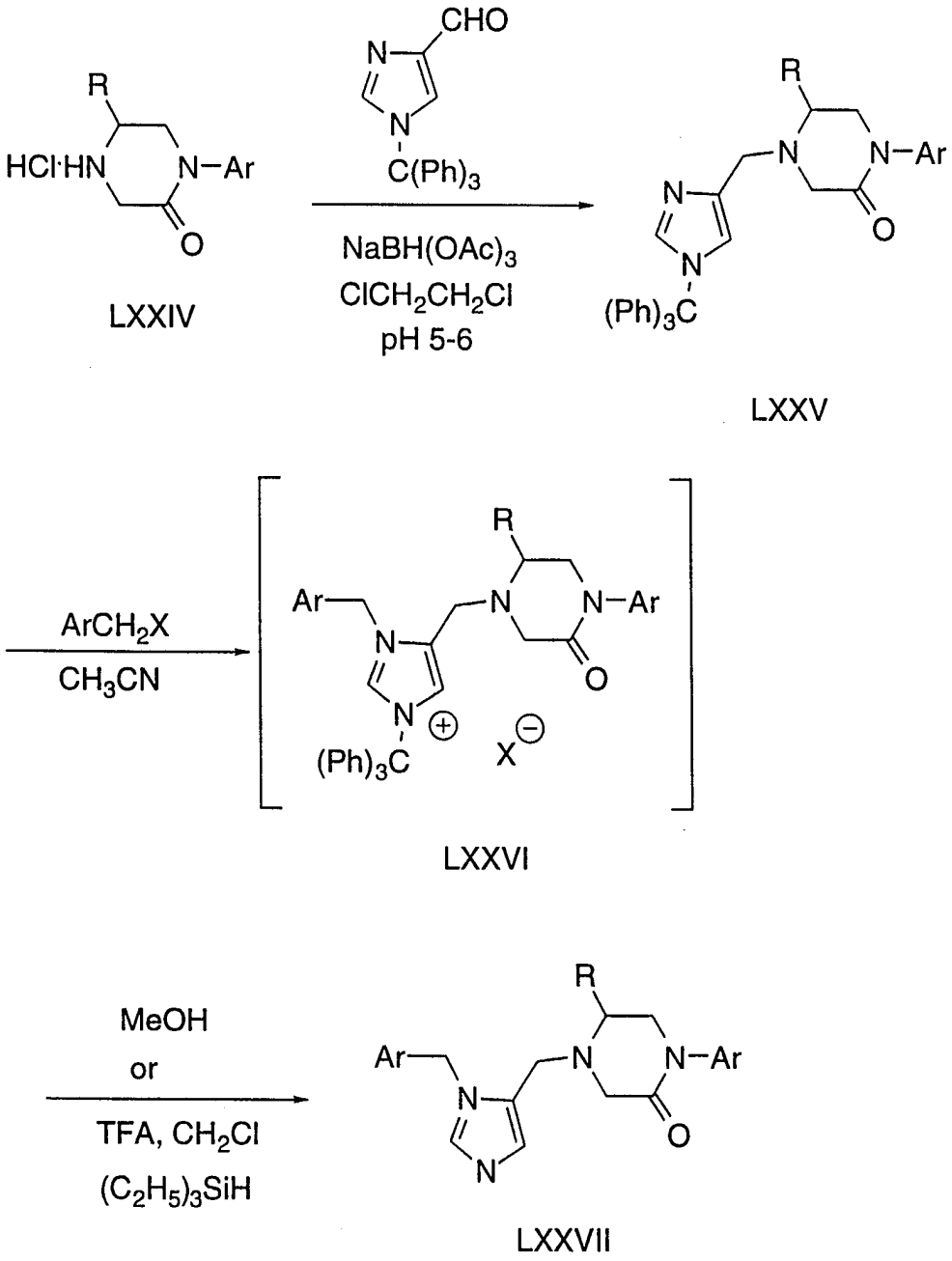


LXXII

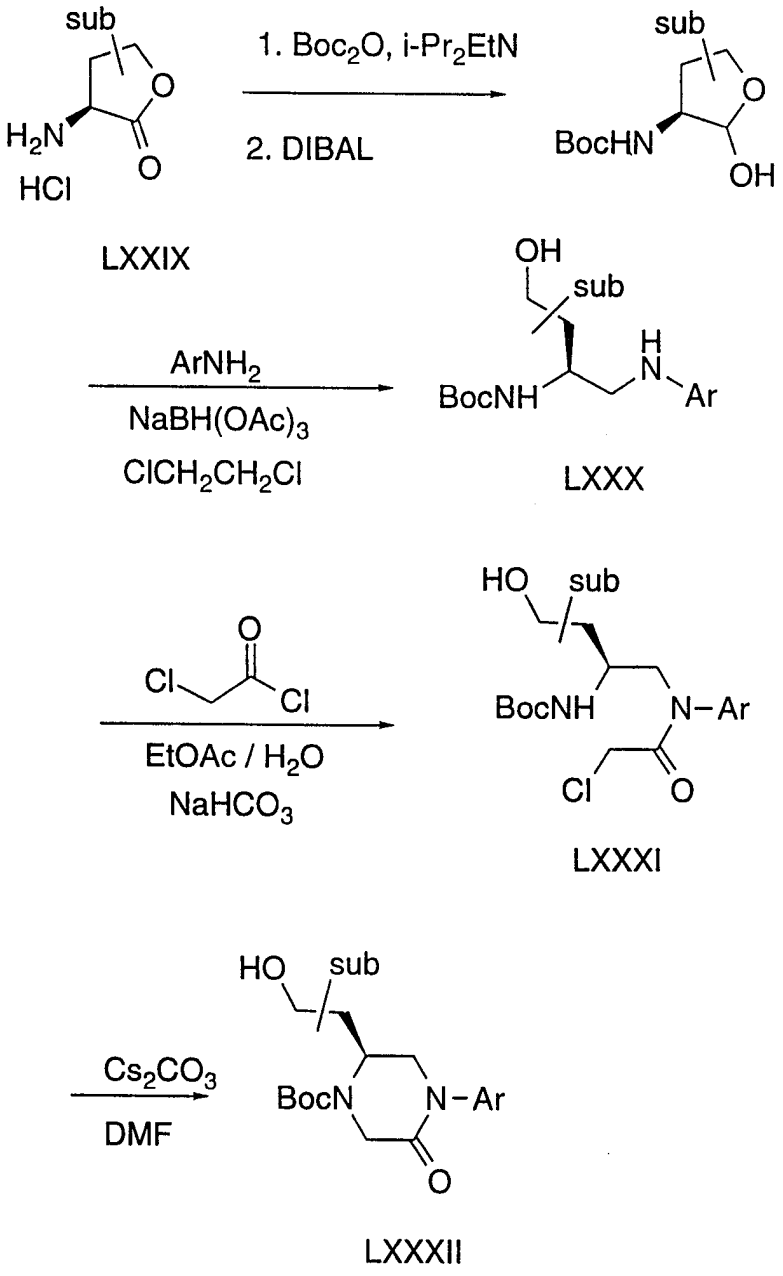


LXXIII

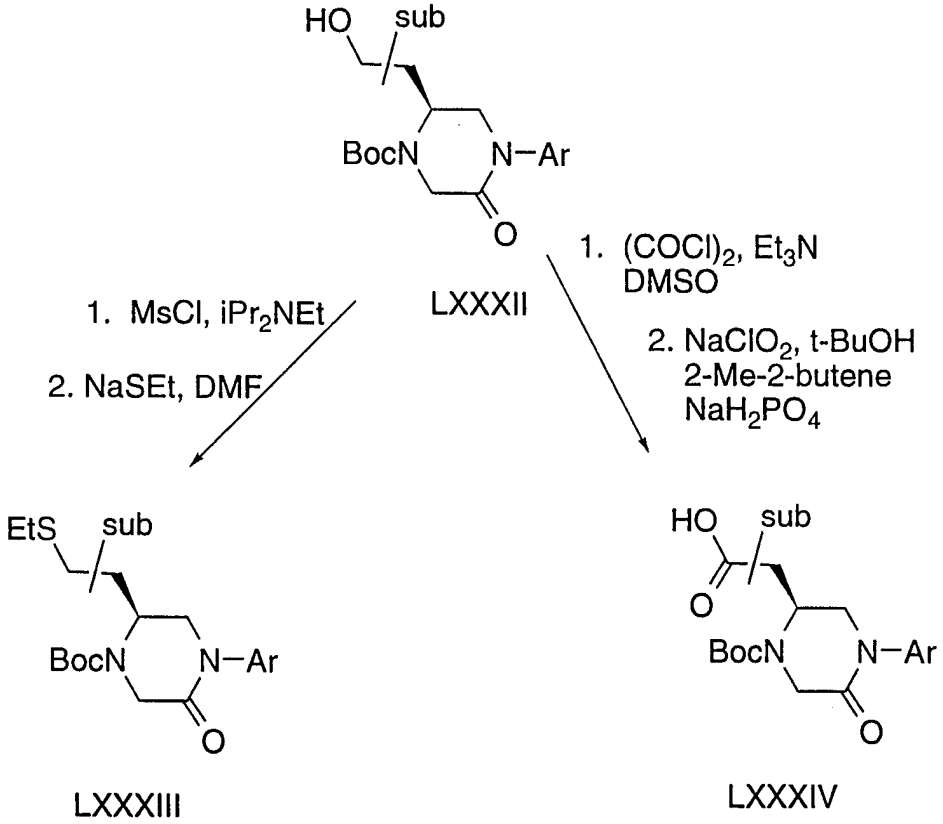
SCHEME 16 (continued)



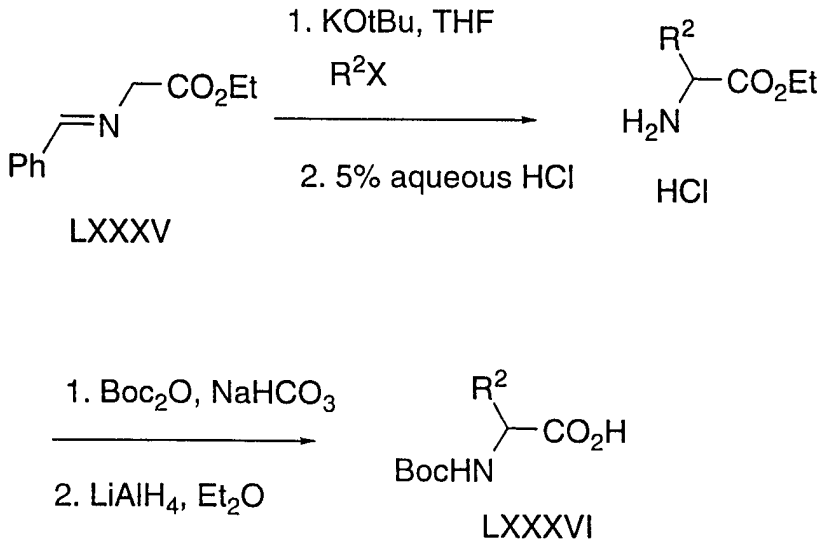
SCHEME 17


sub
1. Boc2O, i-Pr2EtN
2. DIBAL
H2N
HCl
O
BocHN
OH
LXXIX
ArNH2
NaBH(OAc)3
ClCH2CH2Cl
BocNH
N
Ar
LXXX
Cl
EtOAc / H2O
NaHCO3
HO
N−Ar
LXXXI
Cs2CO3
DMF
BocN
LXXXII

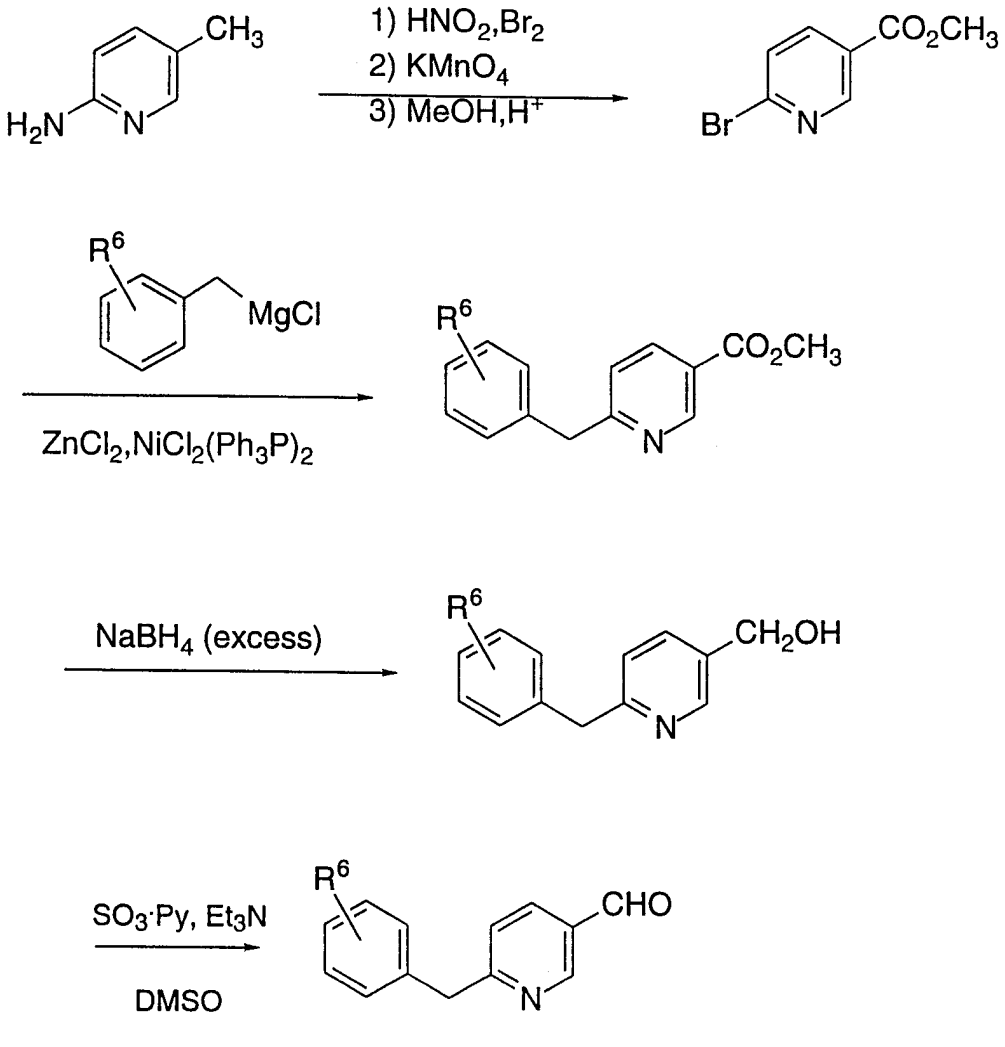
SCHEME 17 (continued)



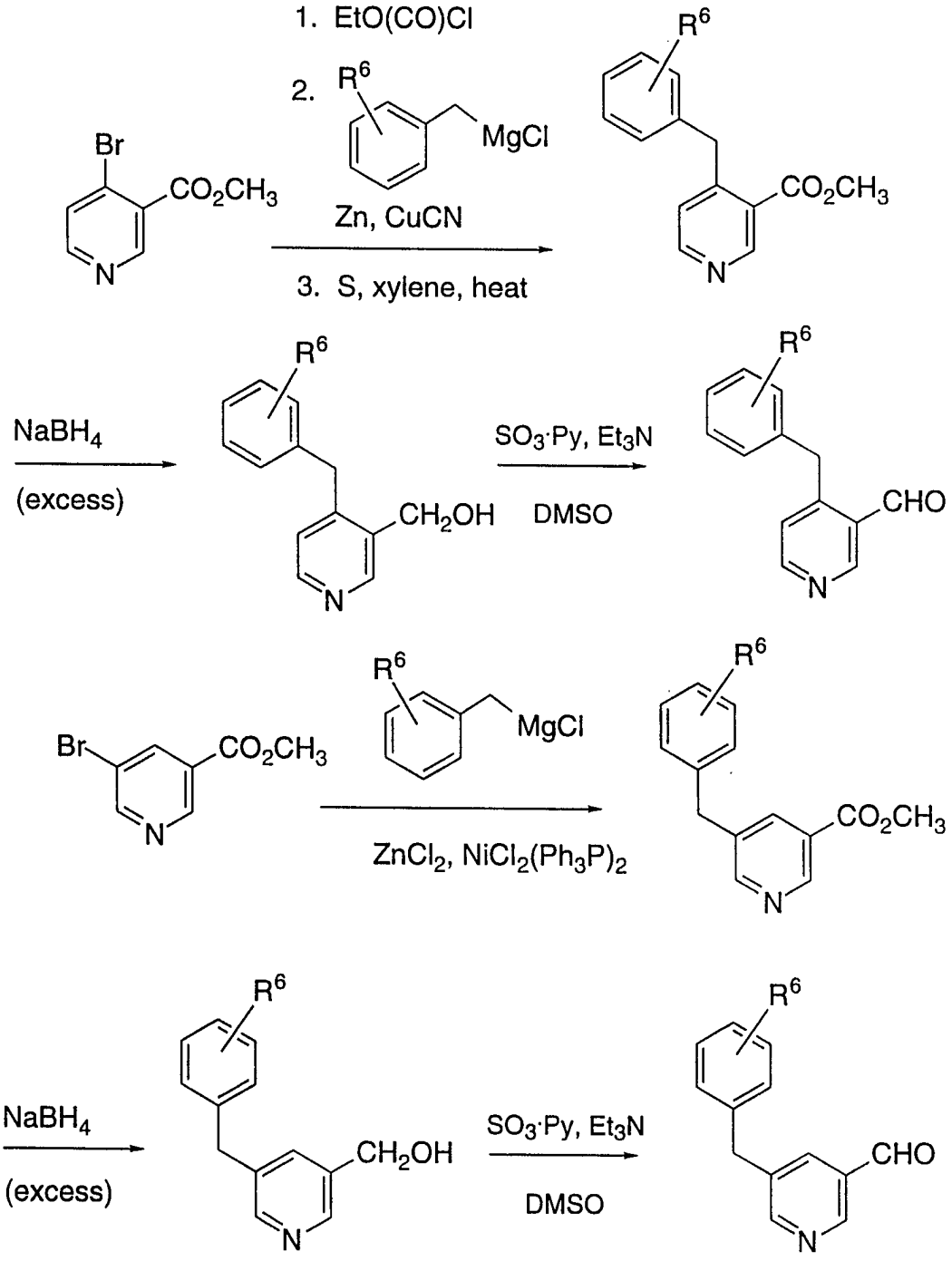
SCHEME 18


1. KOtBu, THF
R2X
2. 5% aqueous HCl
CO2Et
N
Ph
LXXXV
R2
CO2Et
H2N
HCl
1. Boc2O, NaHCO3
2. LiAlH4, Et2O
R2
CO2H
BocHN
LXXXVI

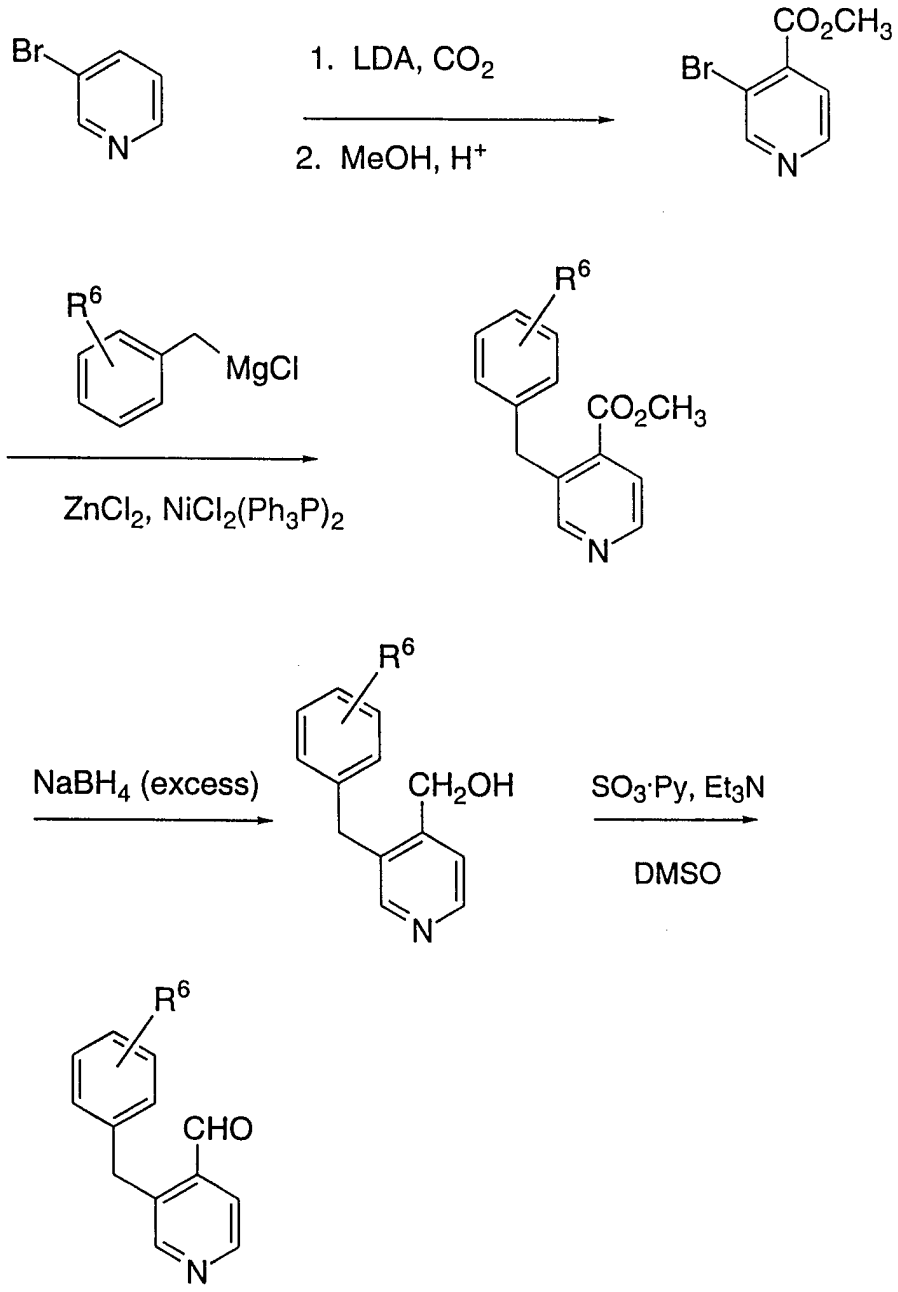
REACTION SCHEME 19



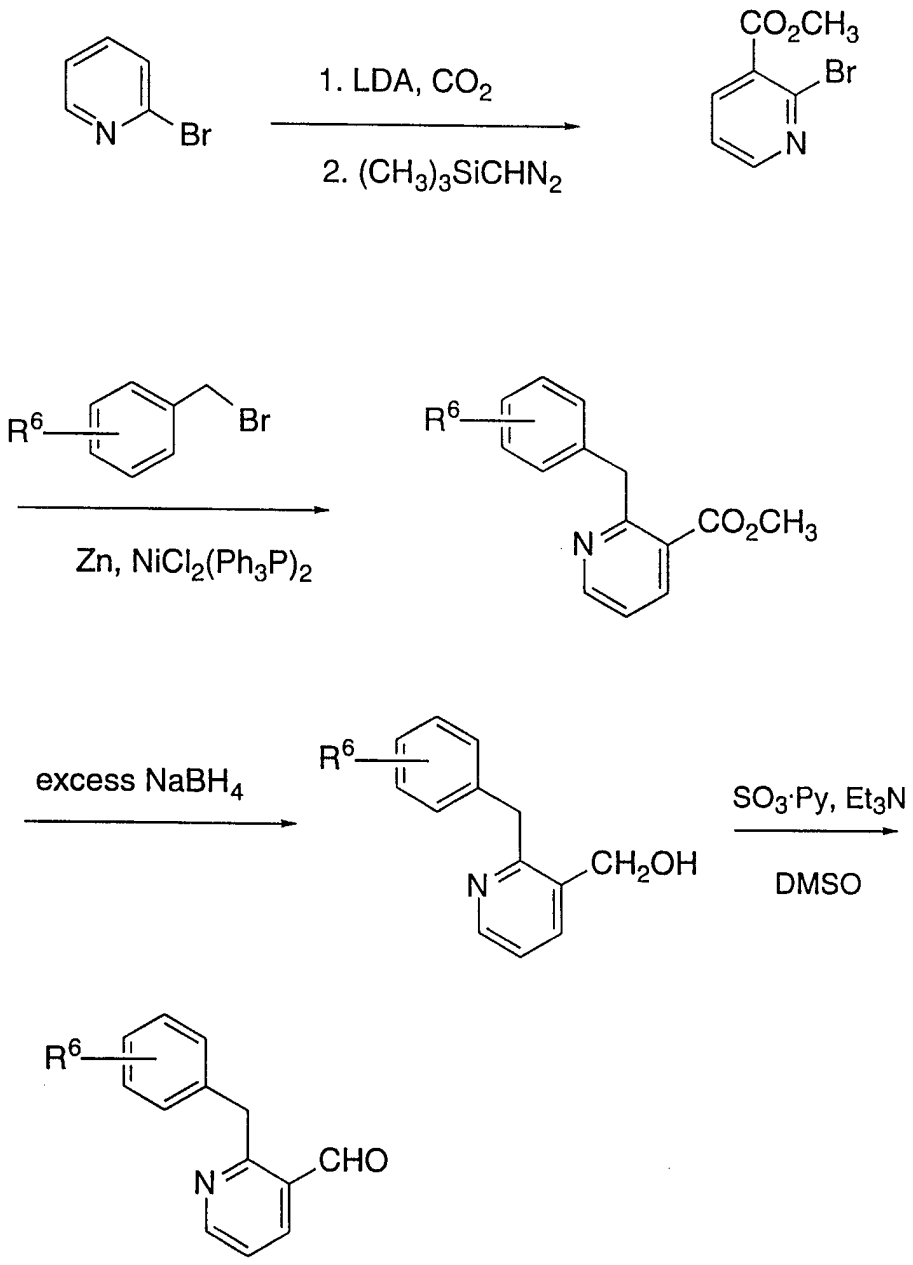
REACTION SCHEME 20



REACTION SCHEME 21



REACTION SCHEME 22



The farnesyl transferase inhibitors of formula (II-d) can be synthesized in accordance with Schemes 23-36, 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^2, R^6 and R^8, as shown in the Schemes, represent the substituents R^2, R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^8; although only one such R^2, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 23-36 by Roman numerals are numbered starting sequentially with I and ending with XXV.

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. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 23-36:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 23-35 illustrate synthesis of the compounds of the formula II-d which incorporate a preferred benzylimidazolyl sidechain. In Scheme 23, for example, a biaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted phenyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated benzoic acid, such as 4-bromobenzoic acid, to provide the biaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 24-27 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 23. Thus, Scheme 24 illustrates the analogous series of biaryl alcohol forming reactions starting with the halogenated biarylaldehyde.

Scheme 25 illustrates the reaction wherein the "terminal" phenyl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 26.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the biaryl component of the instant compounds, as shown in Scheme 27. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted aryl halide in the presence of nickel (II) to provide the biaryl VII. The aryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 28 illustrates the preparation of a suitably substituted biphenylmethyl bromide which could also be utilized in the reaction with the protected imidazole as described in Scheme 1.

As illustrated in Scheme 29, the sequence of coupling reactions may be modified such that the biphenyl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted phenyl boronic acid.

Scheme 30 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 31 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkyl-imidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well

known in the art with various activated biaryl moieties to provide the instant compounds shown.

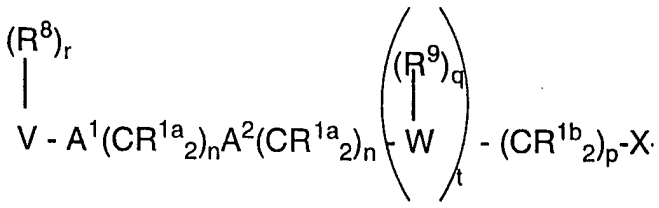
Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 32. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Scheme 33 illustrates an analogous series of reactions wherein the $(CR^{1b}{}_2)_pX(CR^{1b}{}_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted haloaryl alcohol, such as, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a second aryl moiety by Suzuki chemistry to provide the instant compound.

Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 34. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 23) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Grignard chemistry may also be employed to form a substituted alkyl linker between the biaryl and the preferred W (imidazolyl) as shown in Scheme 35. Similar substituent manipulation as shown in Scheme 34 may be performed on the fully functionalized compound which incorporates an R^{1b} hydroxyl moiety.

Scheme 36 illustrates reactions wherein the moiety

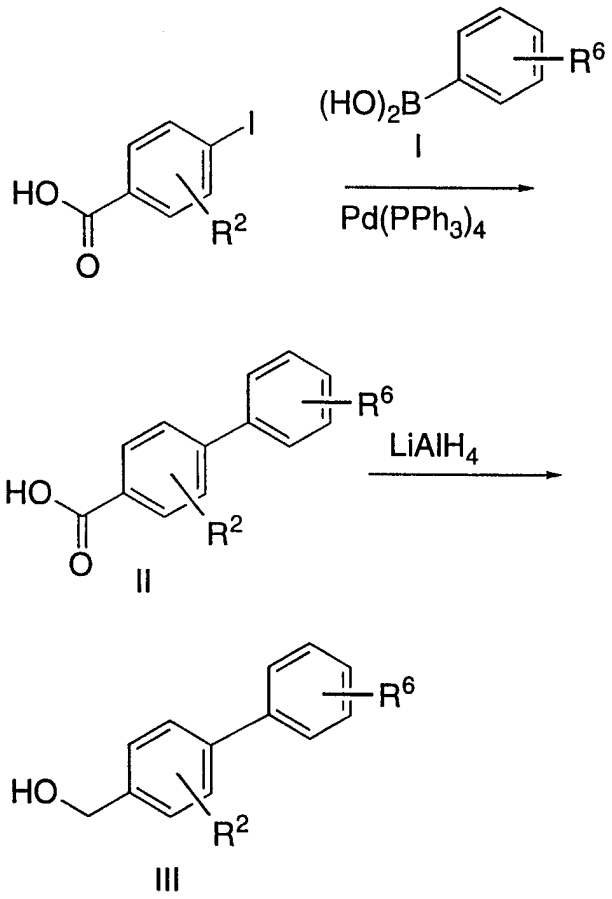


incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

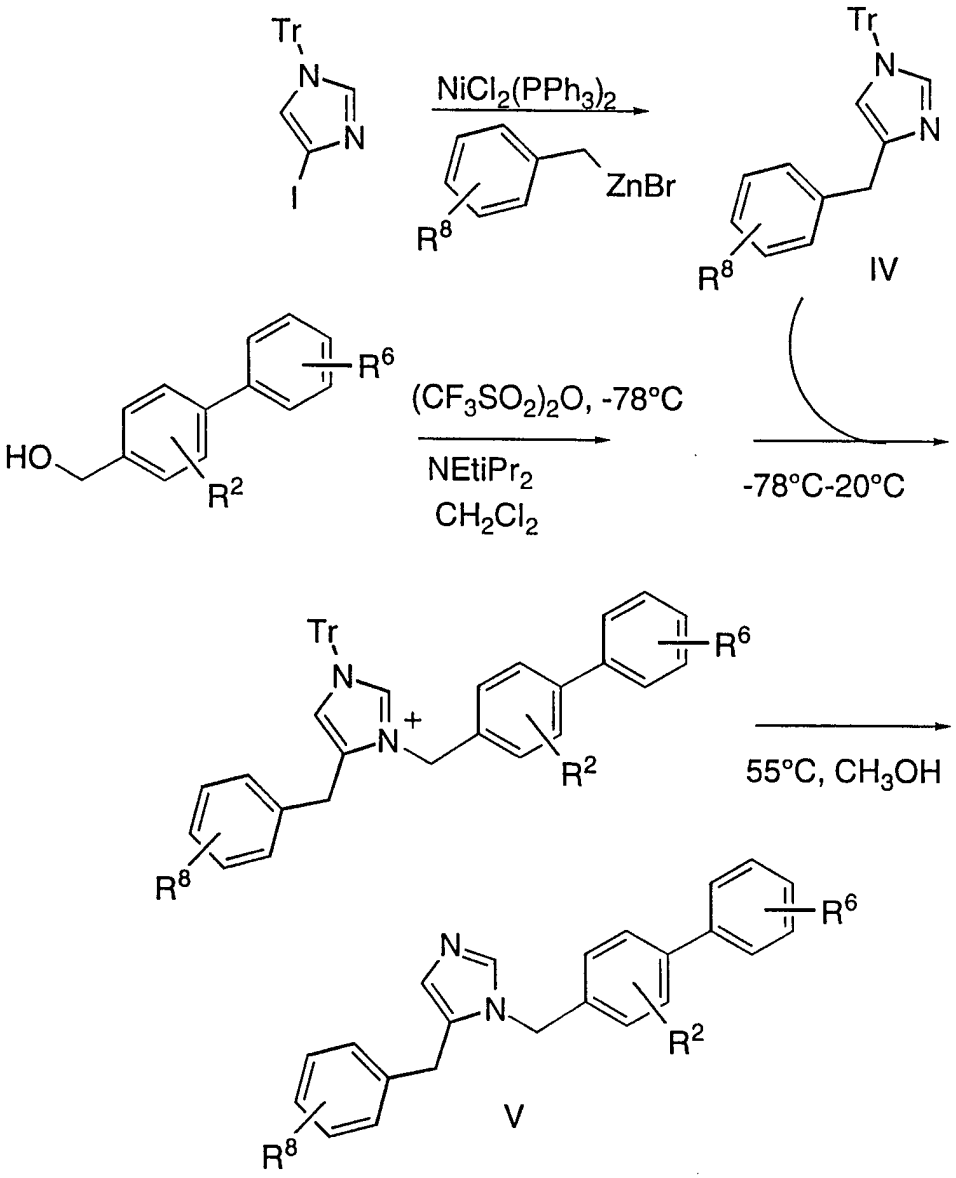
Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other biheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 14). Grignard chemistry may be utilized, as shown in Scheme 36, to incorporate the biaryl moiety. Thus, a suitably substituted biaryl Grignard reagent is reacted with an aldehyde to provide the C-alkylated instant compound XXI. Compound **XXI** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 36 and the intermediates manipulated as illustrated above in Schemes 4-9.

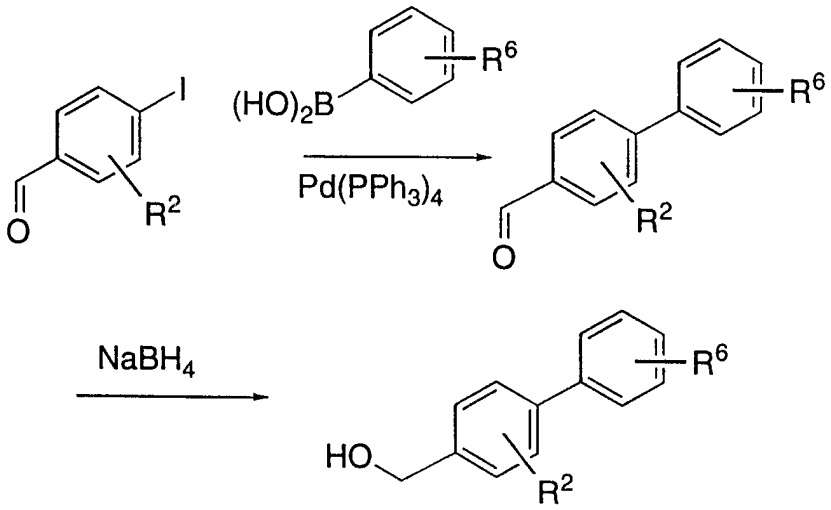
SCHEME 23



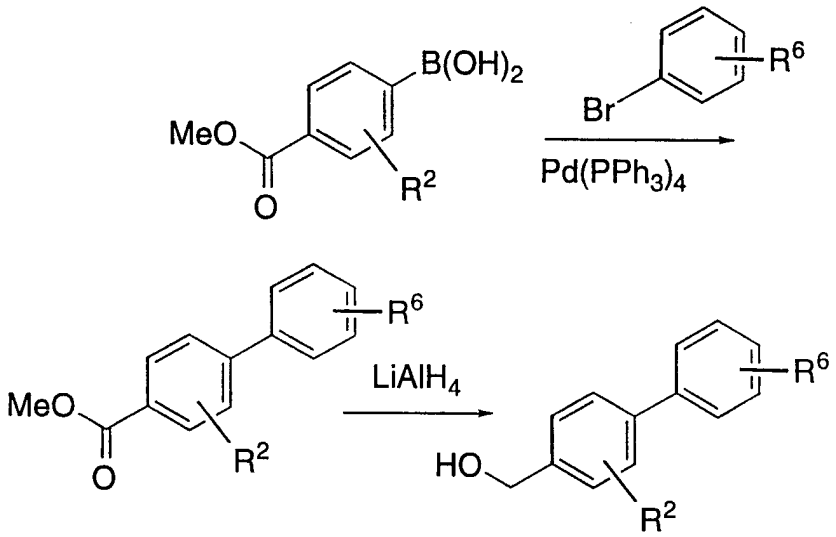
SCHEME 23 (continued)



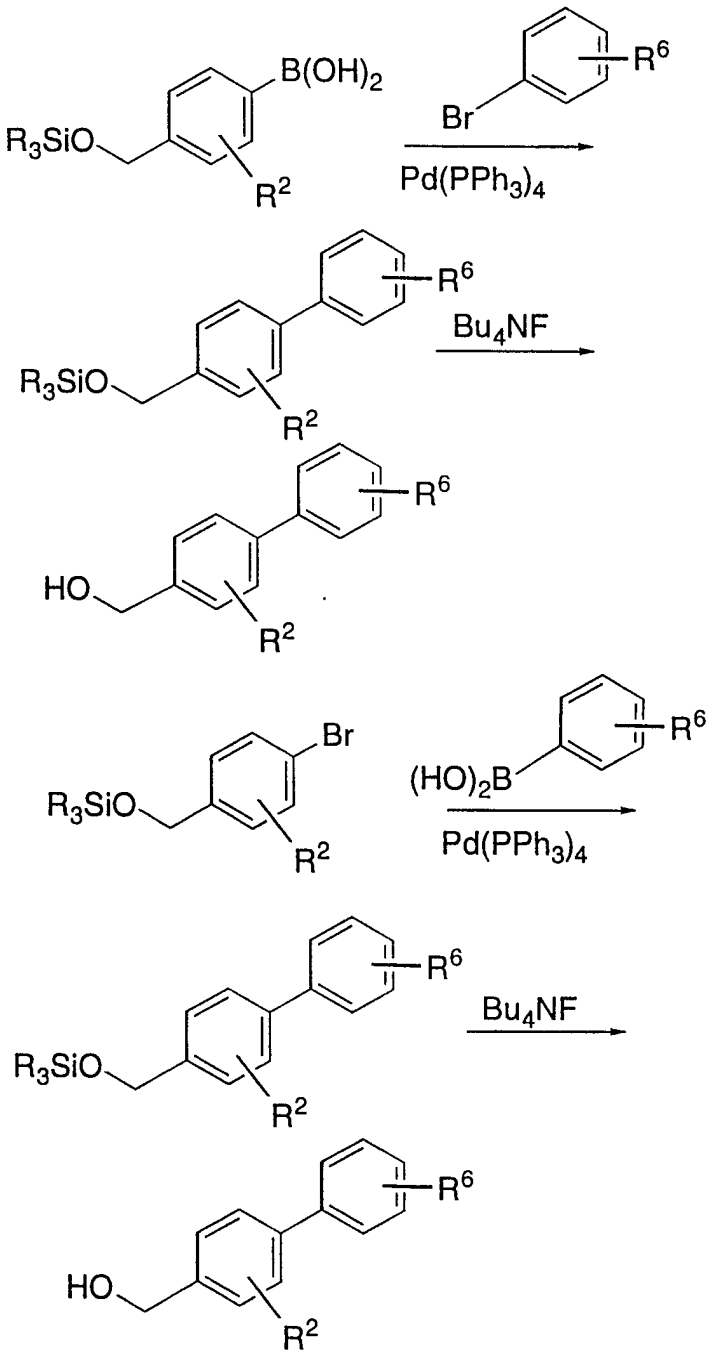
SCHEME 24



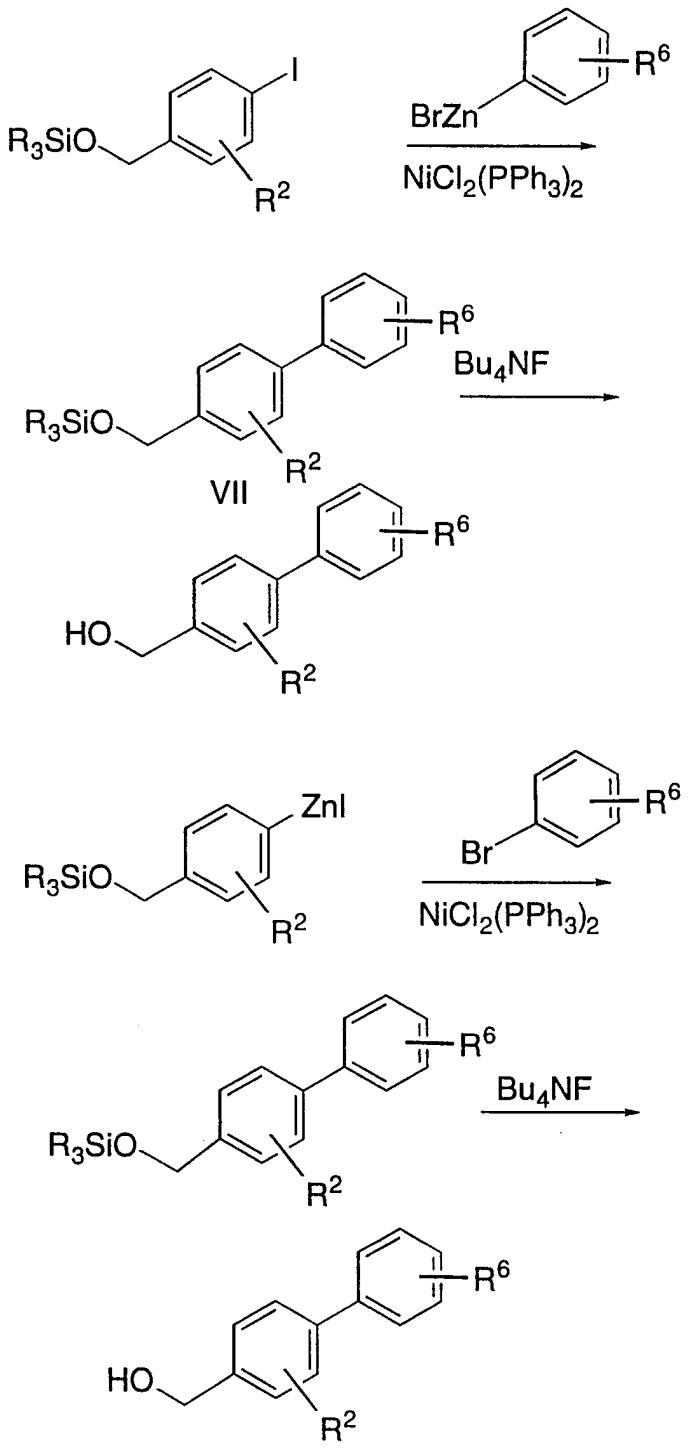
SCHEME 25



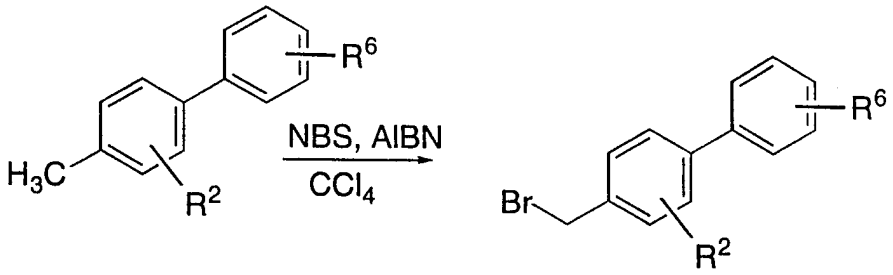
SCHEME 26



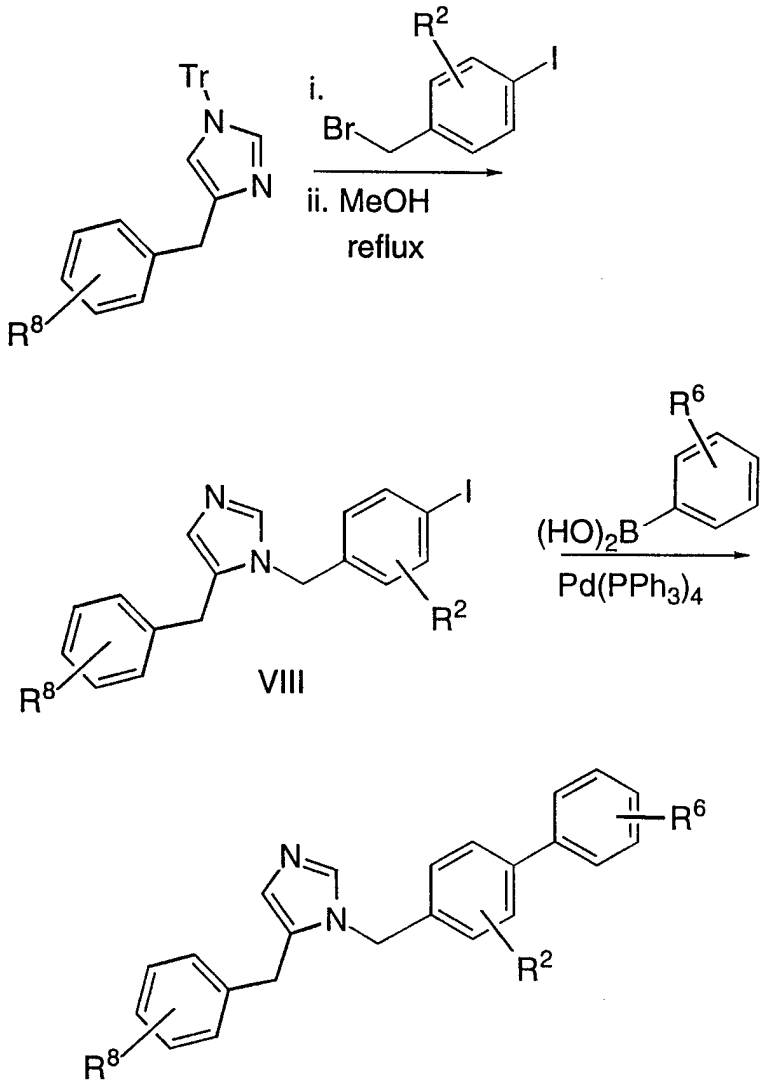
SCHEME 27


I
R3SiO
R2
BrZn
R6
NiCl2(PPh3)2
R6
Bu4NF
R3SiO
R2
VII
R6
HO
R2
ZnI
R3SiO
R2
Br
R6
NiCl2(PPh3)2
R6
Bu4NF
R3SiO
R2
R6
HO
R2

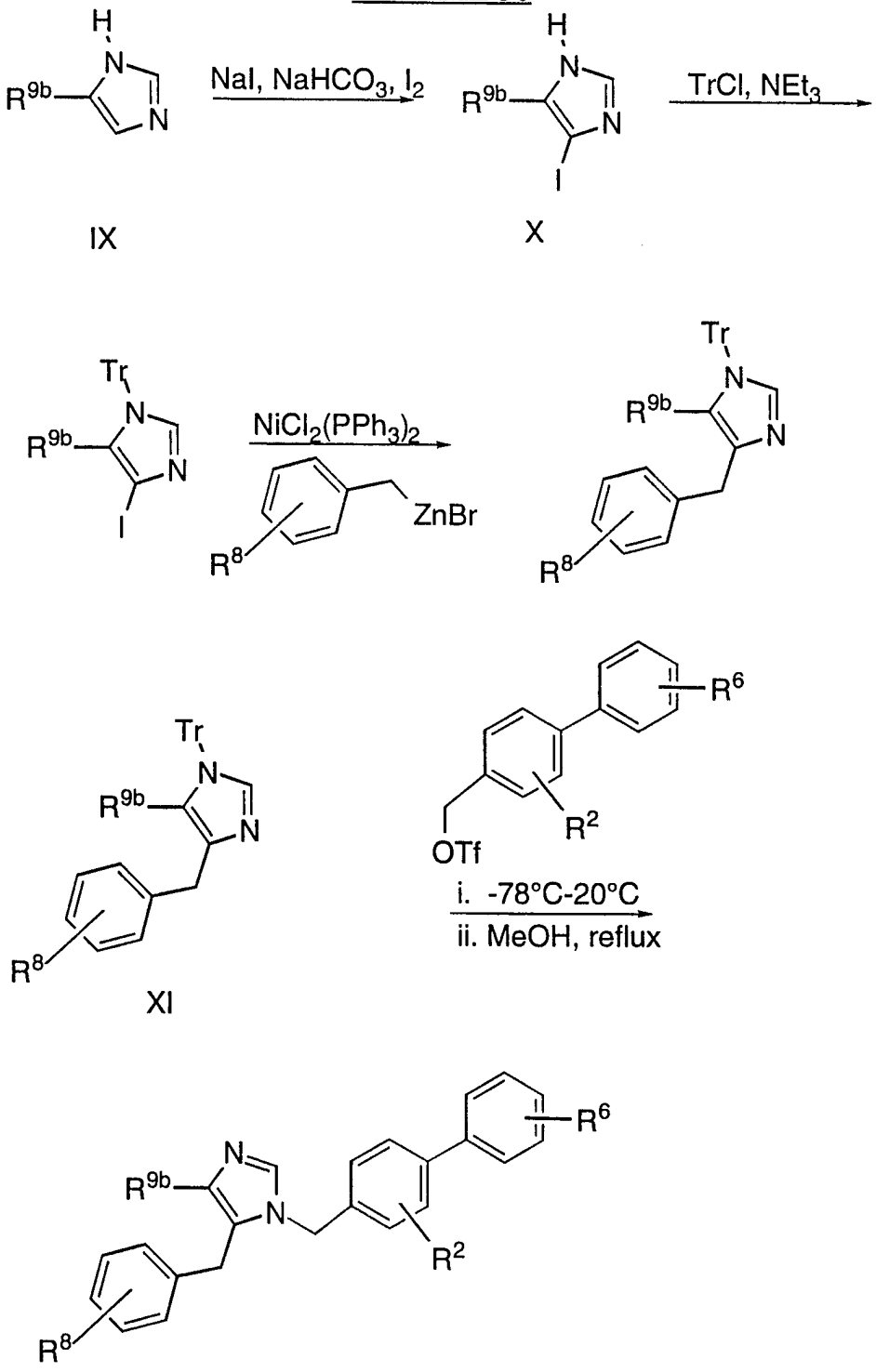
SCHEME 28



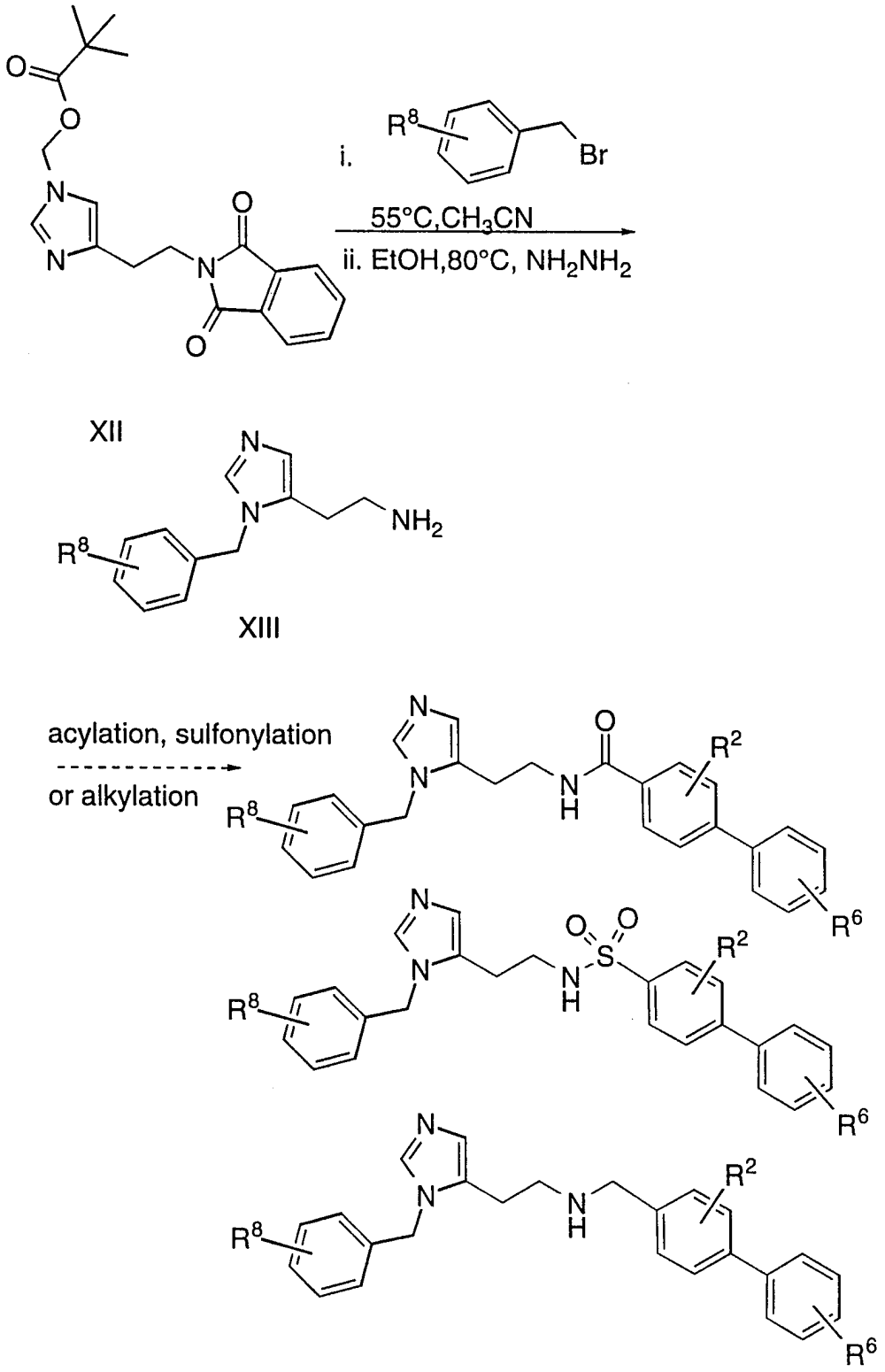
SCHEME 29



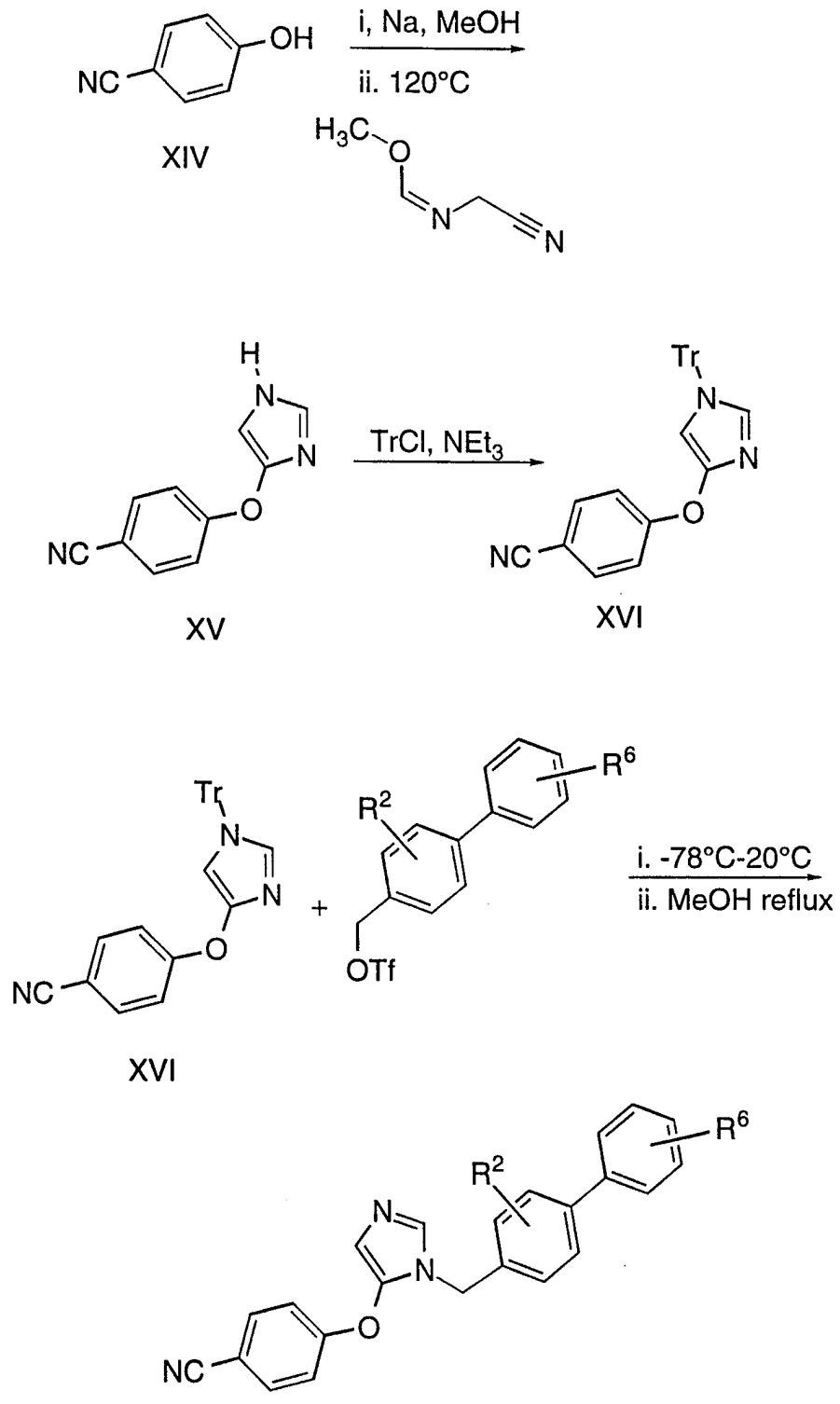
SCHEME 30


NaI, NaHCO3, I2
TrCl, NEt3
IX
X
NiCl2(PPh3)2
ZnBr
XI
OTf
i. -78°C-20°C
ii. MeOH, reflux

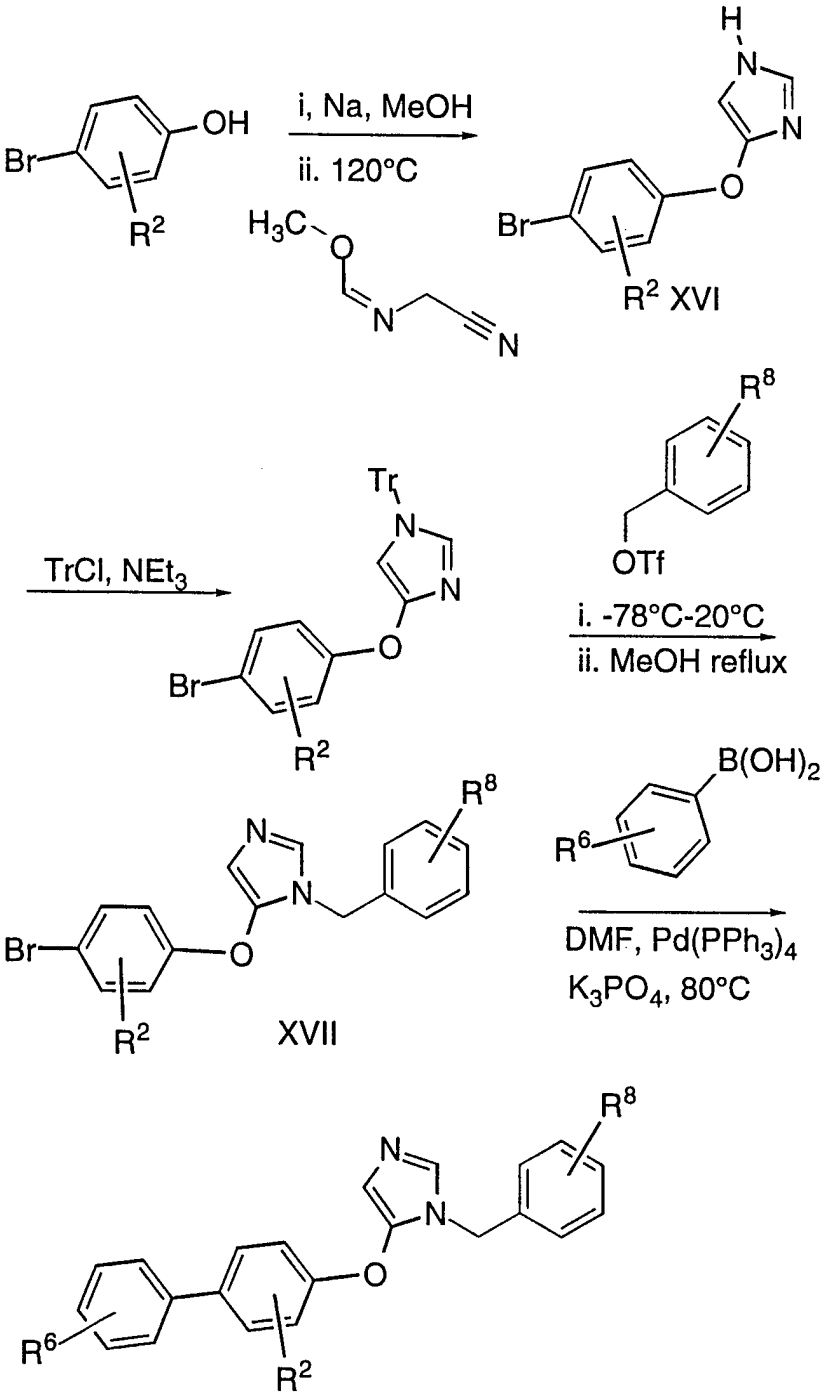
SCHEME 31


i.
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
XII
XIII
acylation, sulfonylation
or alkylation

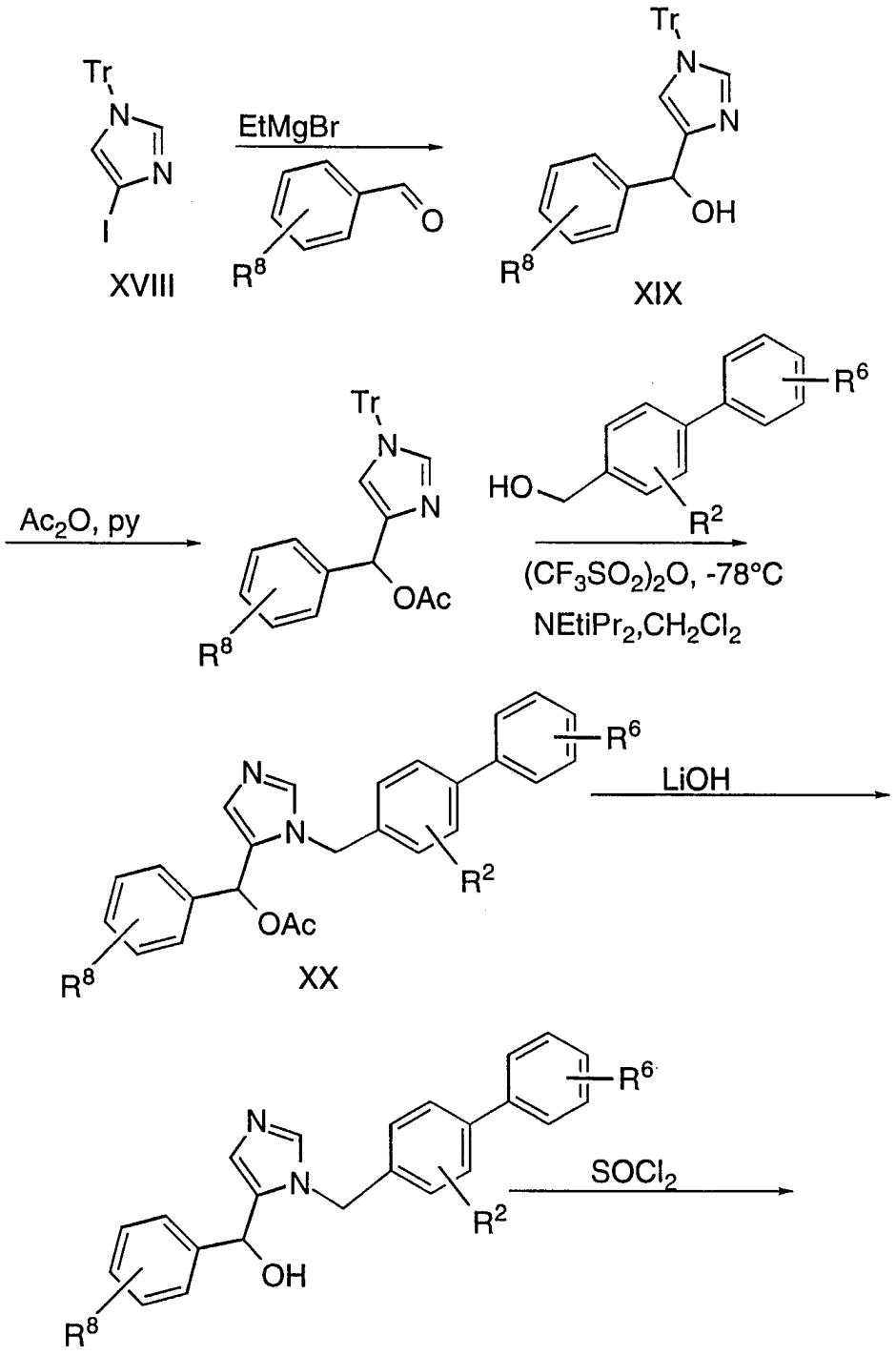
SCHEME 32


OH
NC
i, Na, MeOH
ii. 120°C
XIV
H_3C
O
N
N
H
N
N
O
NC
XV
TrCl, NEt_3
Tr
N
N
O
NC
XVI
Tr
N
N
O
NC
XVI
+
R^2
R^6
OTf
i. -78°C-20°C
ii. MeOH reflux
R^2
R^6
N
N
O
NC

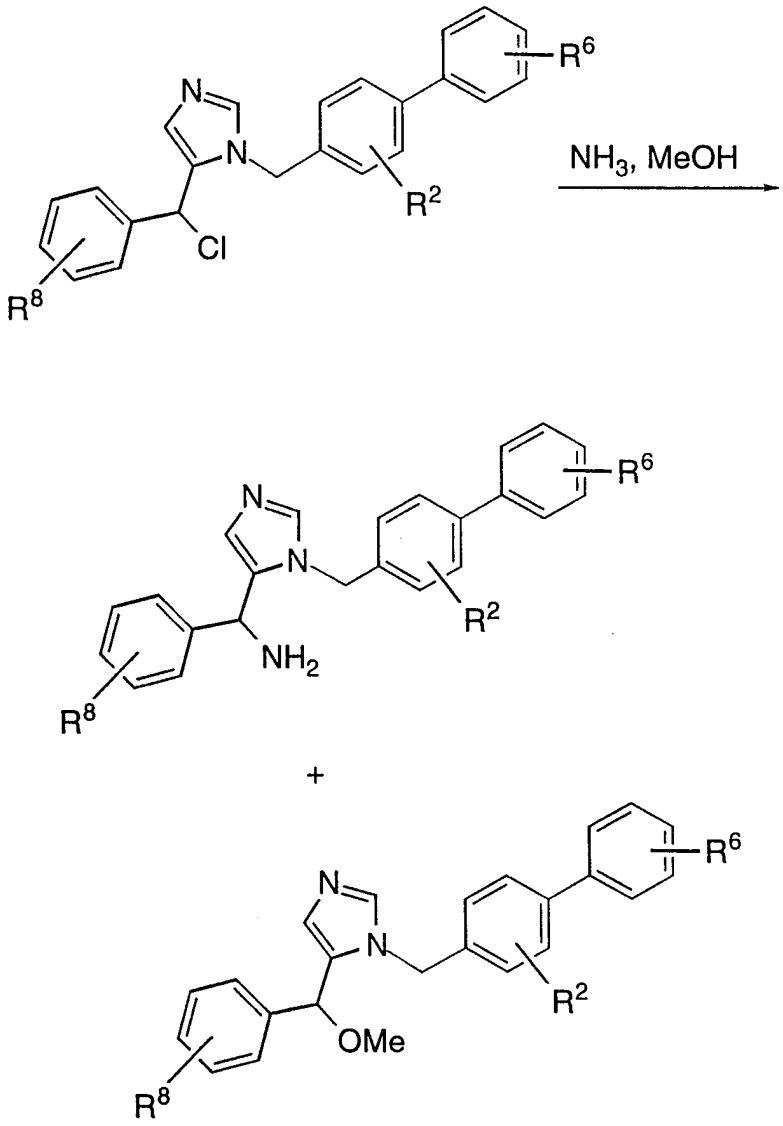
SCHEME 33


i, Na, MeOH
ii. 120°C
TrCl, NEt3
i. -78°C-20°C
ii. MeOH reflux
DMF, Pd(PPh3)4
K3PO4, 80°C
XVI
XVII

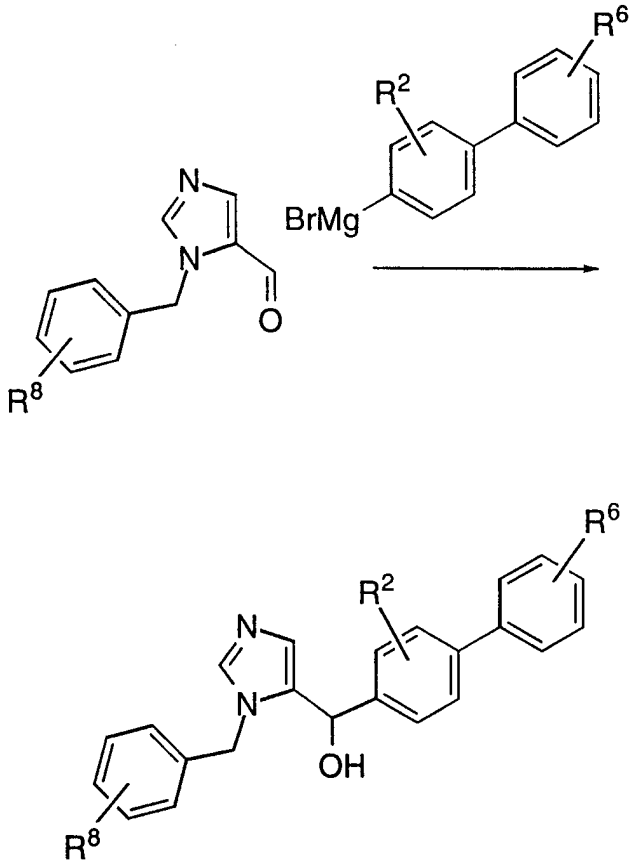
SCHEME 34


Tr
N
N
I
XVIII
EtMgBr
O
R8
Tr
N
N
OH
R8
XIX
R6
HO
R2
Ac2O, py
Tr
N
N
OAc
R8
(CF3SO2)2O, -78°C
NEtiPr2,CH2Cl2
R6
N
N
R2
OAc
R8
XX
LiOH
R6
N
N
R2
OH
R8
SOCl2

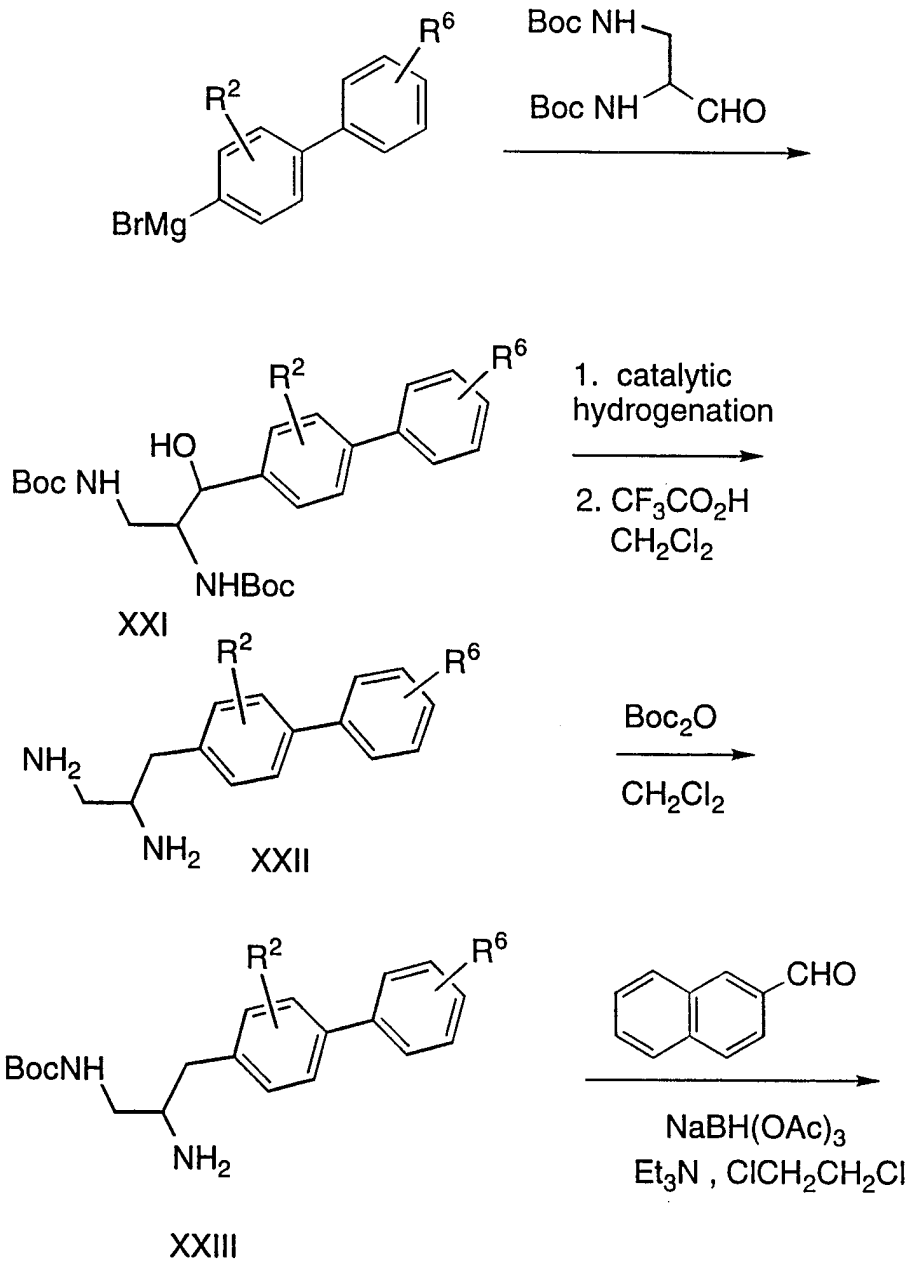
SCHEME 34 (continued)



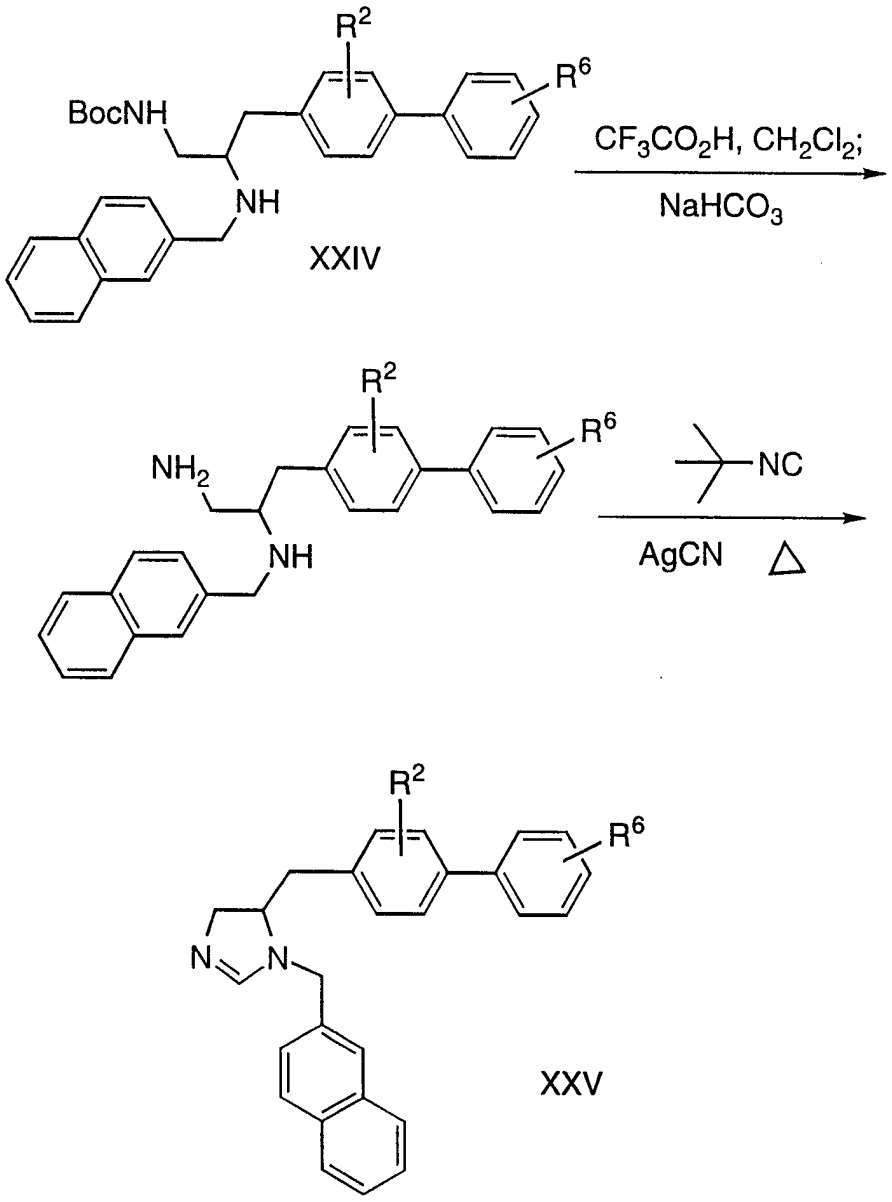
SCHEME 35



SCHEME 36


R6
R2
BrMg
Boc NH
Boc NH
CHO
R2
R6
HO
Boc NH
NHBoc
XXI
1. catalytic hydrogenation
2. CF3CO2H
CH2Cl2
R2
R6
NH2
NH2
XXII
Boc2O
CH2Cl2
R2
R6
BocNH
NH2
XXIII
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl

SCHEME 36 (continued)



The farnesyl transferase inhibitors of formula (II-e) can be synthesized in accordance with Schemes 37-52, 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^2, R^6 and R^8, as shown in

the Schemes, represent the substituents R^2, R^3, R^4, R^5, R^6 and R^8; although only one such R^2, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 37-52 by Roman numerals are numbered starting sequentially with I and ending with XXV.

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. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 37-52:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 37-51 illustrate synthesis of the instant arylheteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 37, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated benzoic acid, such as 4-bromobenzoic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 38-41 illustrate other methods of synthesizing

the key alcohol intermediates, which can then be processed as described in Scheme 1. Thus, Scheme 38 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the halogenated arylaldehyde.

Scheme 39 illustrates the reaction wherein the "terminal" heteroaryl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 40.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant compounds, as shown in Scheme 41. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted aryl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 42 illustrates the preparation of the suitably substituted arylheteroaryl methanol from the pyridyltoluene.

Scheme 43 illustrates the preparation of the suitably substituted pyrazinylaryl methanol starting with alanine.

As illustrated in Scheme 44, the sequence of coupling reactions may be modified such that the arylheteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted heteroaryl boronic acid.

Scheme 45 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 46 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the arylheteroaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 47. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the phenylmethylimidazoles hereinabove.

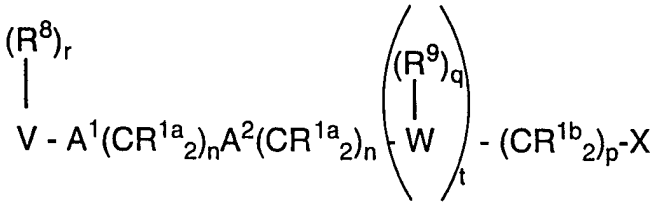
Scheme 48 illustrates an analogous series of reactions wherein the $(CR^{1b}{}_2)_pX(CR^{1b}{}_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted haloaryl alcohol, such as 4-bromophenol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a heteroaryl moiety by Suzuki chemistry to provide the instant compound.

Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 49. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 37) provides the instant compound XX. If other R^1 substituent s are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the arylheteroaryl and the preferred W (imidazolyl) as shown in Scheme 50. Thus a halogenated arylheteroaryl, such as 4-(3-pyridyl)bromobenzene, may undergo metal halogen exchange followed by reaction with a suitably substituted imidazolyl aldehyde and acteylation to form the alcohol. Then, similar substituent manipulation as shown in Scheme 49 may be performed on a fully functionalized compound which incorporates an R^2 hydroxyl moiety.

Scheme 51 illustrates the synthesis of a suitably substituted pyrimidinebromobenzene, which may be employed in the reaction illustrated in Scheme 49. This reaction and other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979).

Schemes 52 illustrates reactions wherein the moiety



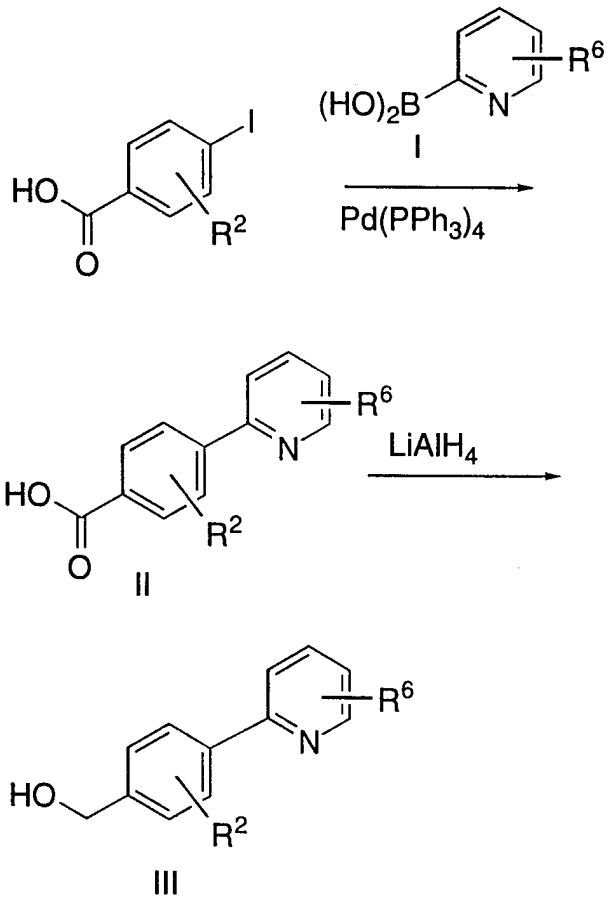
incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid. Metalation chemistry may be utilized, as shown in Scheme 52, to incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl lithium reagent, prepared in situ, is reacted with an aldehyde to provide the C-alkylated instant compound XXI. Compound **XXI** can be deoxygenated by methods known in the art, such as a

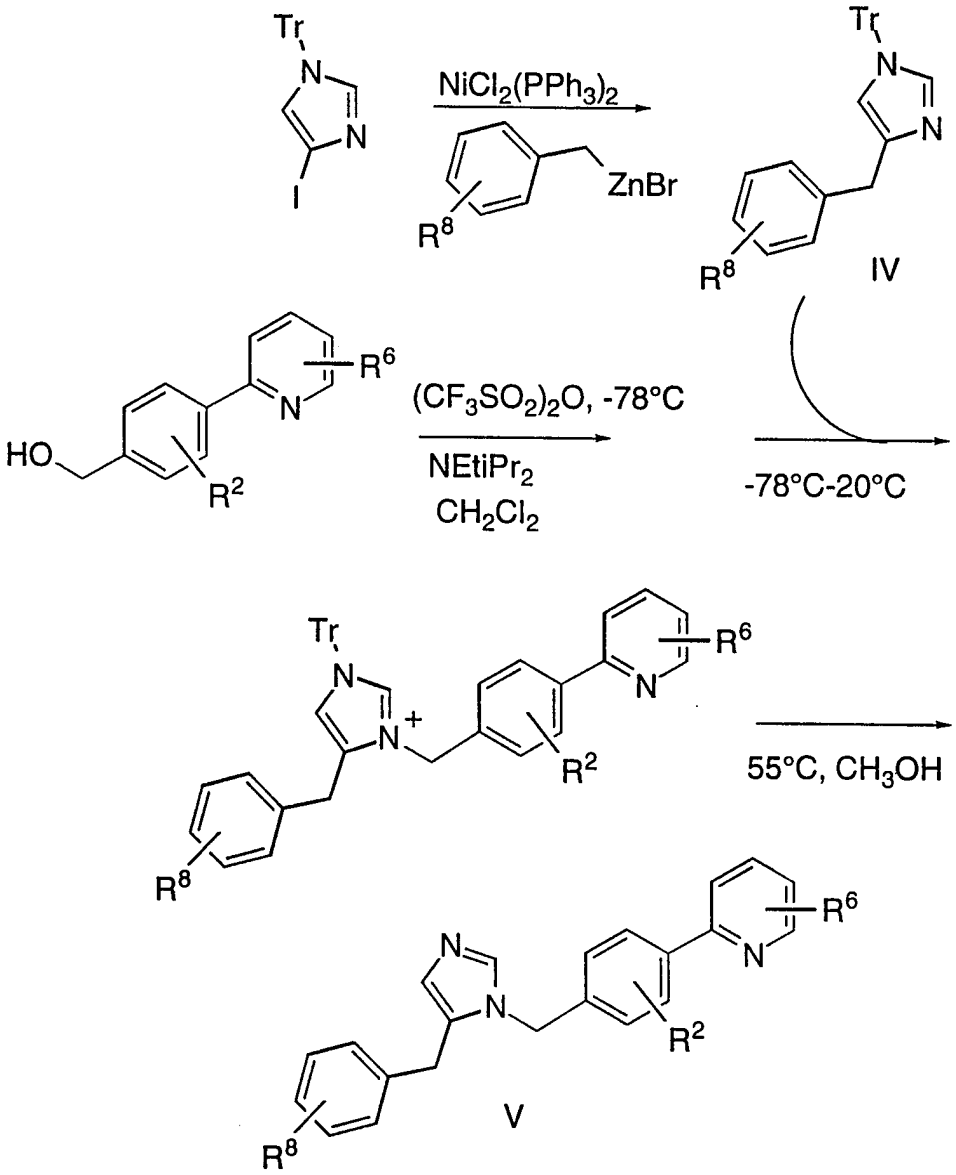
catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 52 and the intermediates manipulated as illustrated above in Schemes 4-9.

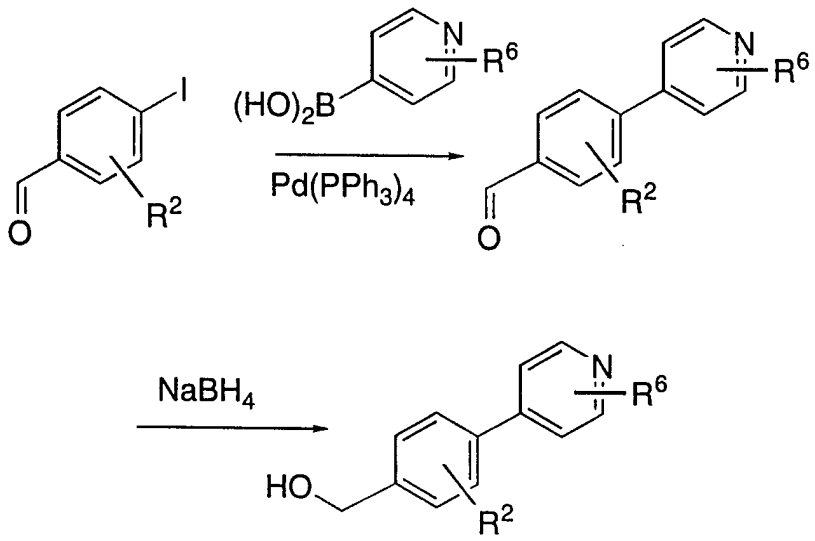
SCHEME 37



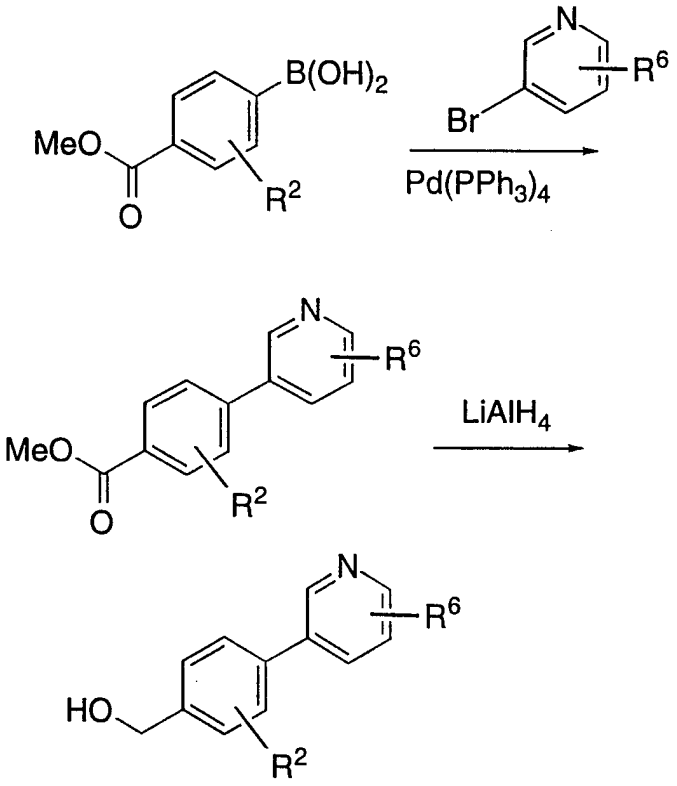
SCHEME 37 (continued)



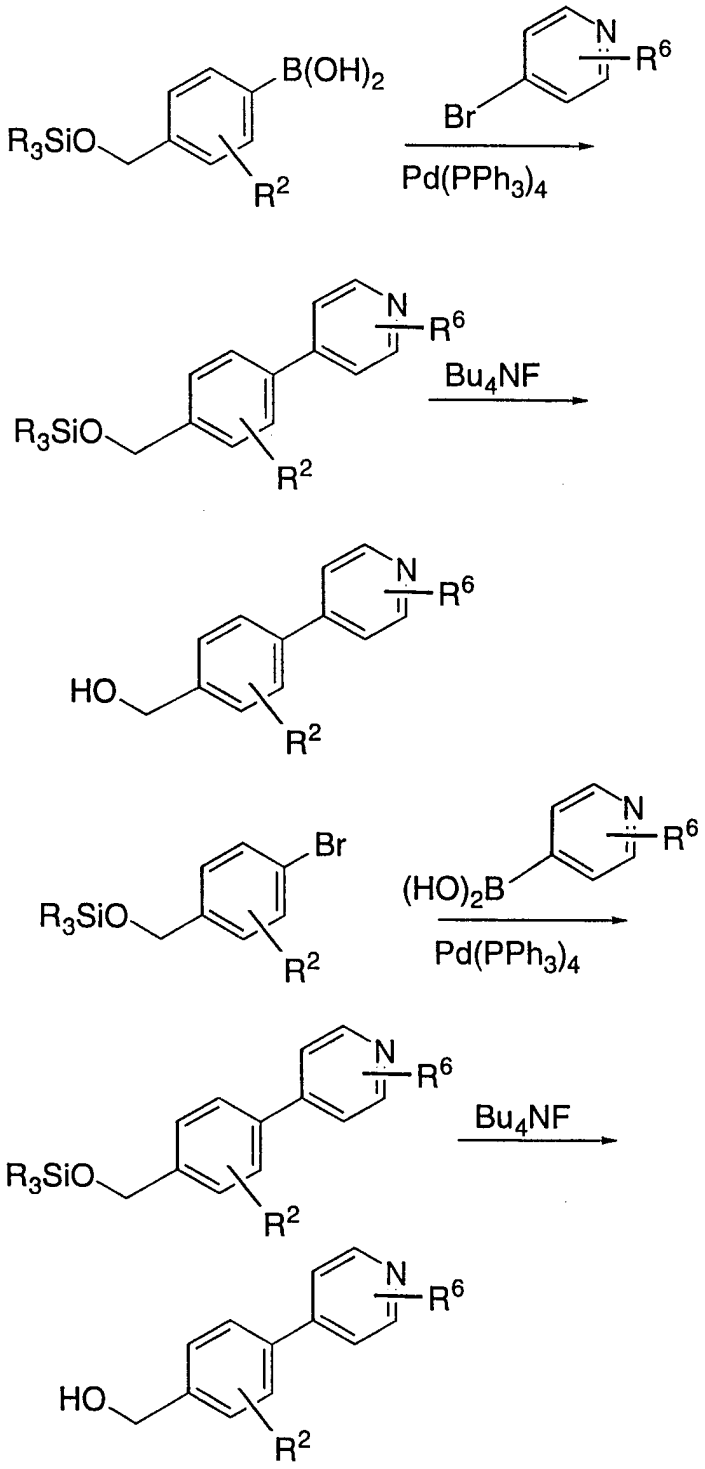
SCHEME 38



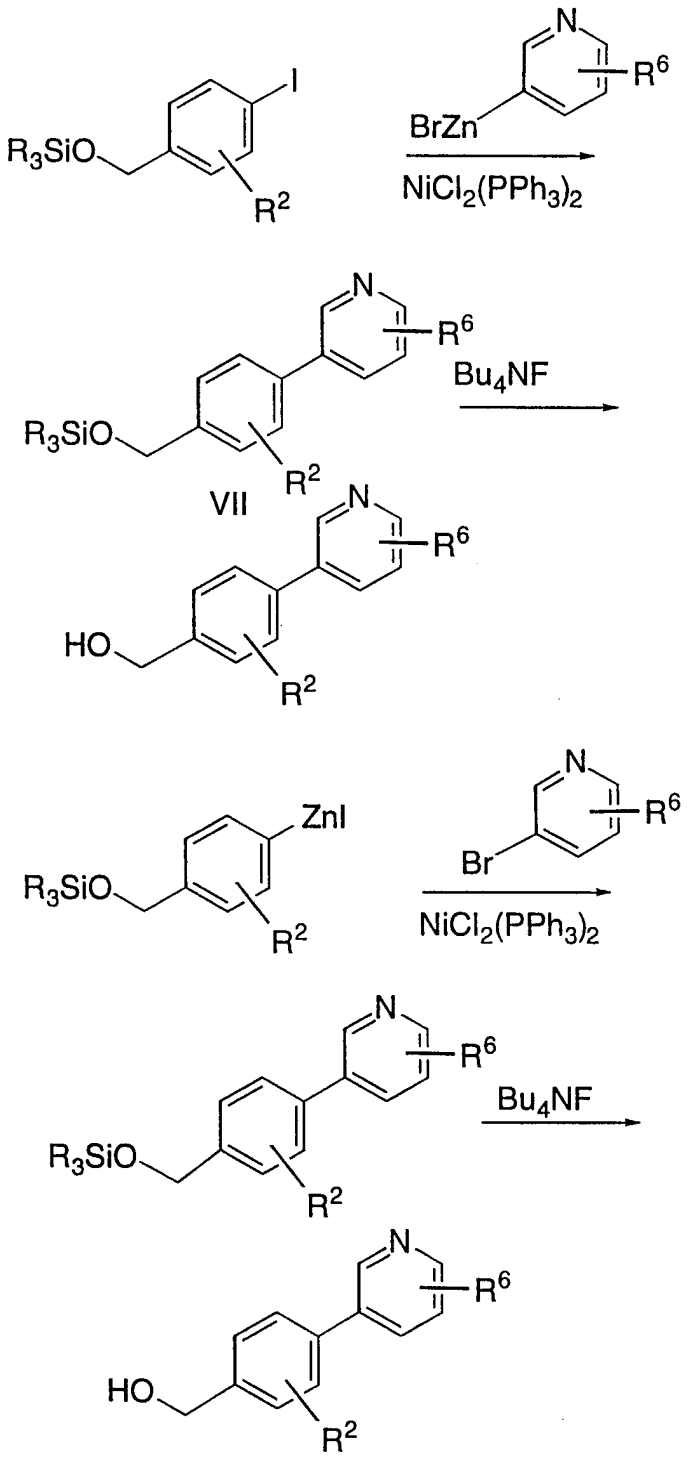
SCHEME 39



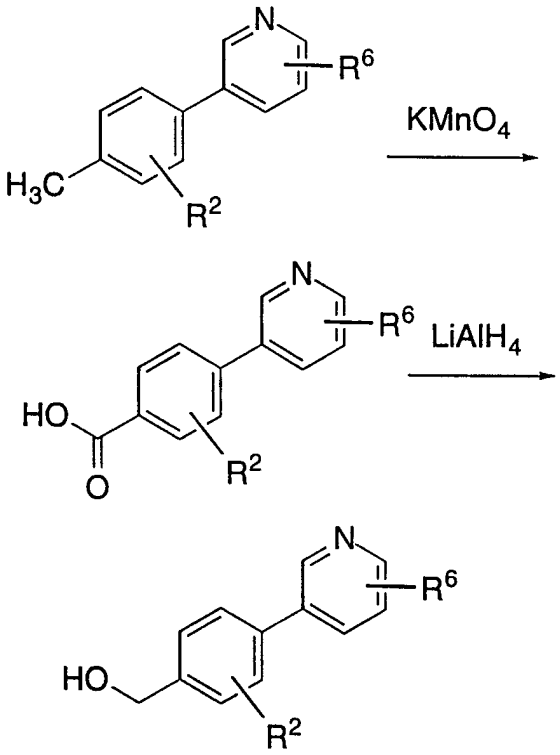
SCHEME 40



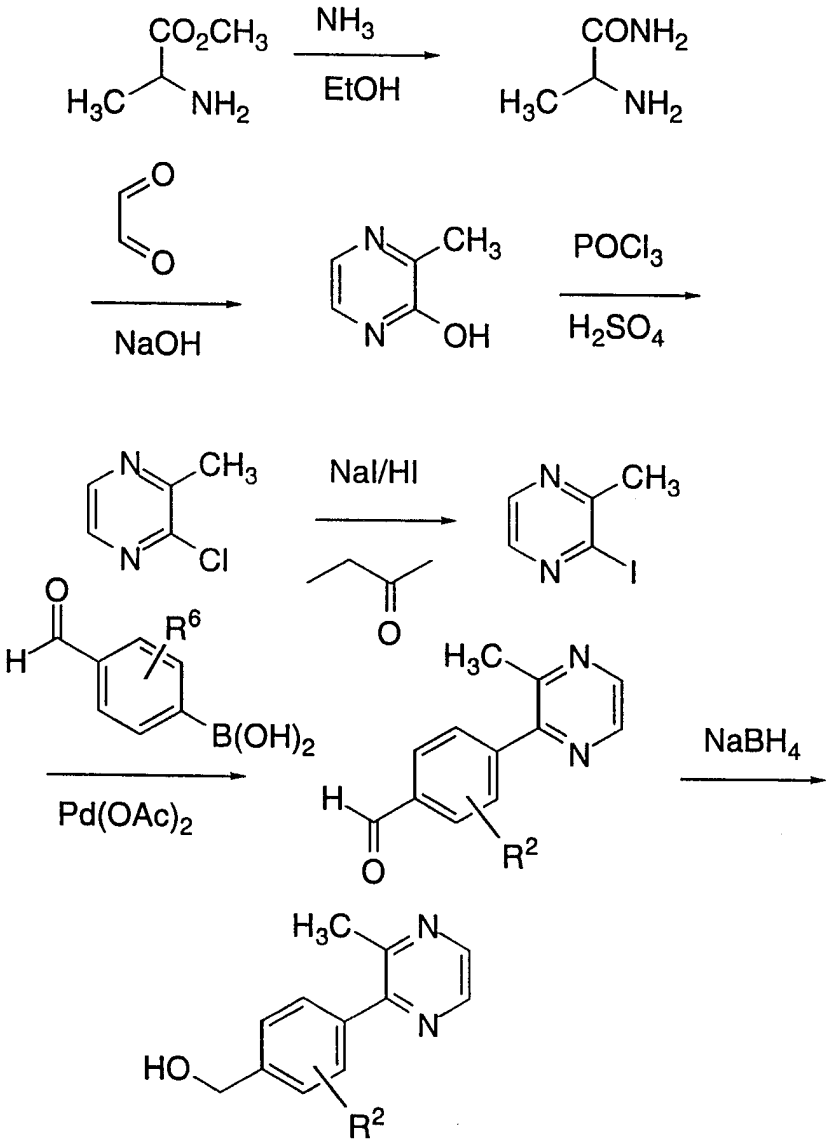
SCHEME 41



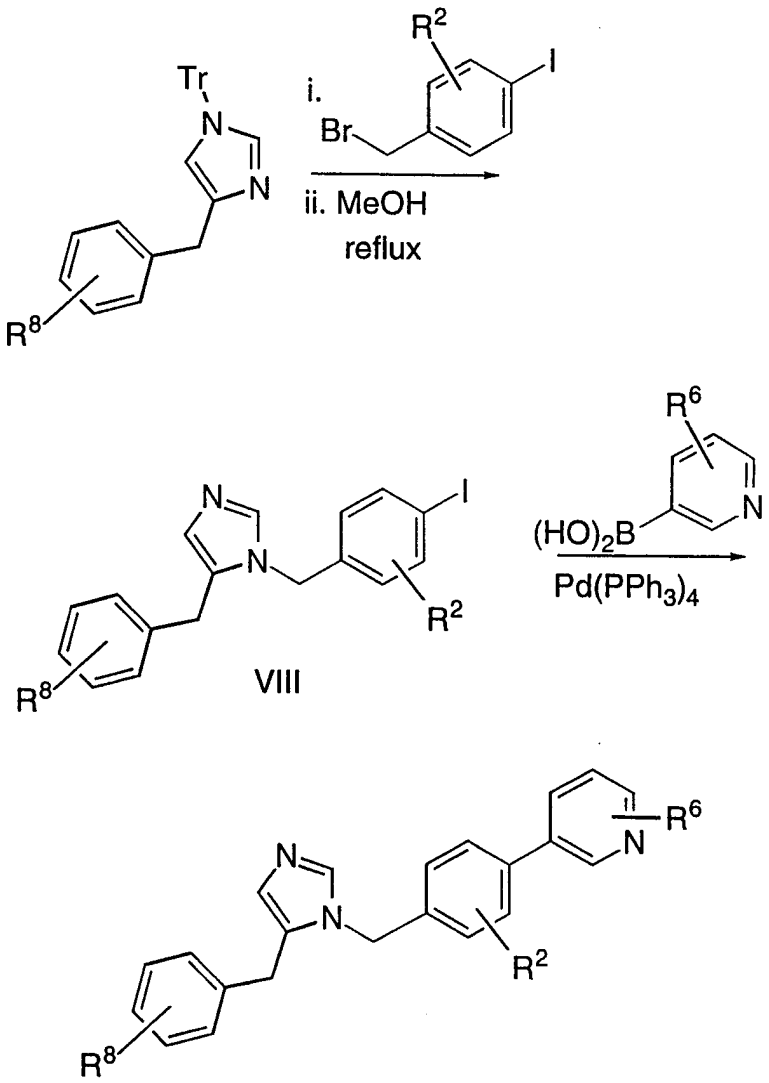
SCHEME 42



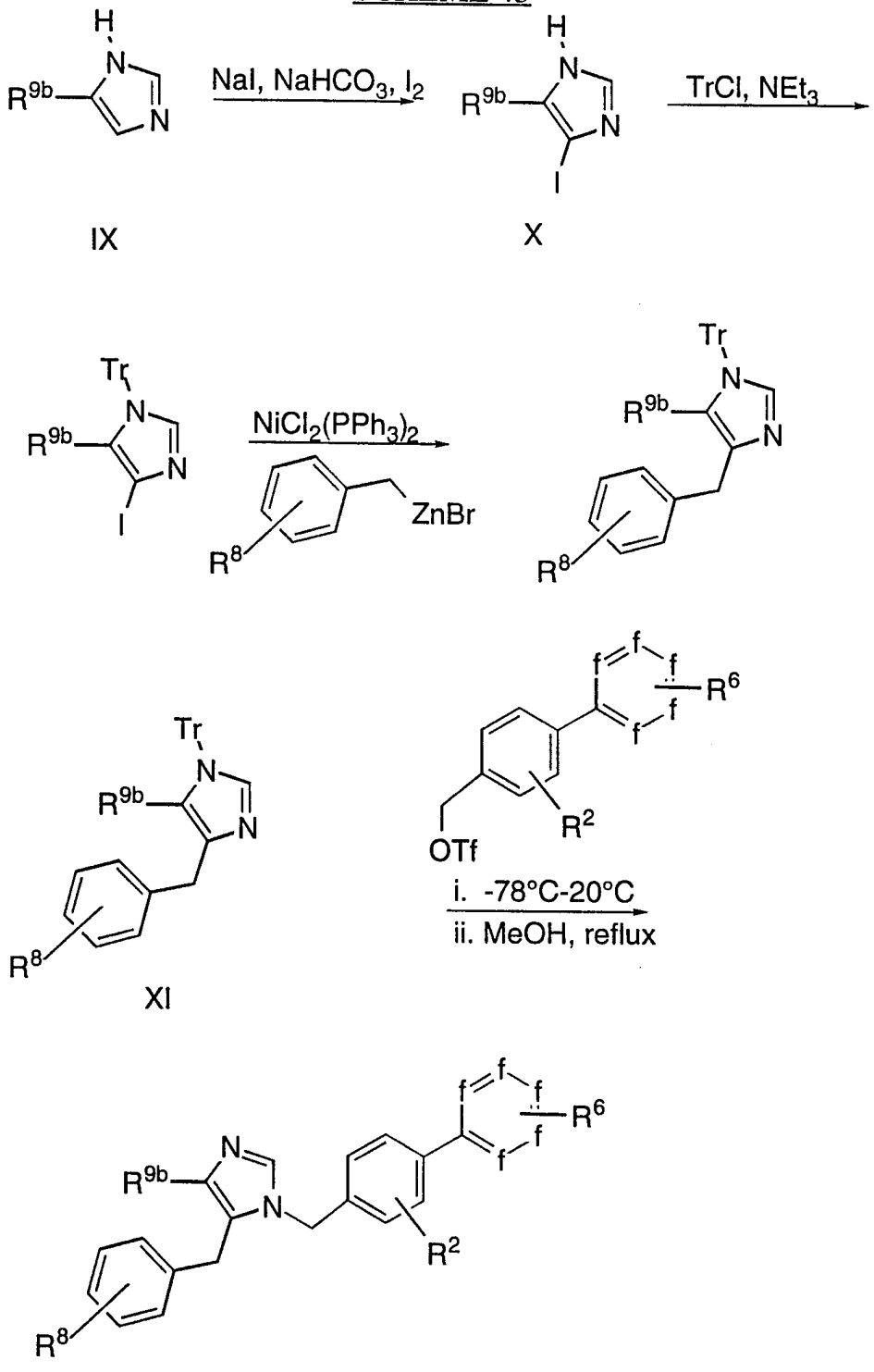
SCHEME 43


CO2CH3
H3C
NH2
NH3
EtOH
CONH2
H3C
NH2
O
O
NaOH
N
CH3
N
OH
POCl3
H2SO4
N
CH3
N
Cl
NaI/HI
N
CH3
N
I
O
O
R6
H
B(OH)2
Pd(OAc)2
H3C
N
N
H
O
R2
NaBH4
H3C
N
N
HO
R2

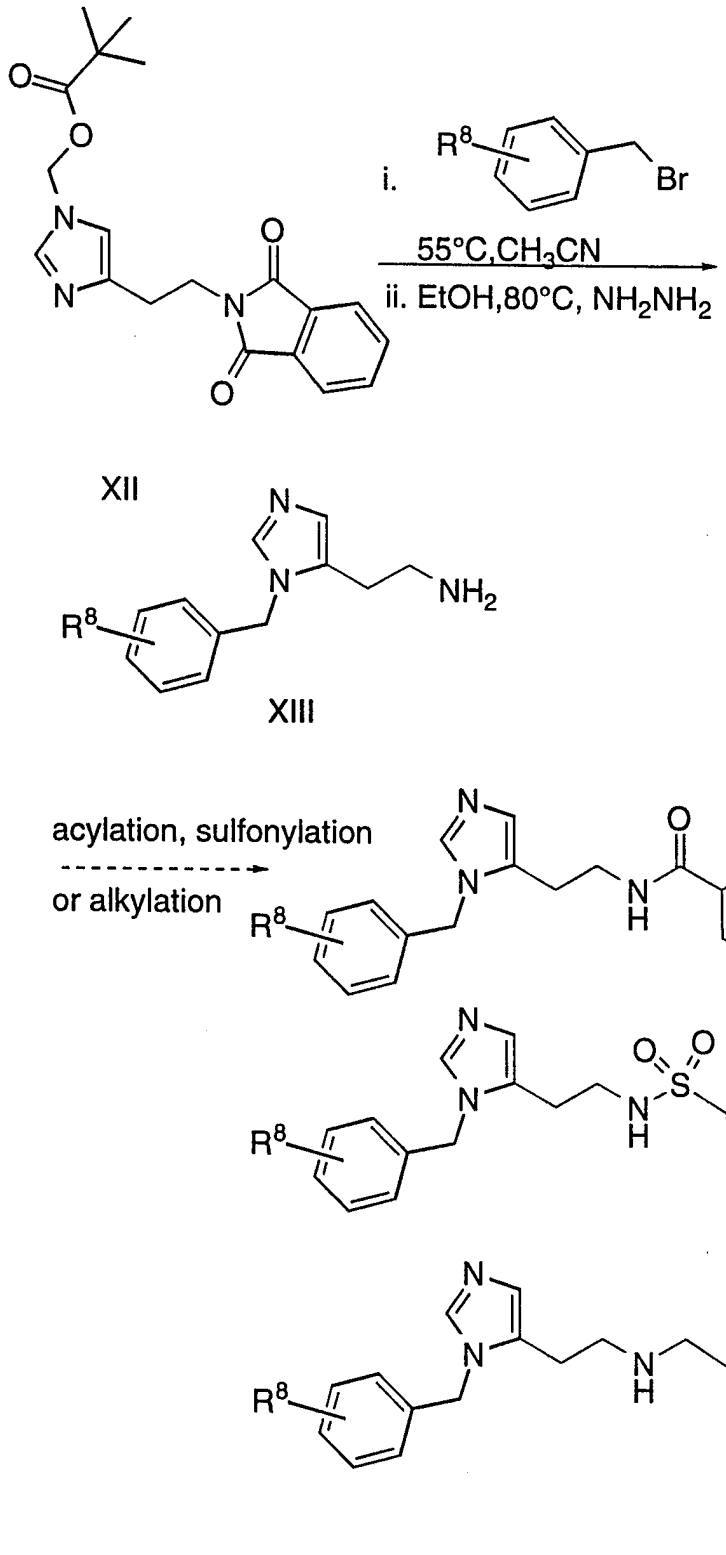
SCHEME 44


Tr
N
N
R8
i.
Br
R2
I
ii. MeOH
reflux
N
N
I
R2
R8
VIII
R6
N
(HO)2B
Pd(PPh3)4
N
N
R6
N
R2
R8

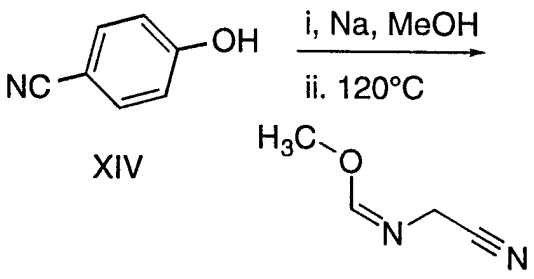
SCHEME 45


NaI, NaHCO3, I2
TrCl, NEt3
IX
X
NiCl2(PPh3)2
ZnBr
XI
i. -78°C-20°C
ii. MeOH, reflux

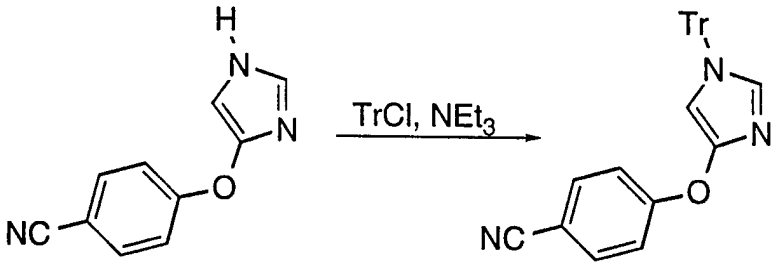
SCHEME 46


i.
Br
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
XII
XIII
acylation, sulfonylation
or alkylation

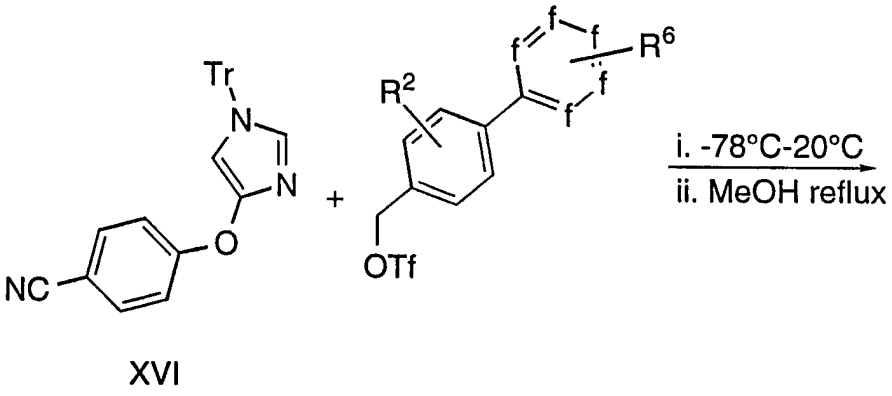
SCHEME 47



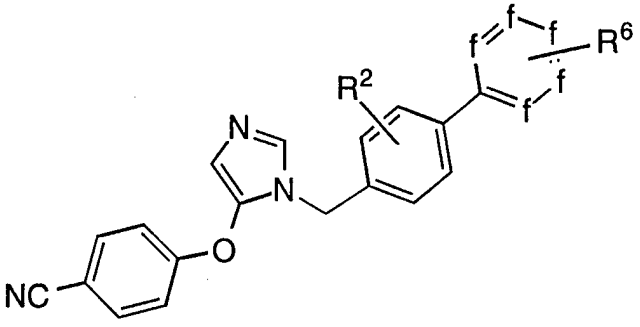
XIV



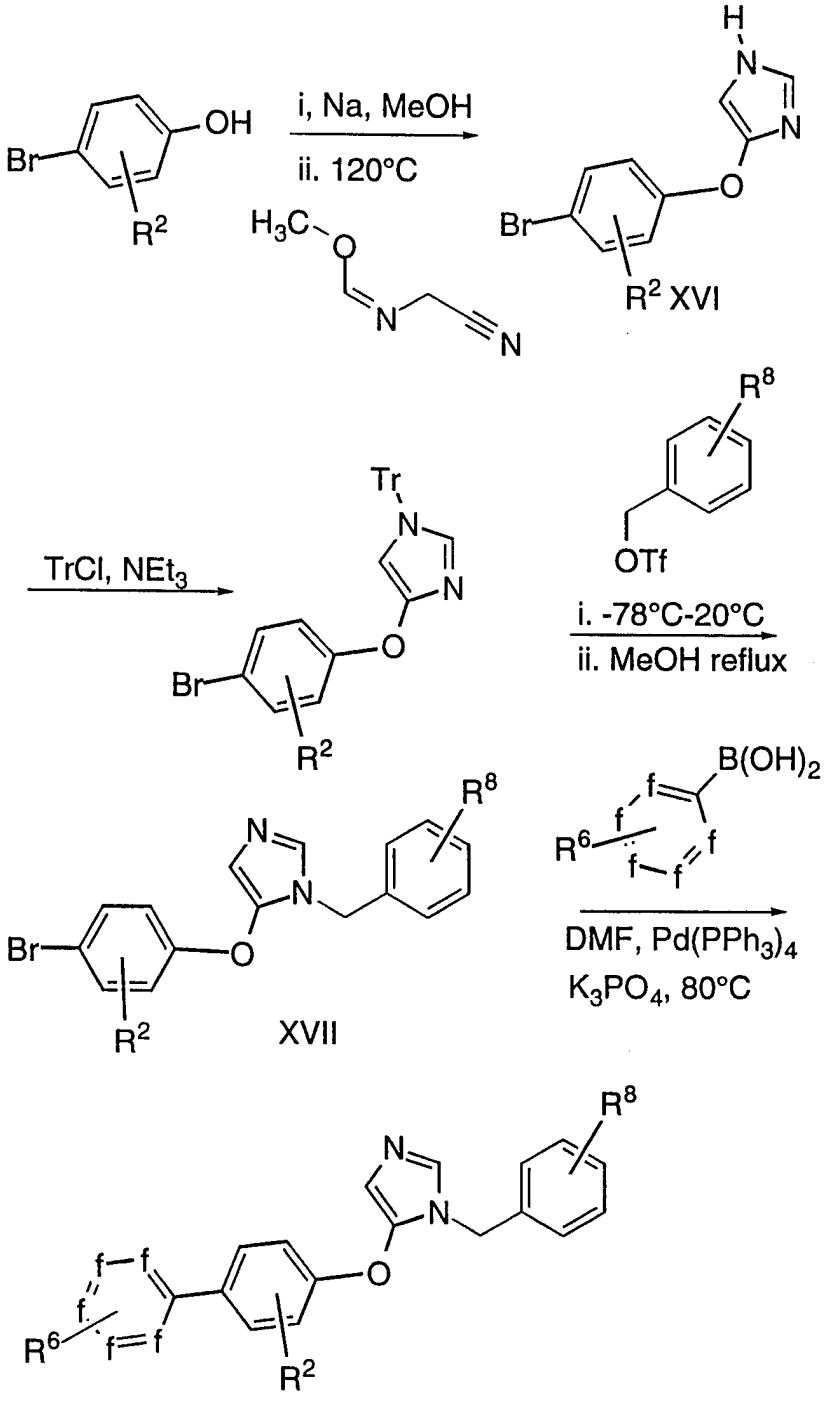
XV XVI



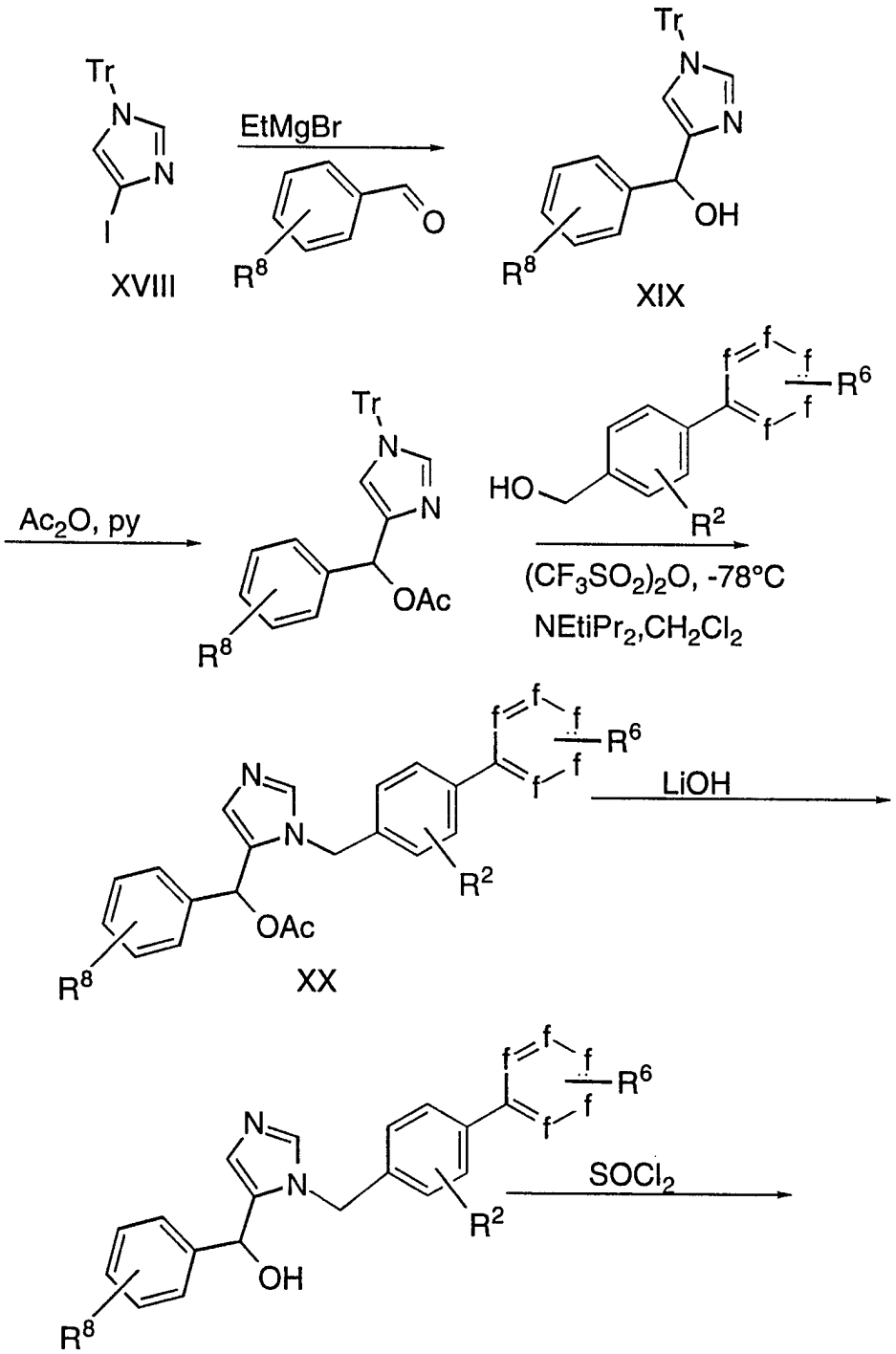
XVI



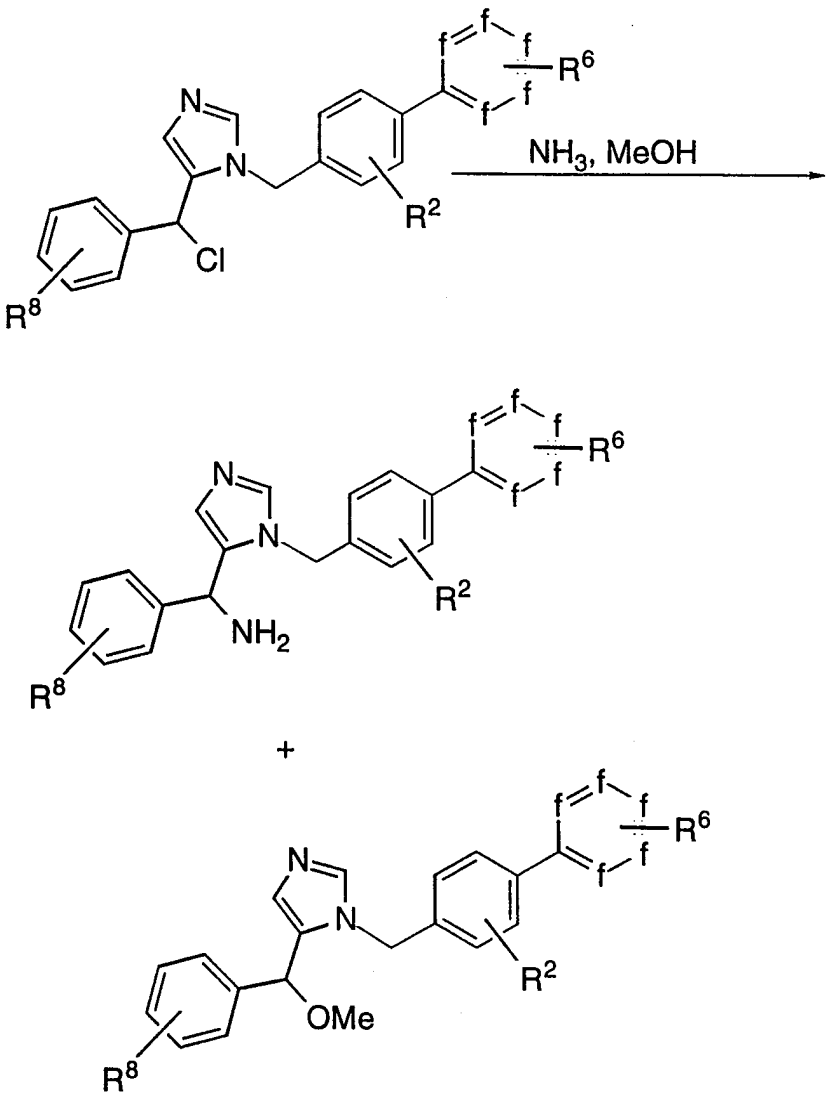
SCHEME 48


i, Na, MeOH
ii. 120°C
TrCl, NEt3
i. -78°C-20°C
ii. MeOH reflux
DMF, Pd(PPh3)4
K3PO4, 80°C
XVII

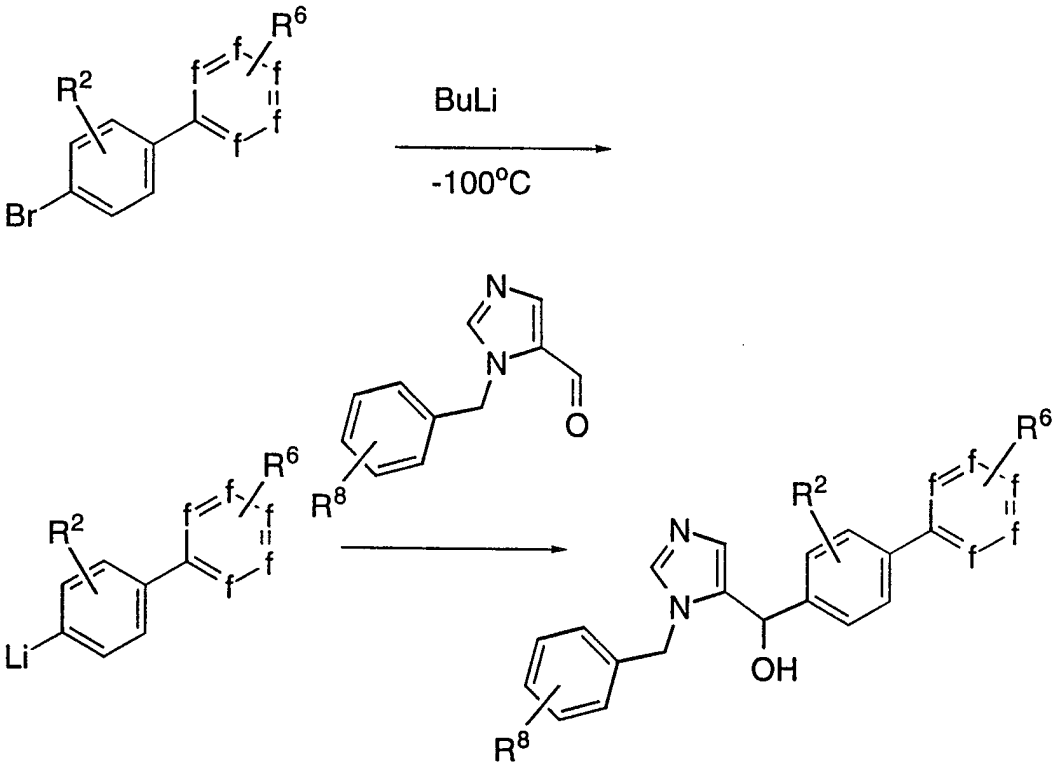
SCHEME 49


Tr
N
N
I
XVIII
EtMgBr
O
R8
Tr
N
N
OH
R8
XIX
Ac2O, py
Tr
N
N
OAc
R8
HO
R2
f
f
f
f
f
f
R6
(CF3SO2)2O, -78°C
NEtiPr2,CH2Cl2
N
N
OAc
R8
R2
R6
LiOH
XX
N
N
OH
R8
R2
R6
SOCl2

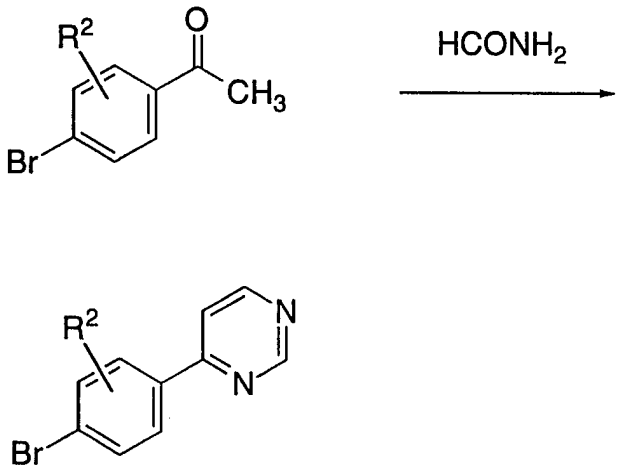
SCHEME 49 (continued)



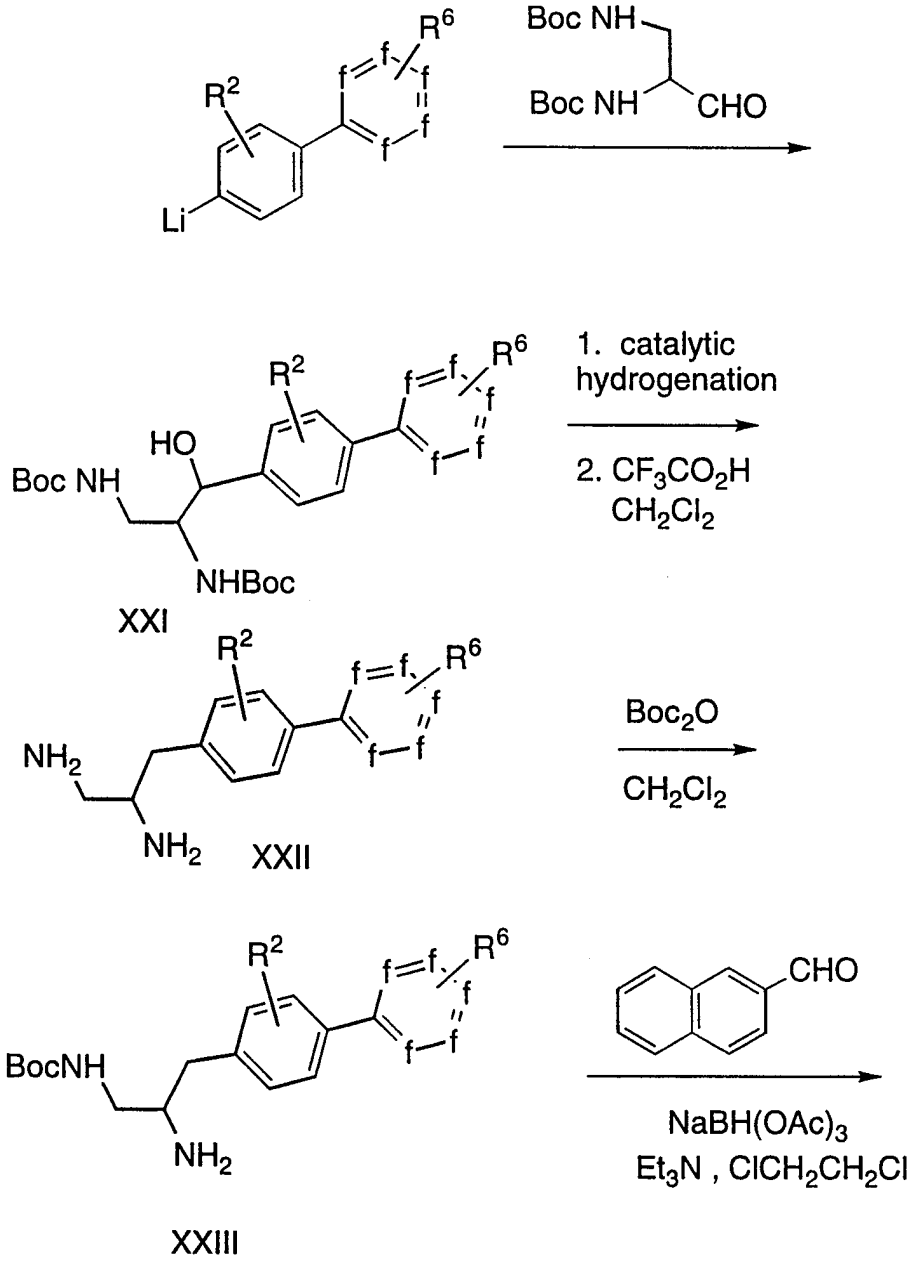
SCHEME 50



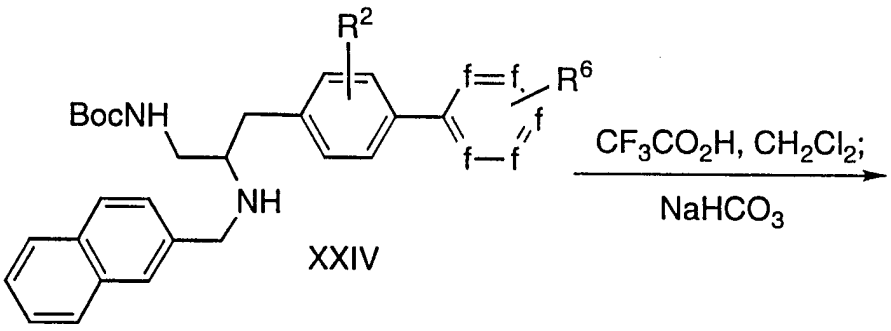
SCHEME 51



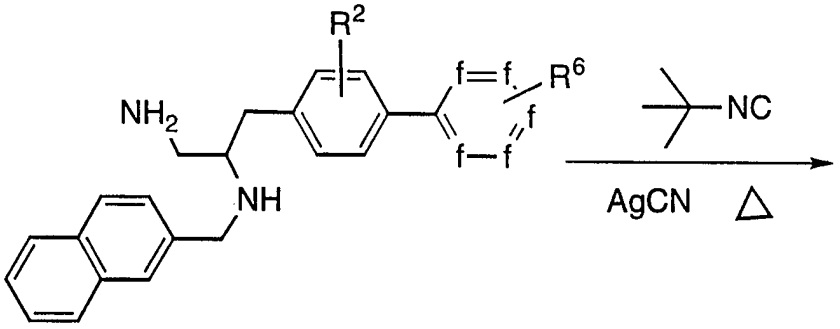
SCHEME 52

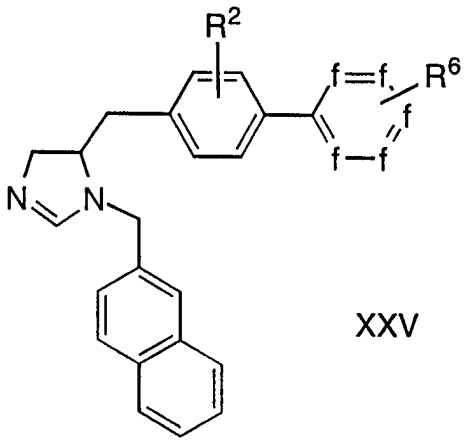

R6
R2
Li
Boc NH
Boc NH
CHO
1. catalytic hydrogenation
2. CF3CO2H
CH2Cl2
HO
Boc NH
NHBoc
XXI
NH2
NH2
XXII
Boc2O
CH2Cl2
BocNH
NH2
XXIII
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl

SCHEME 52 (continued)



XXIV





XXV

The farnesyl transferase inhibitors of formula (II-f) can be synthesized in accordance with Schemes 53-66, 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^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d},

R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 53-66 by Roman numerals are numbered starting sequentially with I and ending with XXX.

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. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 53-66:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 53-64 illustrate synthesis of the instant arylheteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 53, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted phenyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated nicotinic acid, such as 4-bromonicotinic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 54-55 illustrate other methods of synthesizing

the key alcohol intermediates, which can then be processed as described in Scheme 53. Thus, Scheme 54 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the methyl nicotinate boronic acid and the "terminal" phenyl moiety employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 55.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant compounds, as shown in Scheme 56. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 57 illustrates the preparation of a suitably substituted 3-hydroxymethyl-5-phenyl pyridine which could also be utilized in the reaction with the protected imidazole as described in Scheme 53. An Alternative preparation of a suitably substituted 5-hydroxymethyl-2-phenyl pyridine is also illustrated.

As illustrated in Scheme 58, the sequence of coupling reactions may be modified such that the aryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted phenyl boronic acid.

Scheme 59 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 60 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the

biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 61. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

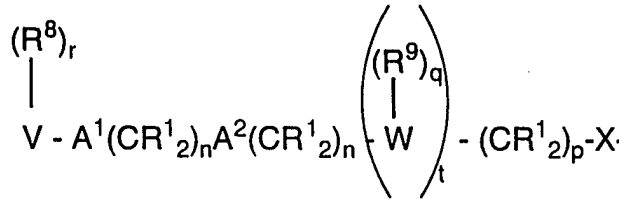
Scheme 62 illustrates an analogous series of reactions wherein the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted halopyridinol, such as 3-chloro-2-pyridinol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a aryl moiety by Suzuki chemistry to provide the instant compound.

Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 63. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 53) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the biheteroaryl and the preferred W (imidazolyl) as shown in

Scheme 64. Thus a sutiably substituted phenyl lithium can be reacted with pyridine to form the 2-substituted N-lithio-1,2-dihydropyridine XXa. Intermediate XXa can then react with a aldehyde to provide a suitably substituted instant compound. Similar substituent manipulation as shown in Scheme 63 may be performed on the fully functionalized compound which incorporates an R^2 hydroxyl moiety.

Scheme 65 illustrate reactions wherein the moiety



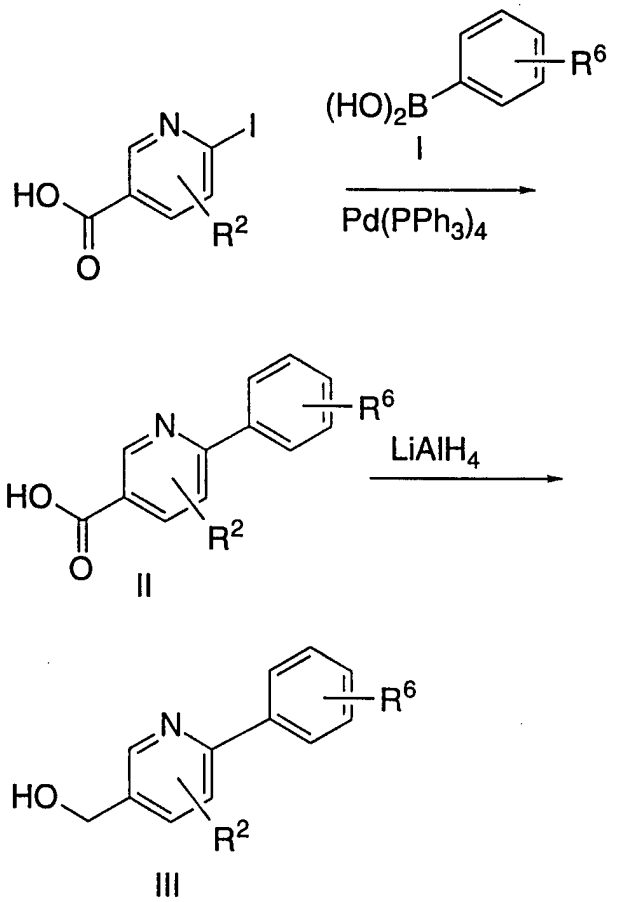
incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid. Lithioheteroaryl chemistry may be utilized, as shown in Scheme 65, to incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl N-lithio reagent is reacted with an aldehyde to provide the C-alkylated instant compound XXI. Compound **XXI** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

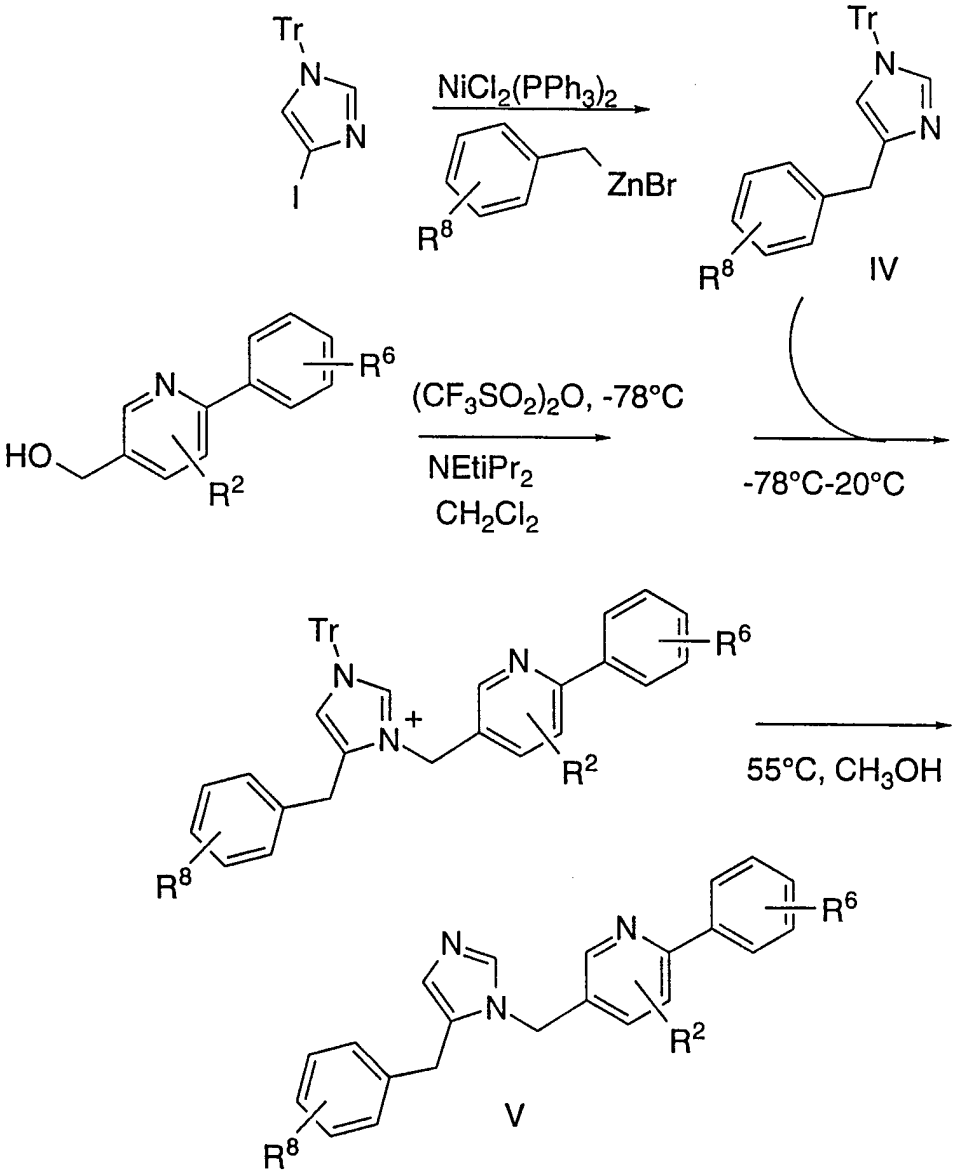
If the arylheteroaryl subunit reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **XXVI** in Scheme 66, the protecting groups can be subsequently removed to unmask the hydroxyl group. The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as alkyl lithium reagents, to obtain secondary alcohols such as **XXX**.

Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 65-66 and the intermediates manipulated as illustrated above in Schemes 4-9.

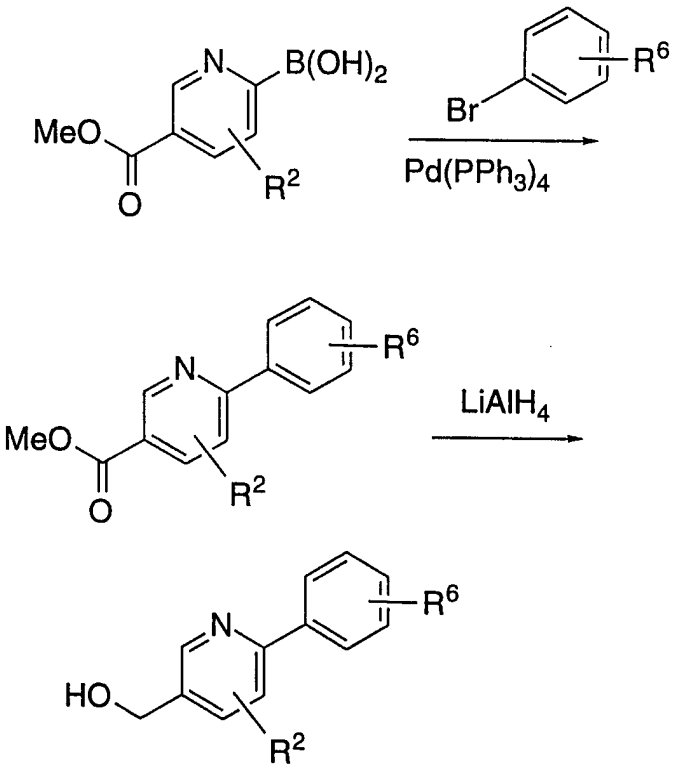
SCHEME 53



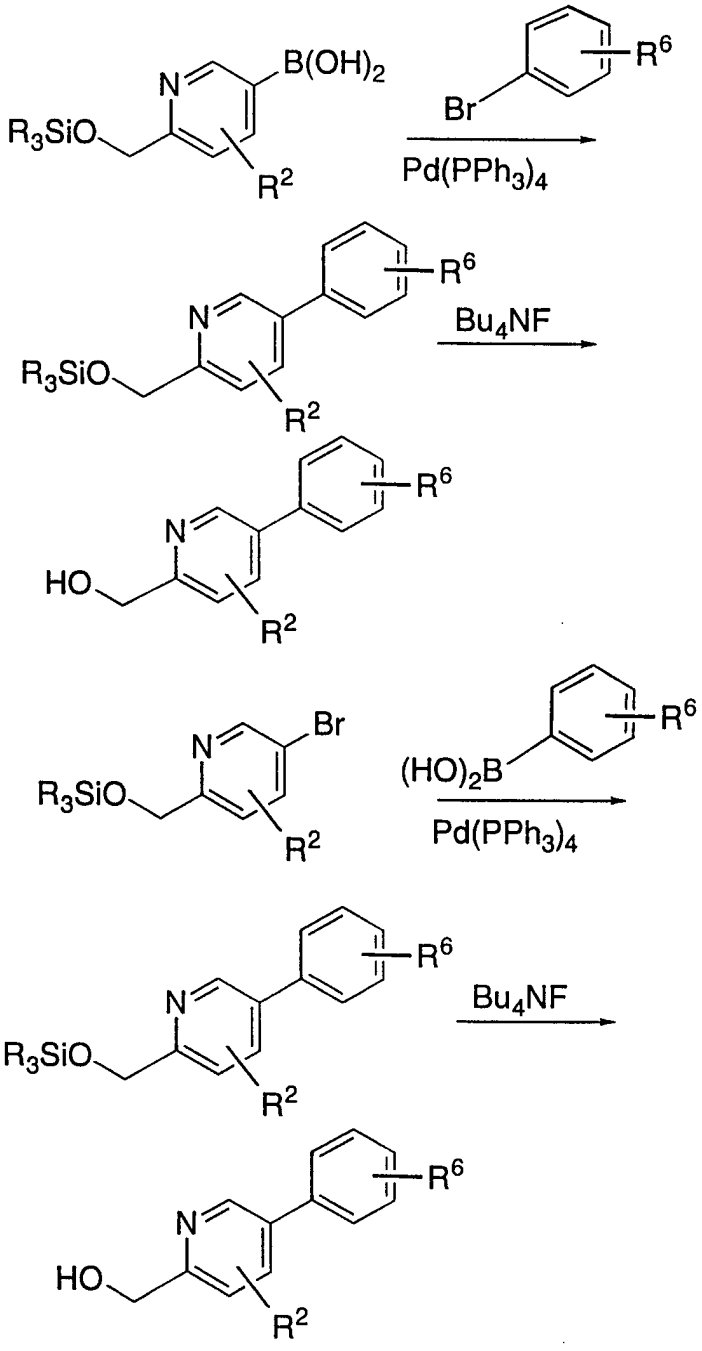
SCHEME 53 (continued)



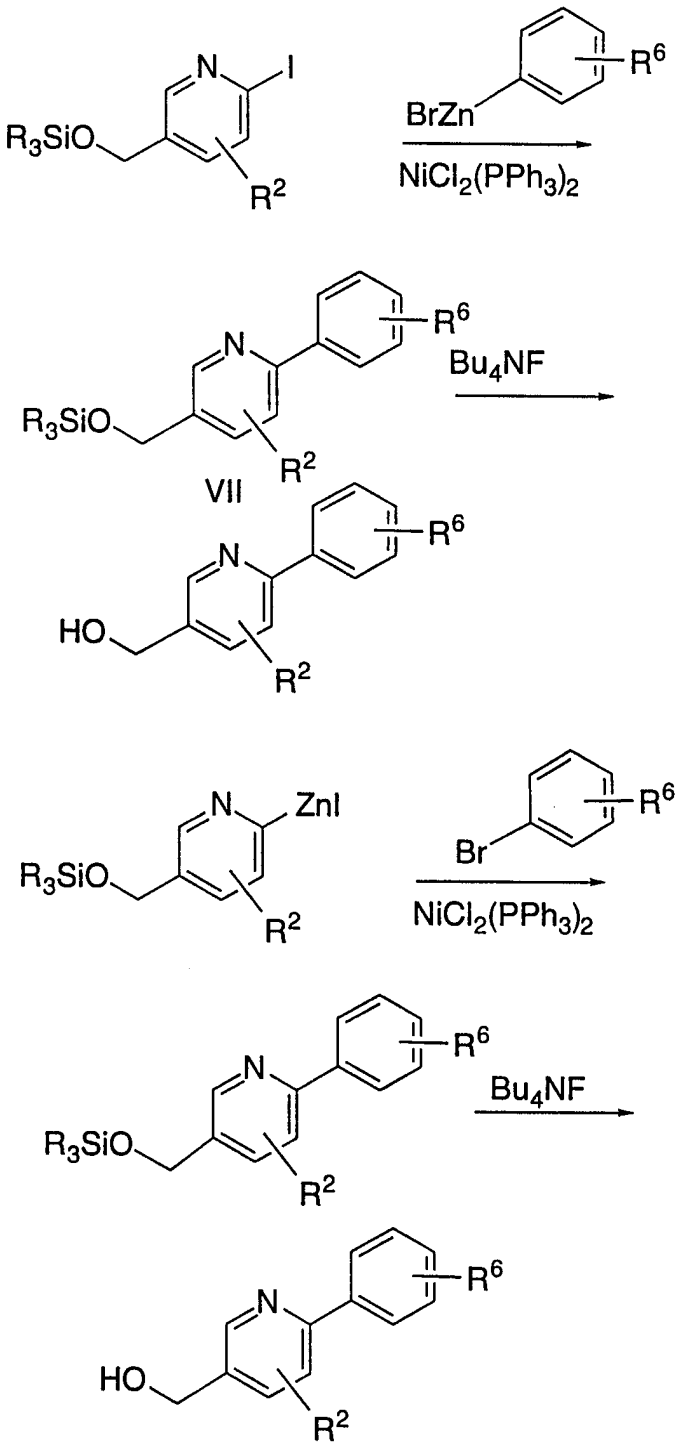
SCHEME 54



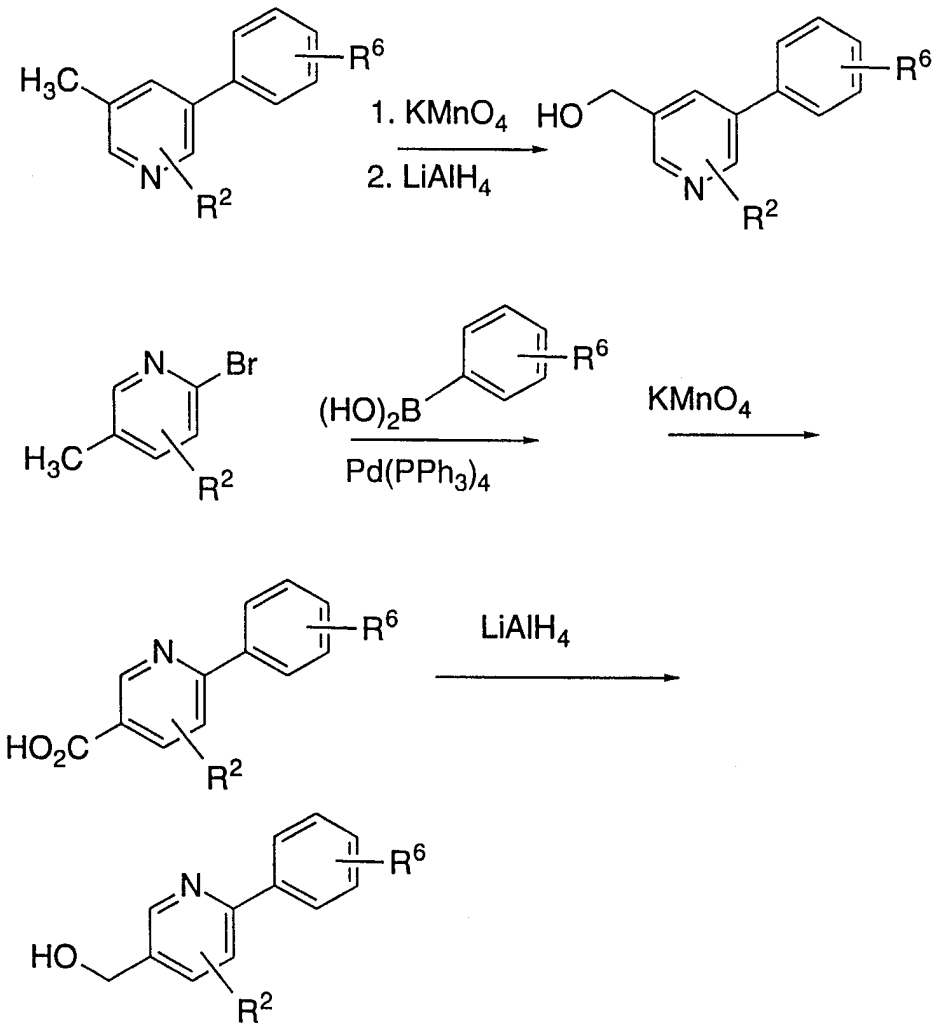
SCHEME 55



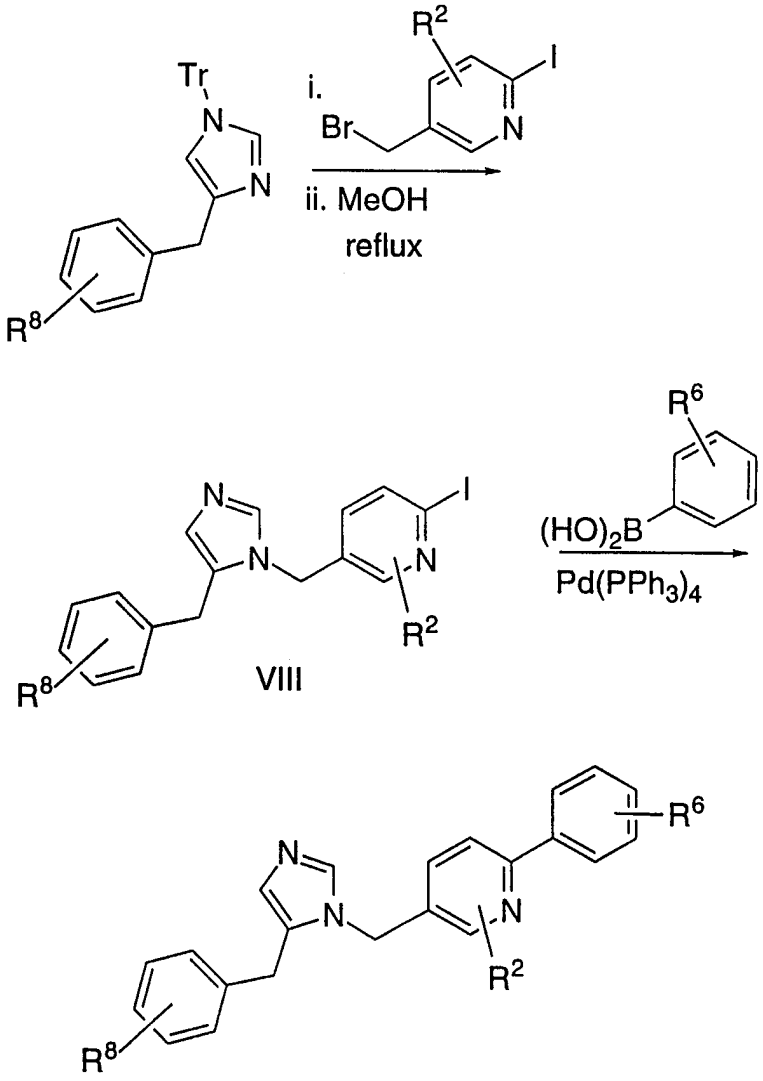
SCHEME 56



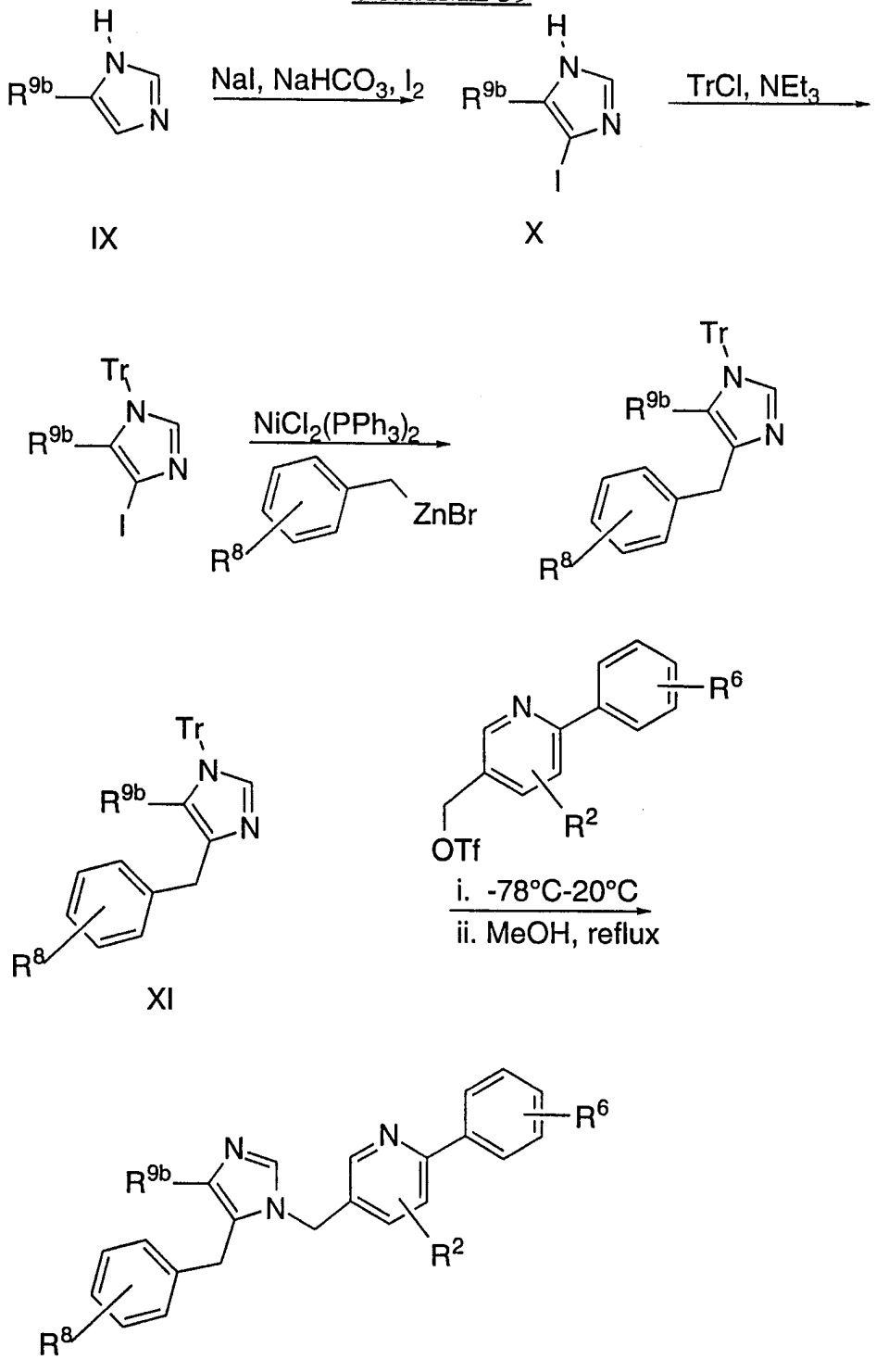
SCHEME 57


H3C
R6
1. KMnO4
2. LiAlH4
HO
N
R2
Br
(HO)2B
Pd(PPh3)4
KMnO4
LiAlH4
HO2C

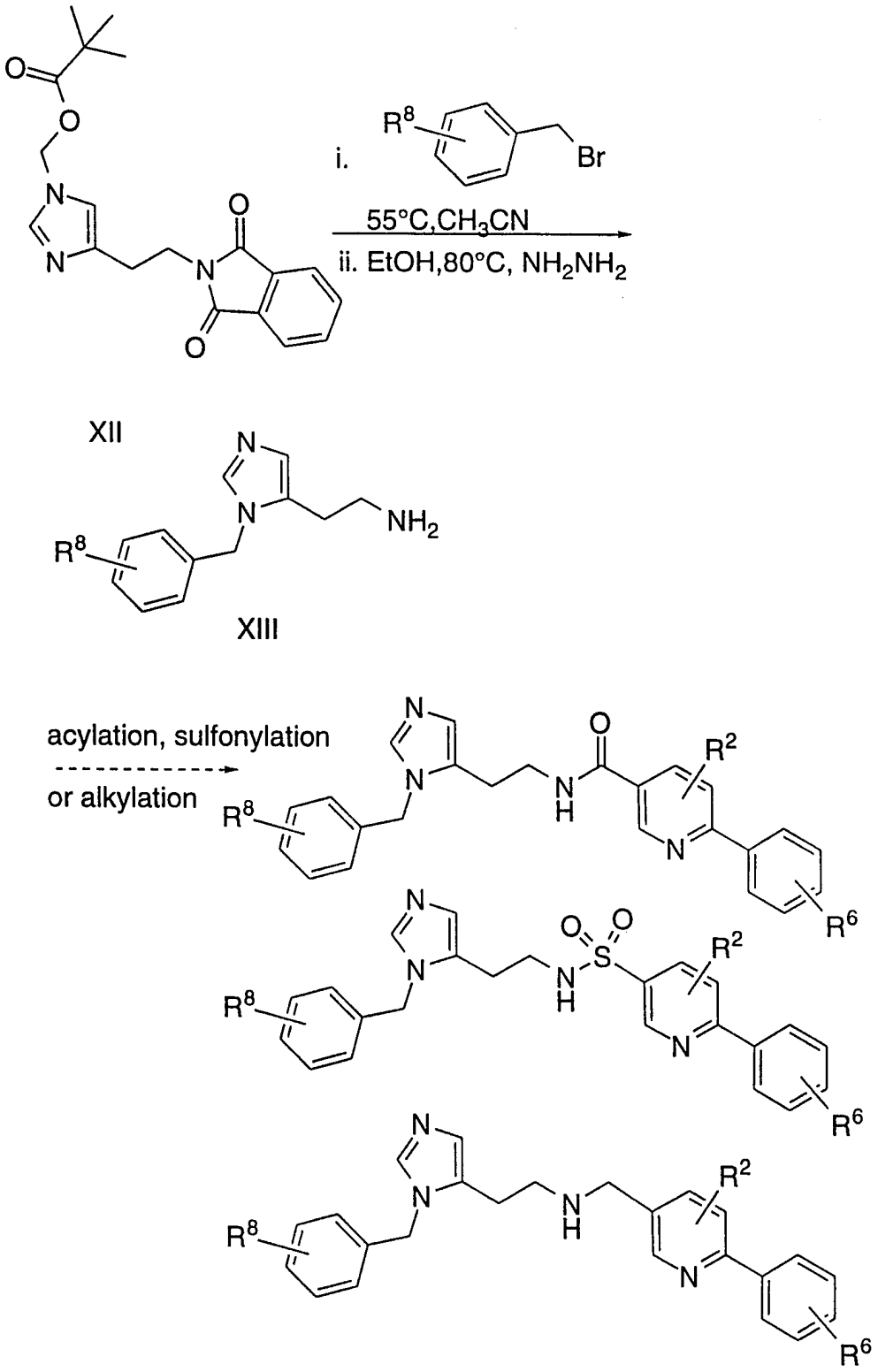
SCHEME 58


Tr
N
N
R8
i.
Br
R2
I
N
ii. MeOH
reflux
N
N
I
N
R2
R8
VIII
R6
(HO)2B
Pd(PPh3)4
N
N
N
R2
R8
R6

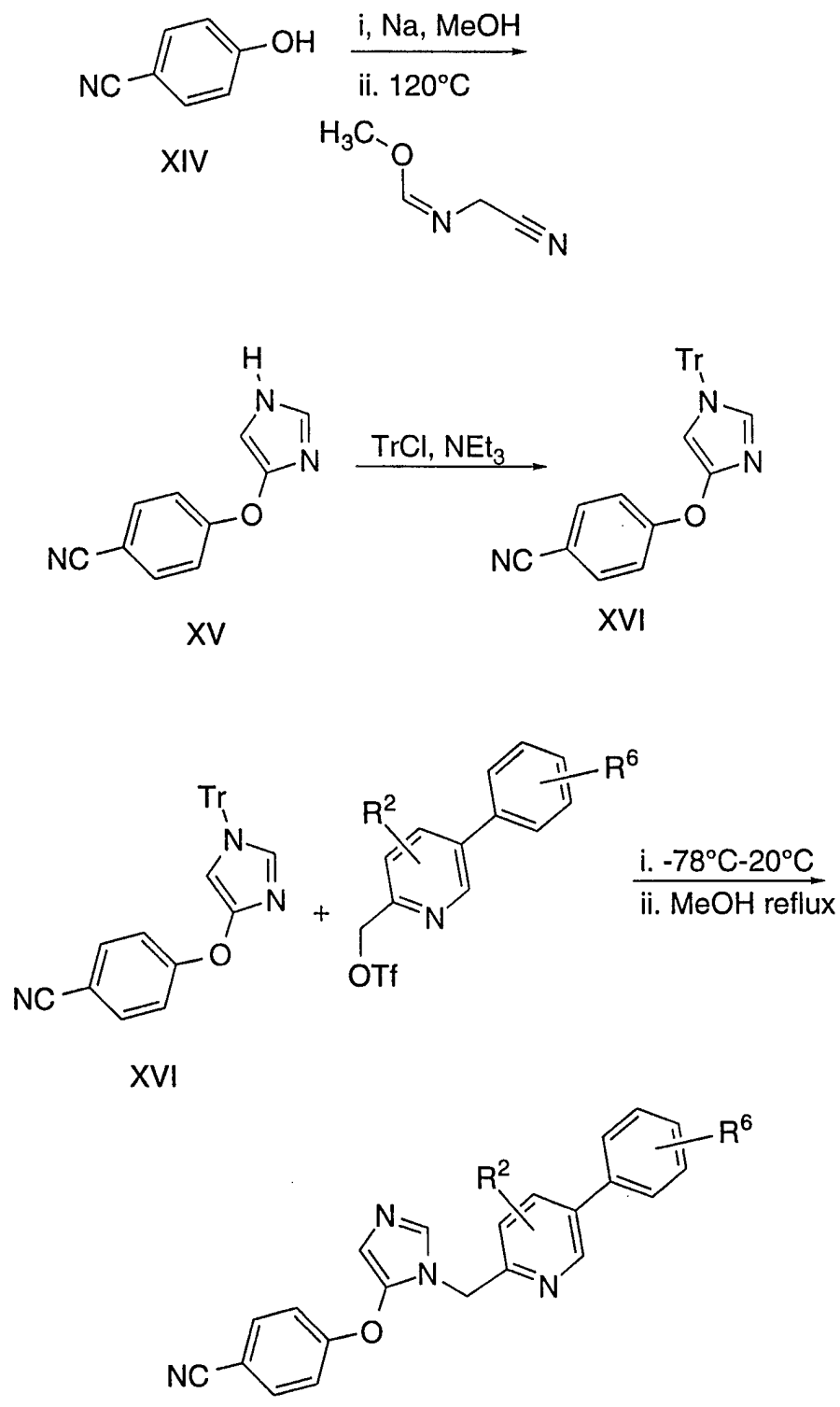
SCHEME 59


NaI, NaHCO3, I2
TrCl, NEt3
IX
X
NiCl2(PPh3)2
ZnBr
i. -78°C-20°C
ii. MeOH, reflux
XI

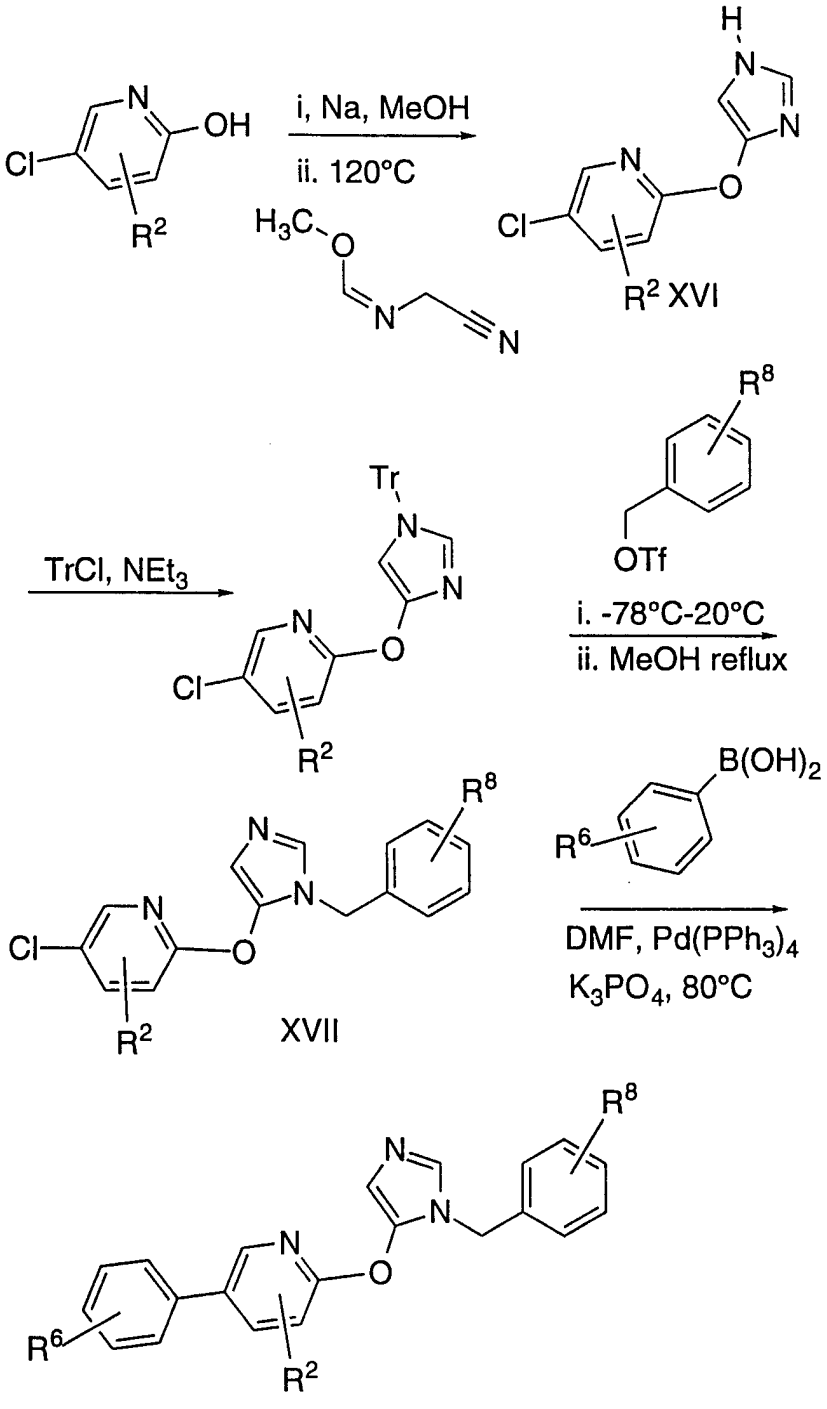
SCHEME 60


i.
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
XII
XIII
acylation, sulfonylation
or alkylation

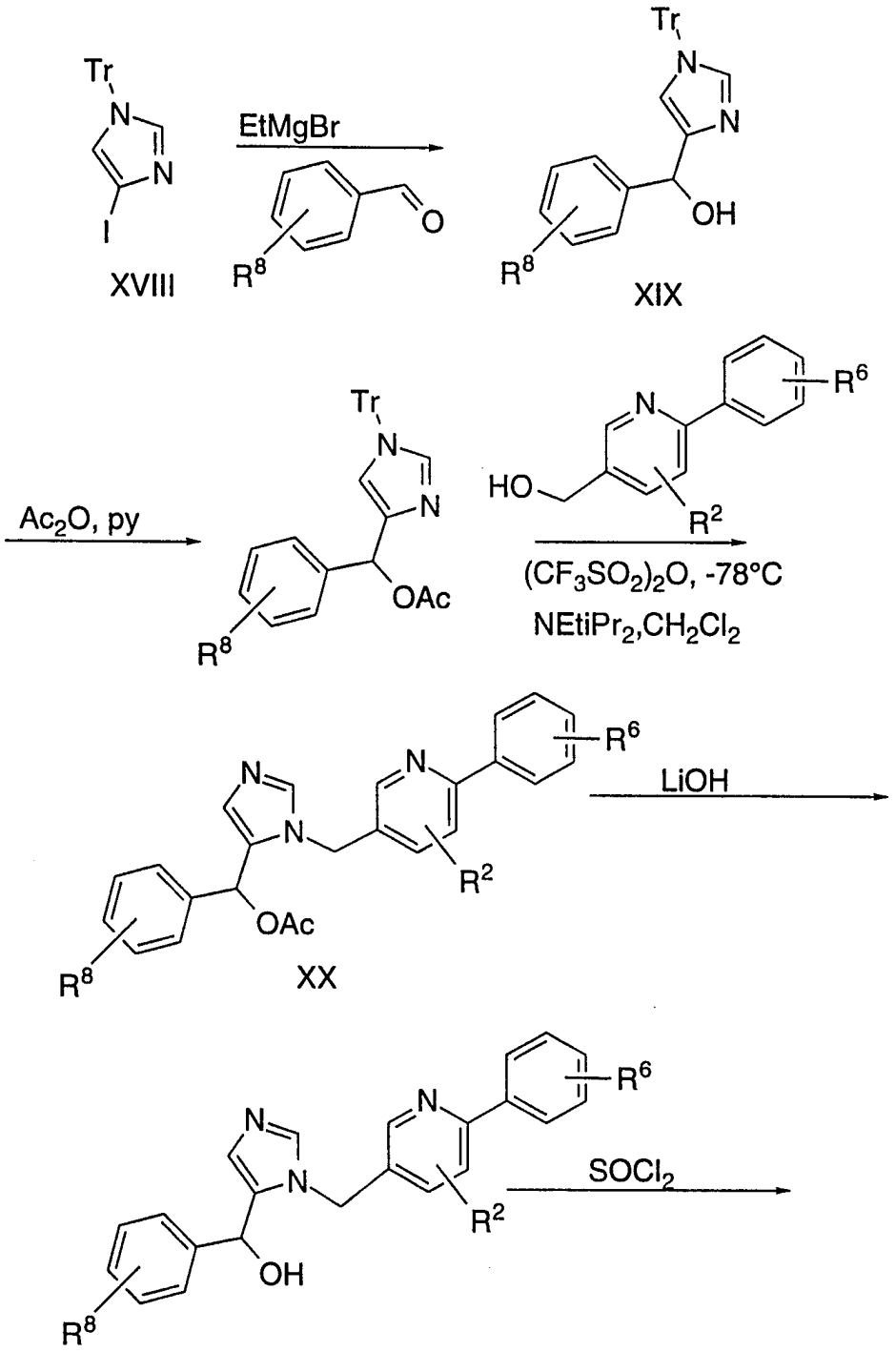
SCHEME 61


OH
NC
i, Na, MeOH
ii. 120°C
XIV
H3C
O
N
N
H
N
N
O
NC
XV
TrCl, NEt3
Tr
N
N
O
NC
XVI
Tr
N
N
O
NC
XVI
+
R6
R2
N
OTf
i. -78°C-20°C
ii. MeOH reflux
R6
R2
N
N
N
O
NC

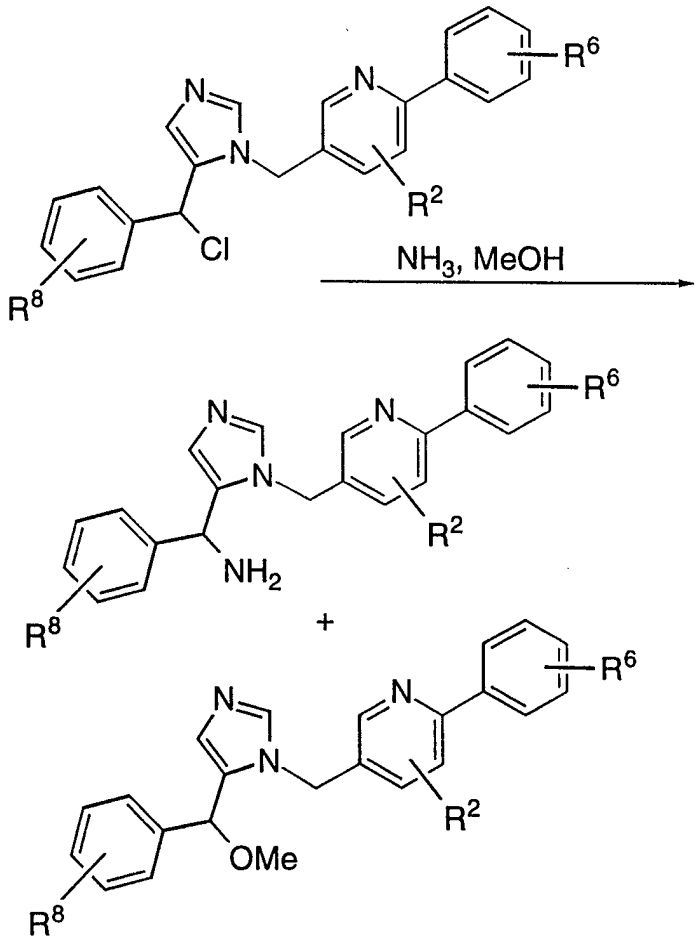
SCHEME 62


i, Na, MeOH
ii. 120°C
TrCl, NEt3
i. -78°C-20°C
ii. MeOH reflux
DMF, Pd(PPh3)4
K3PO4, 80°C
XVII

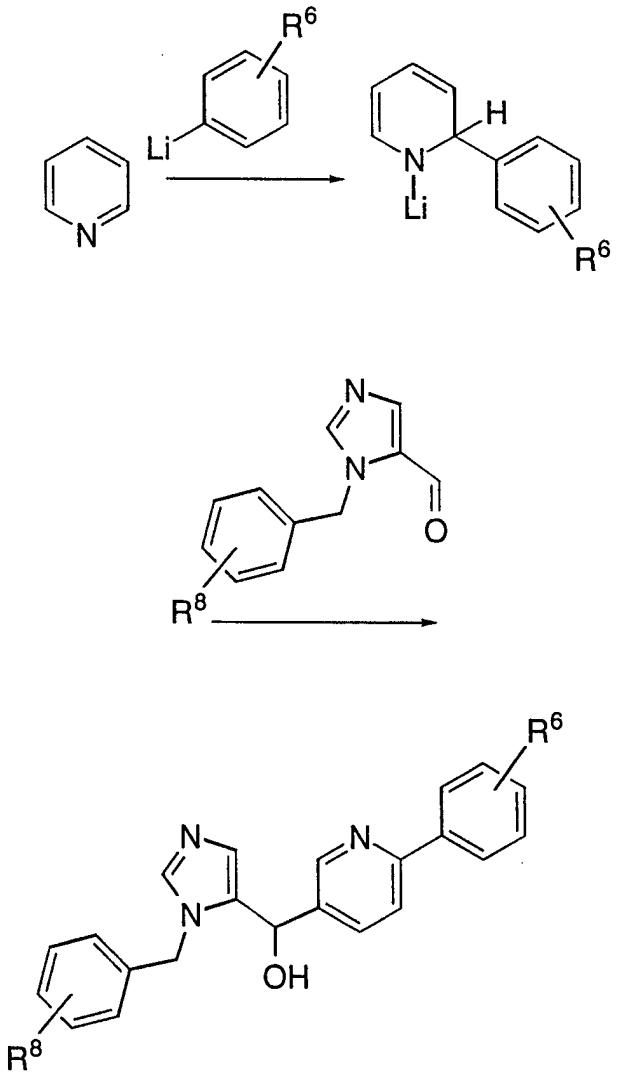
SCHEME 63


Tr
N
N
I
XVIII
EtMgBr
O
R8
Tr
N
N
OH
R8
XIX
Ac2O, py
Tr
N
N
OAc
R8
HO
N
R6
R2
(CF3SO2)2O, -78°C
NEtiPr2,CH2Cl2
N
N
N
R6
R2
OAc
R8
XX
LiOH
N
N
N
R6
R2
OH
R8
SOCl2

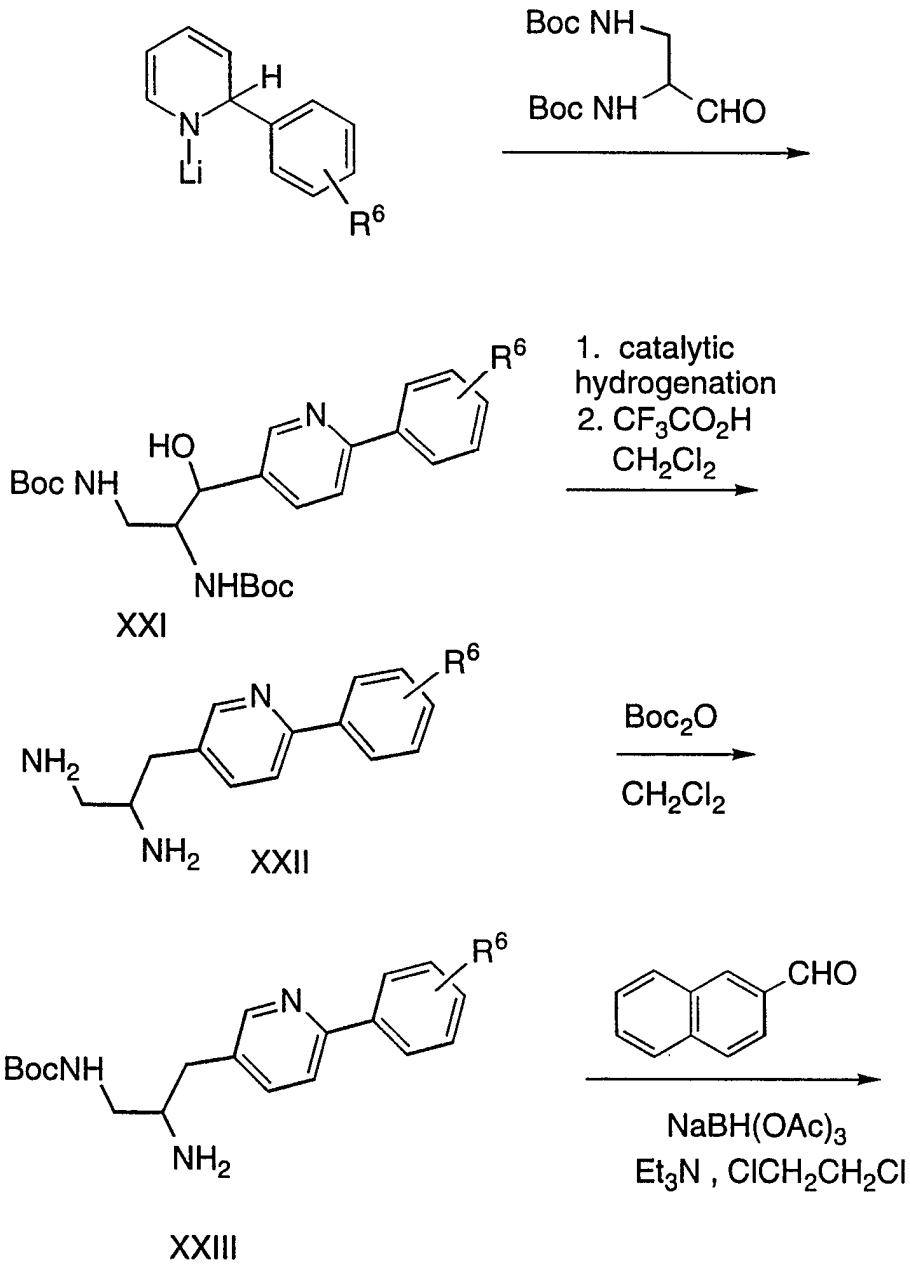
SCHEME 63 (continued)



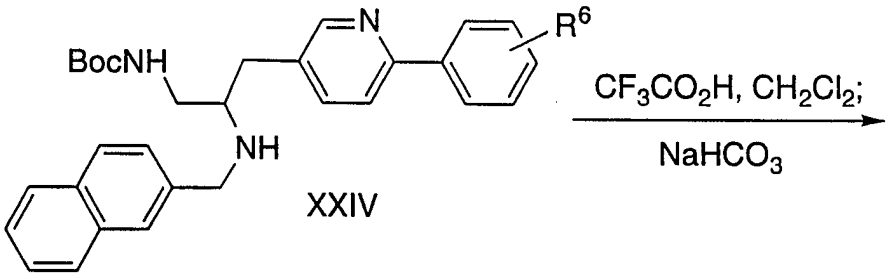
SCHEME 64

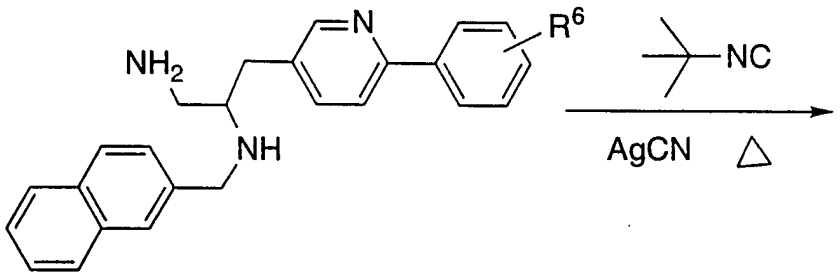


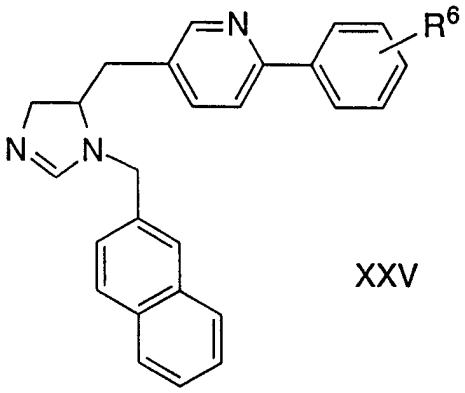
SCHEME 65


Boc NH
Boc NH
CHO
H
N
Li
R6
1. catalytic hydrogenation
2. CF3CO2H
CH2Cl2
HO
Boc NH
NHBoc
XXI
NH2
NH2
XXII
Boc2O
CH2Cl2
BocNH
NH2
XXIII
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl

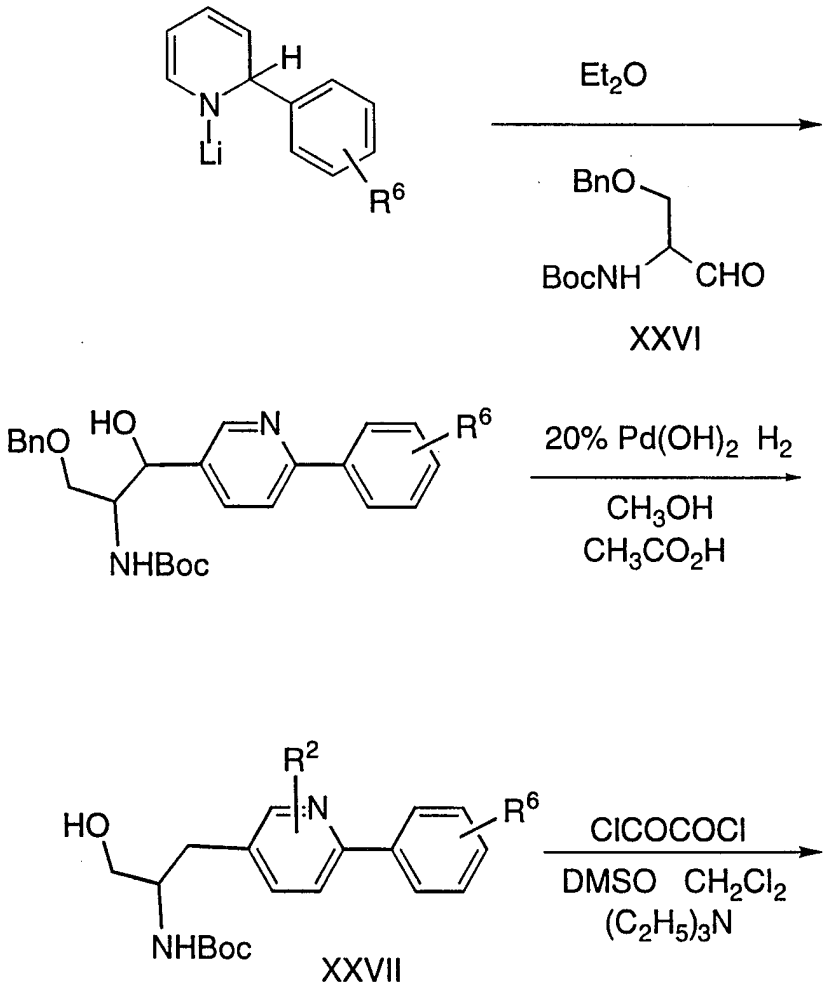
SCHEME 65 (continued)



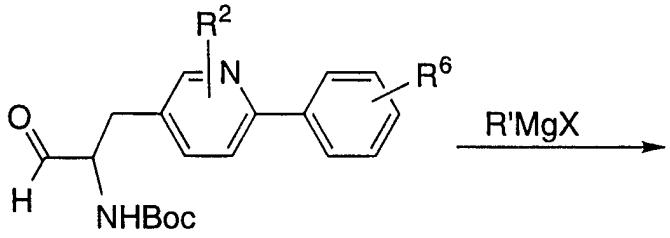




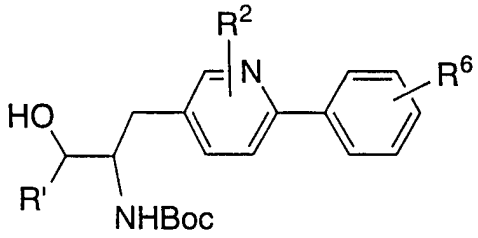
SCHEME 66


H
N
Li
R6
Et2O
BnO
BocNH
CHO
XXVI
BnO
HO
N
R6
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
R2
N
R6
HO
NHBoc
XXVII
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N

SCHEME 66 (continued)



XXIX



XXX

The farnesyl transferase inhibitors of formula (II-g) can be synthesized in accordance with Schemes 67-78, 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^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^6 and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 67-78 by Roman numerals are numbered starting sequentially with I and ending with XX.

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. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described

in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 67-78:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 67-78 illustrate synthesis of the instant biheteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 67, for example, a biheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated nicotinic acid, such as 4-bromonicotinic acid, to provide the biheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 68-71 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 67. Thus, Scheme 68 illustrates the analogous series of biheteroaryl alcohol forming reactions starting with the methyl nicotinate boronic acid and the "terminal" heteroaryl moiety employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 69.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the biheteroaryl component of the instant compounds, as shown in Scheme 70. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the biheteroaryl VII. The heteroaryl

halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 71 illustrates the preparation of the pyridylmethanol intermediate starting with the 3-methyl pyridine.

As illustrated in Scheme 72, the sequence of coupling reactions may be modified such that the heteroaryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted pyridyl boronic acid.

Scheme 73 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 74 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-amino-alkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated biheteroaryl moieties to provide the instant compounds shown.

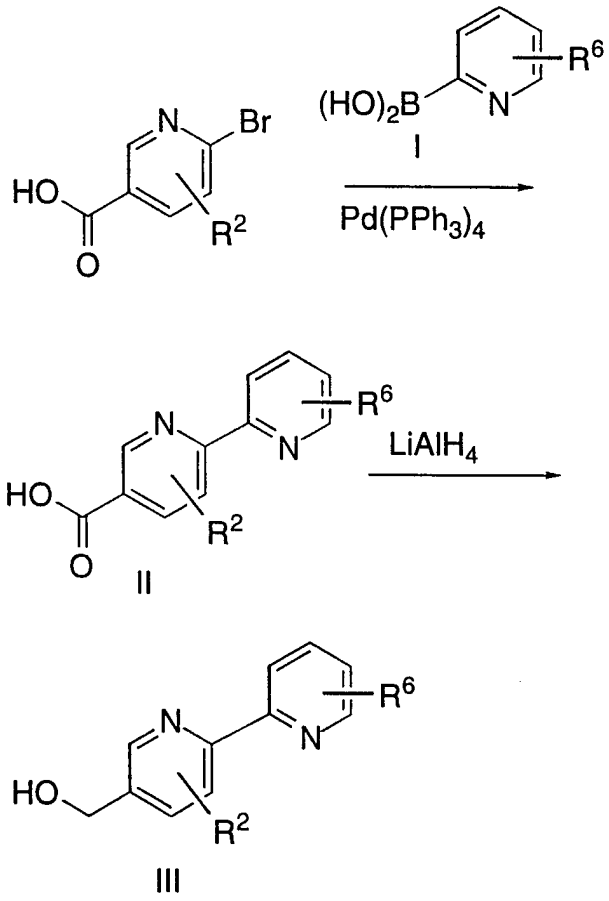
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 75. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Scheme 76 illustrates an analogous series of reactions wherein the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted halopyridinol, such as 3-chloro-2-pyridinol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a heteroaryl moiety by Suzuki chemistry to provide the instant compound.

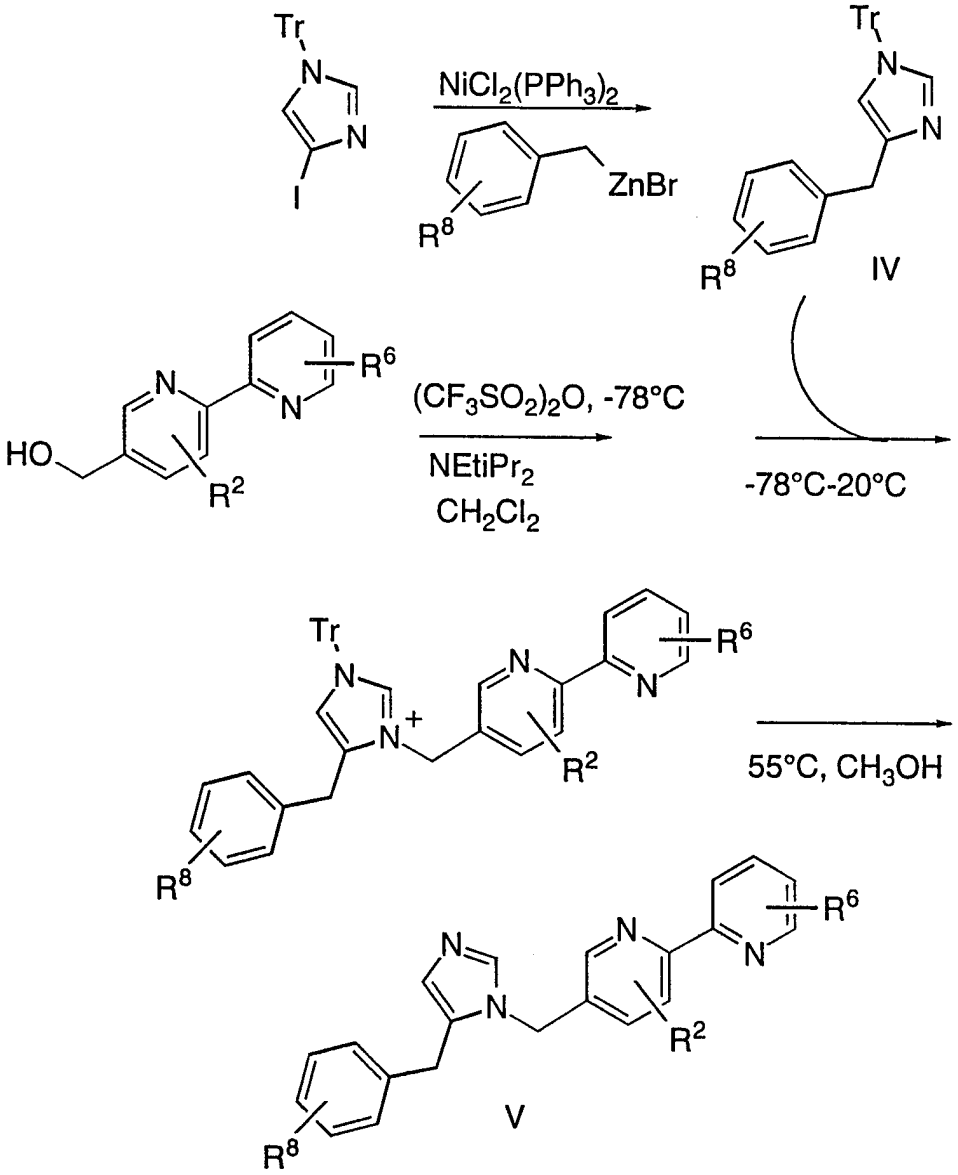
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 77. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 67) provides the instant compound XX. If other R^1 substituent s are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 78 illustrates the use of halogenated 2-aminopyrimidine in the preapration of compounds of the instant invention.

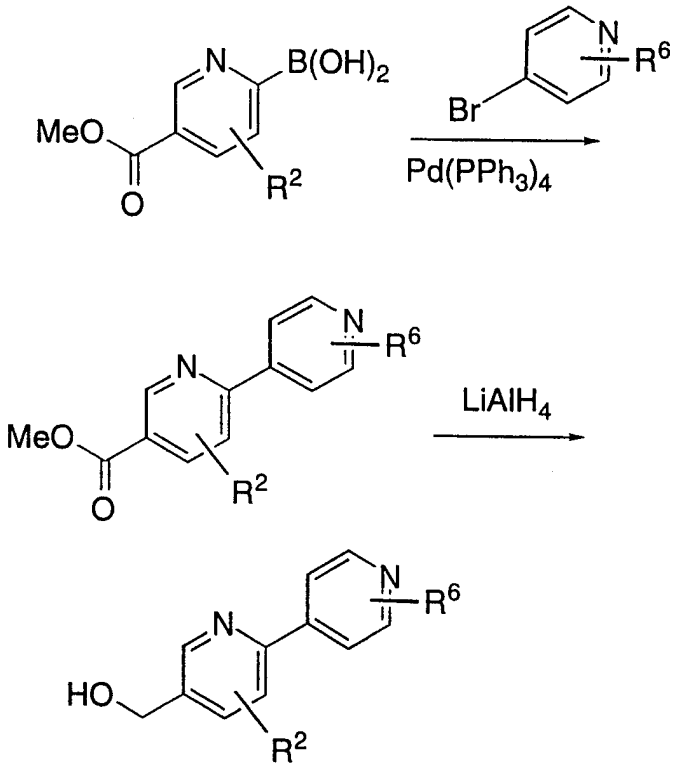
SCHEME 67



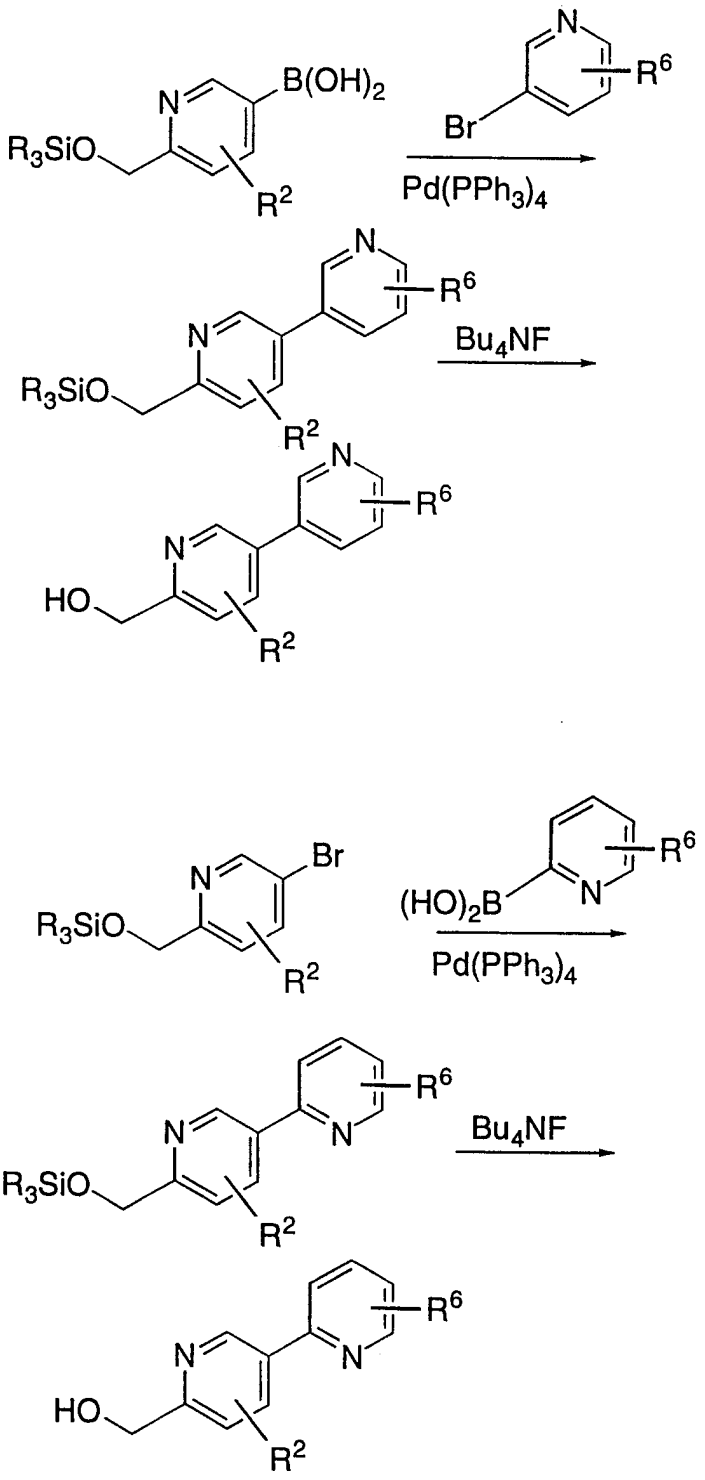
SCHEME 67 (continued)



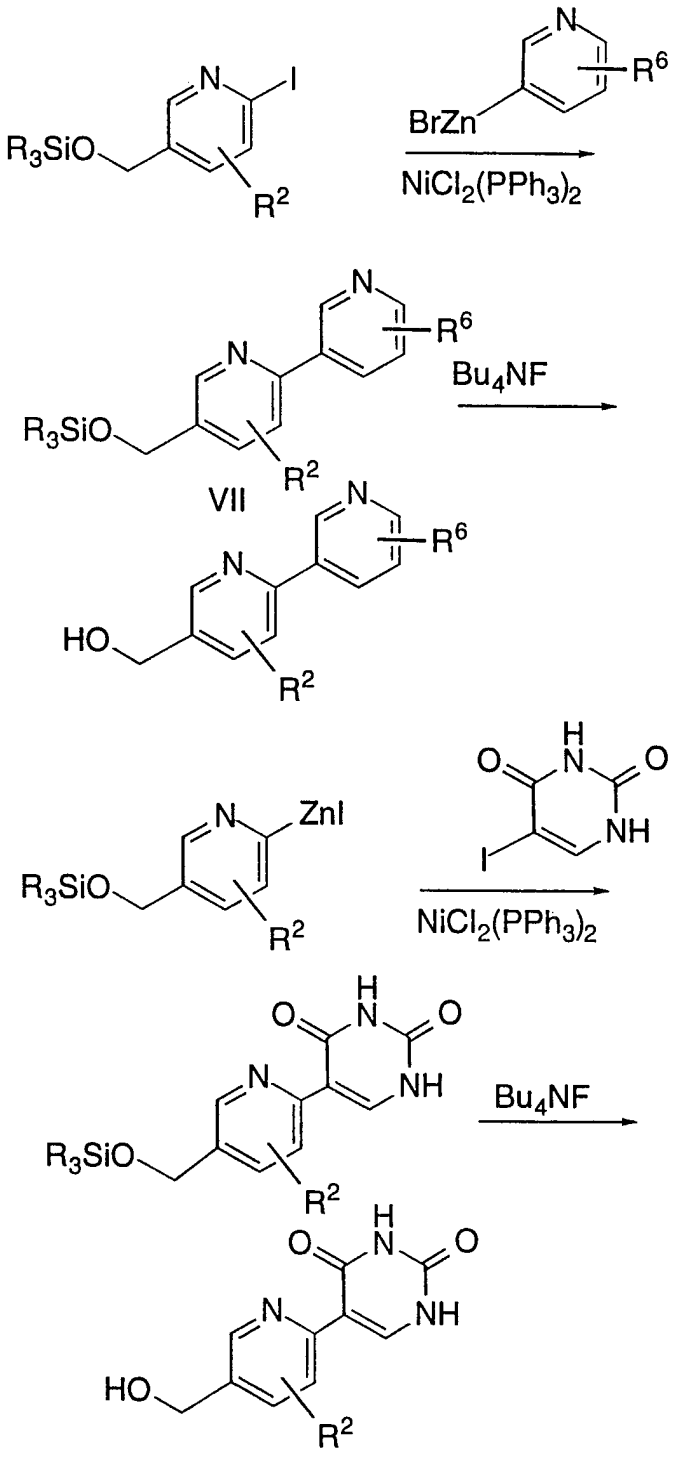
SCHEME 68



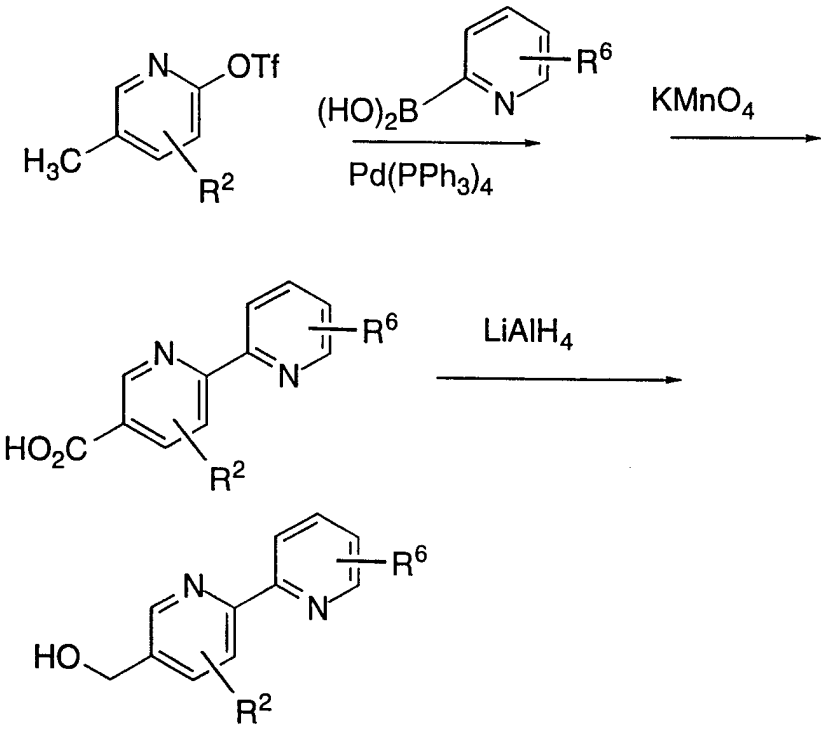
SCHEME 69



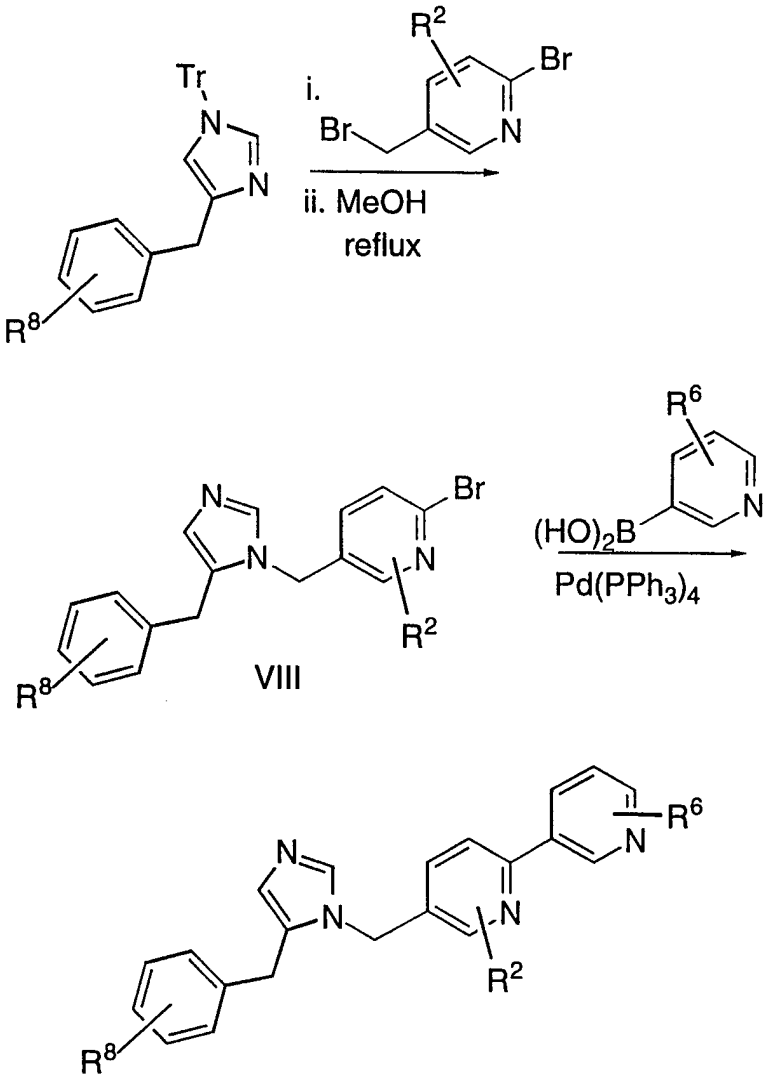
SCHEME 70



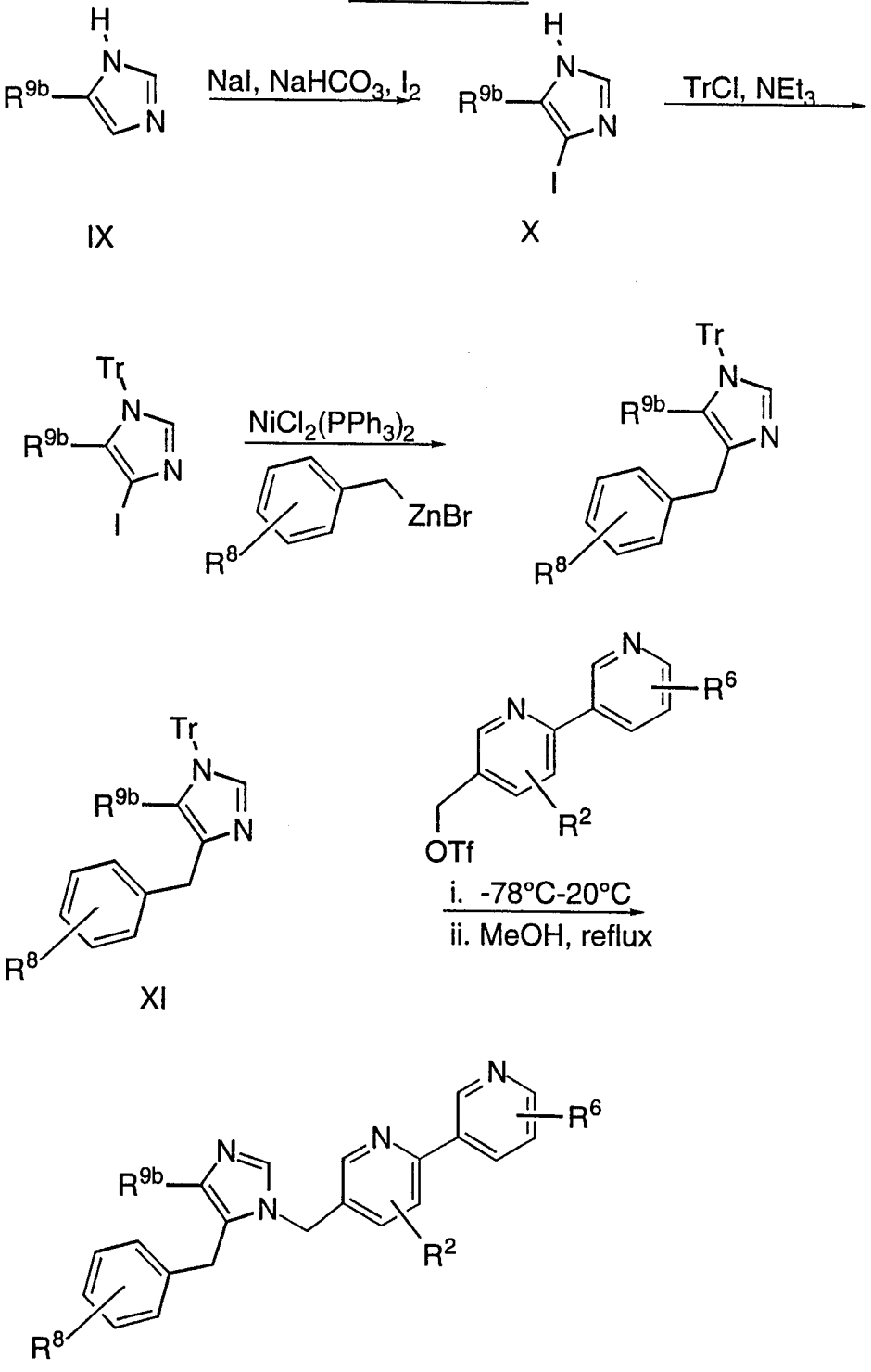
SCHEME 71


N
OTf
H3C
R2
(HO)2B
R6
N
Pd(PPh3)4
KMnO4
R6
N
N
HO2C
R2
LiAlH4
R6
N
N
HO
R2

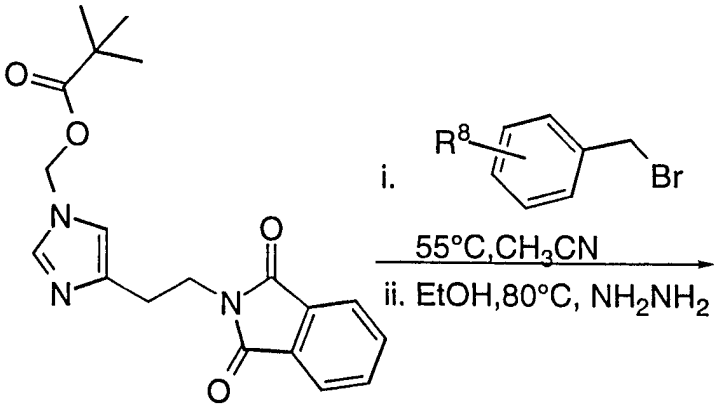
SCHEME 72



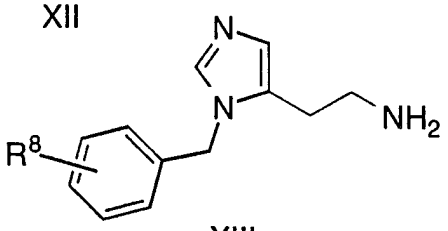
SCHEME 73


NaI, NaHCO3, I2
TrCl, NEt3
IX
X
NiCl2(PPh3)2
ZnBr
OTf
i. -78°C-20°C
ii. MeOH, reflux
XI

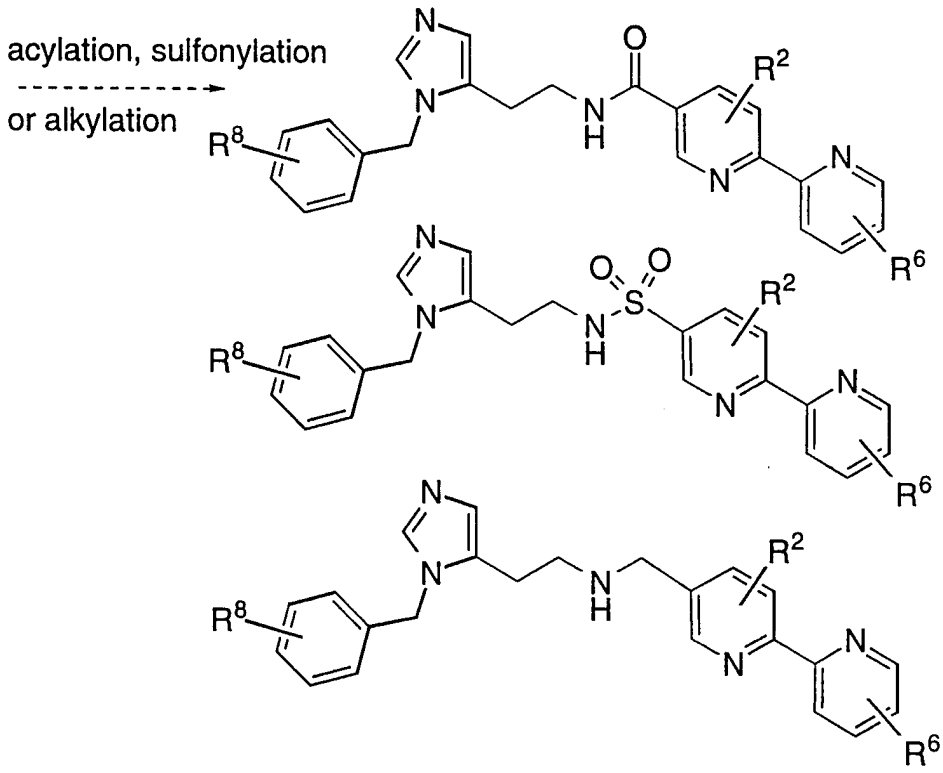
SCHEME 74



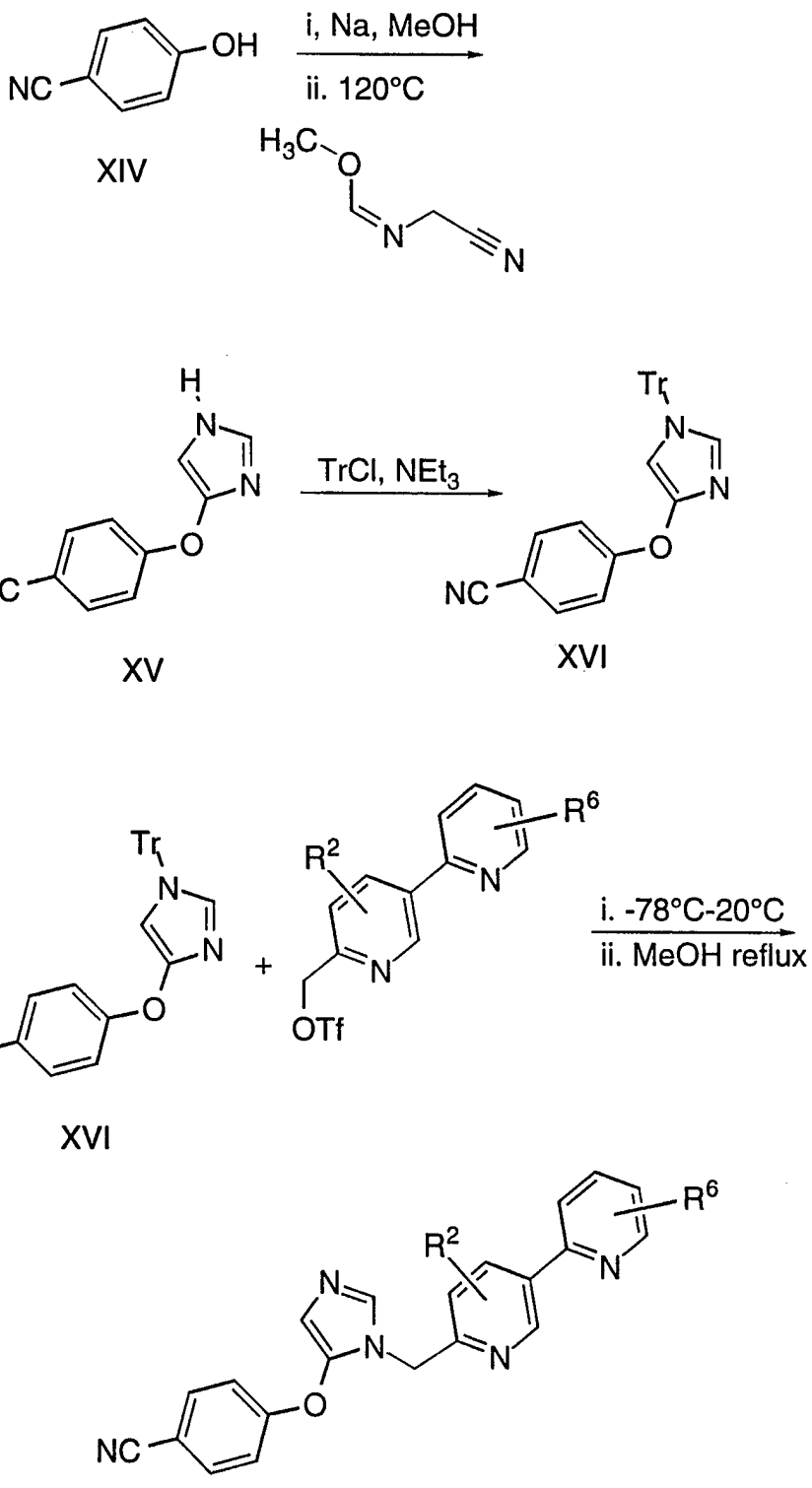
XII



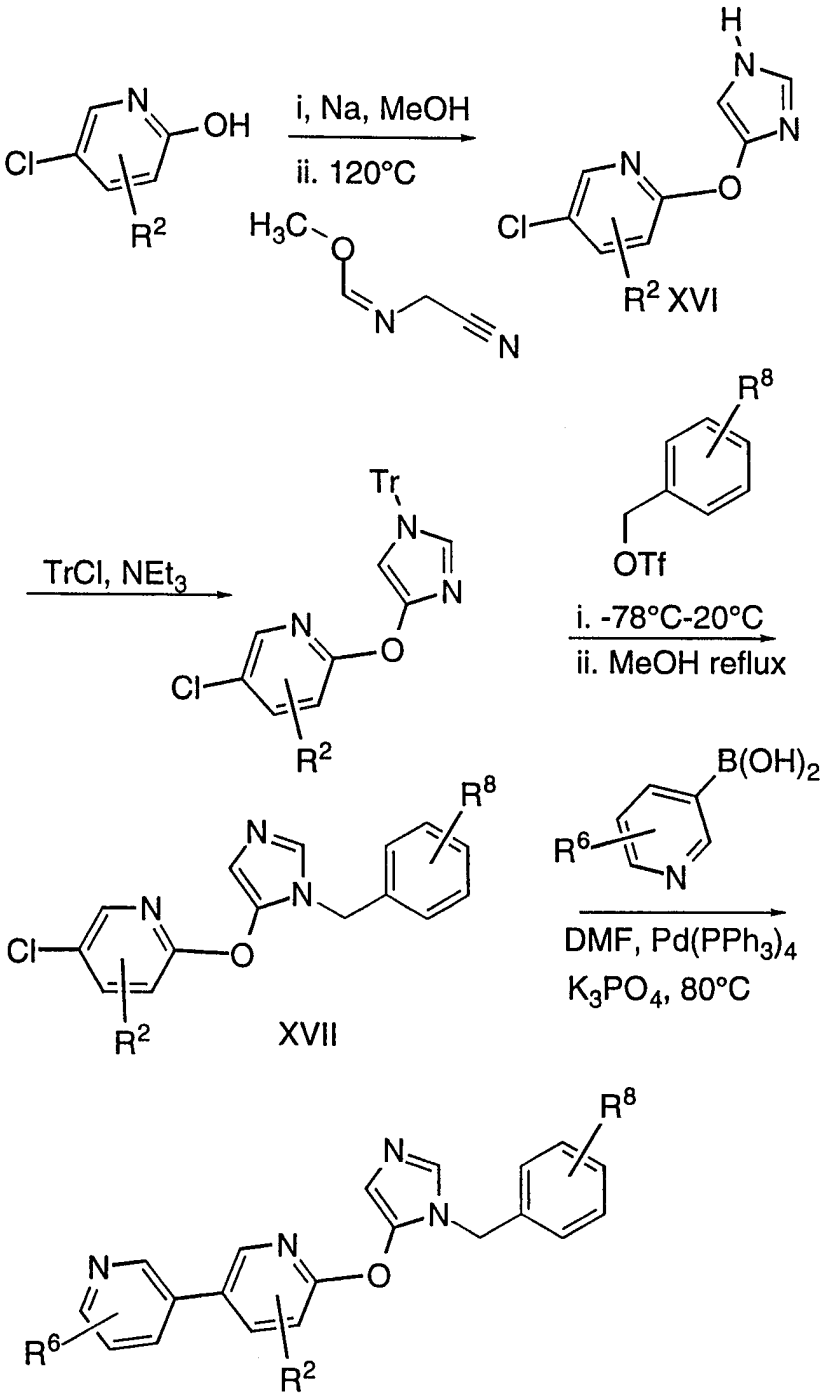
XIII



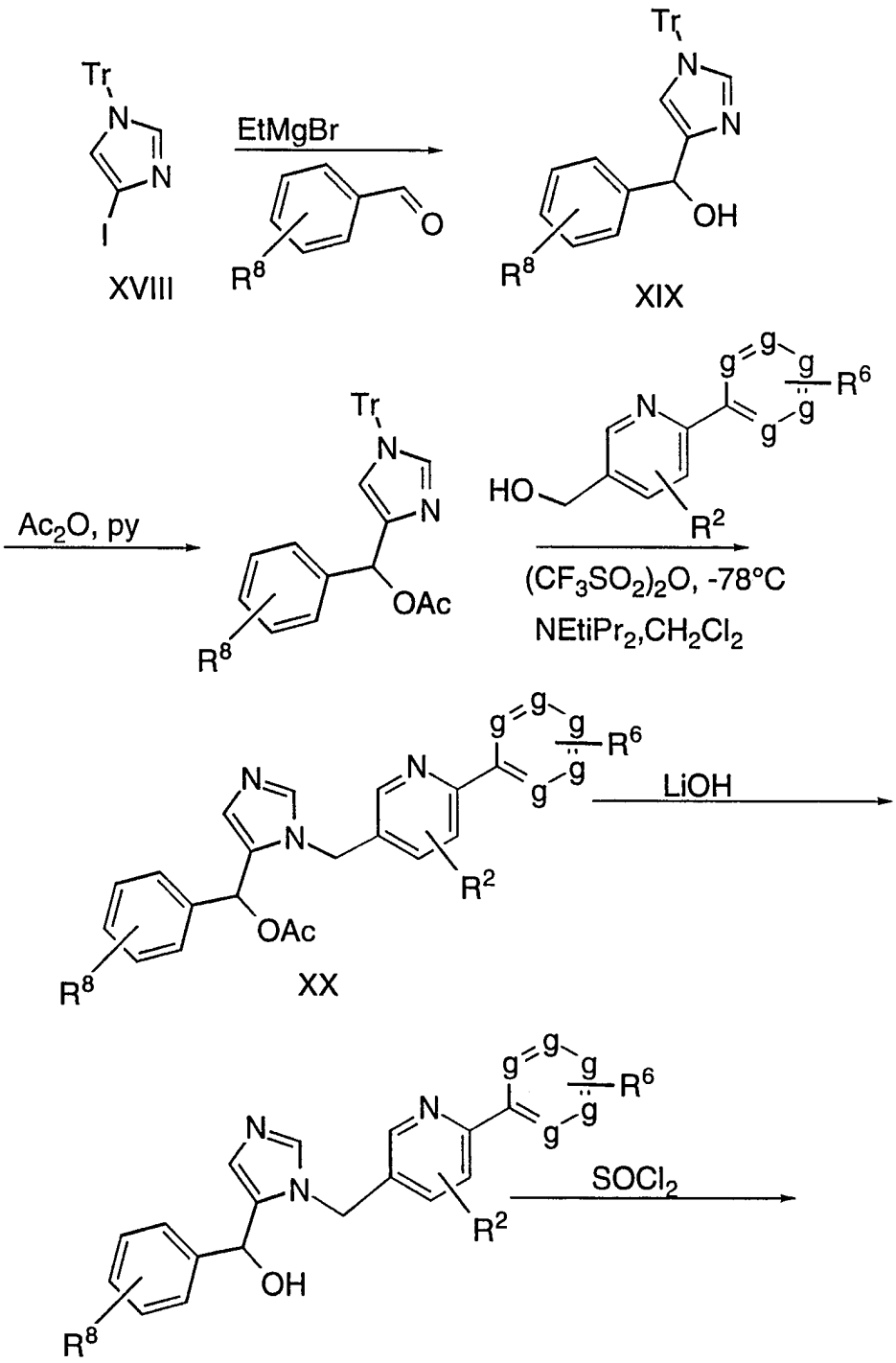
SCHEME 75


i, Na, MeOH
ii. 120°C
XIV
TrCl, NEt3
XV
XVI
i. -78°C-20°C
ii. MeOH reflux
XVI

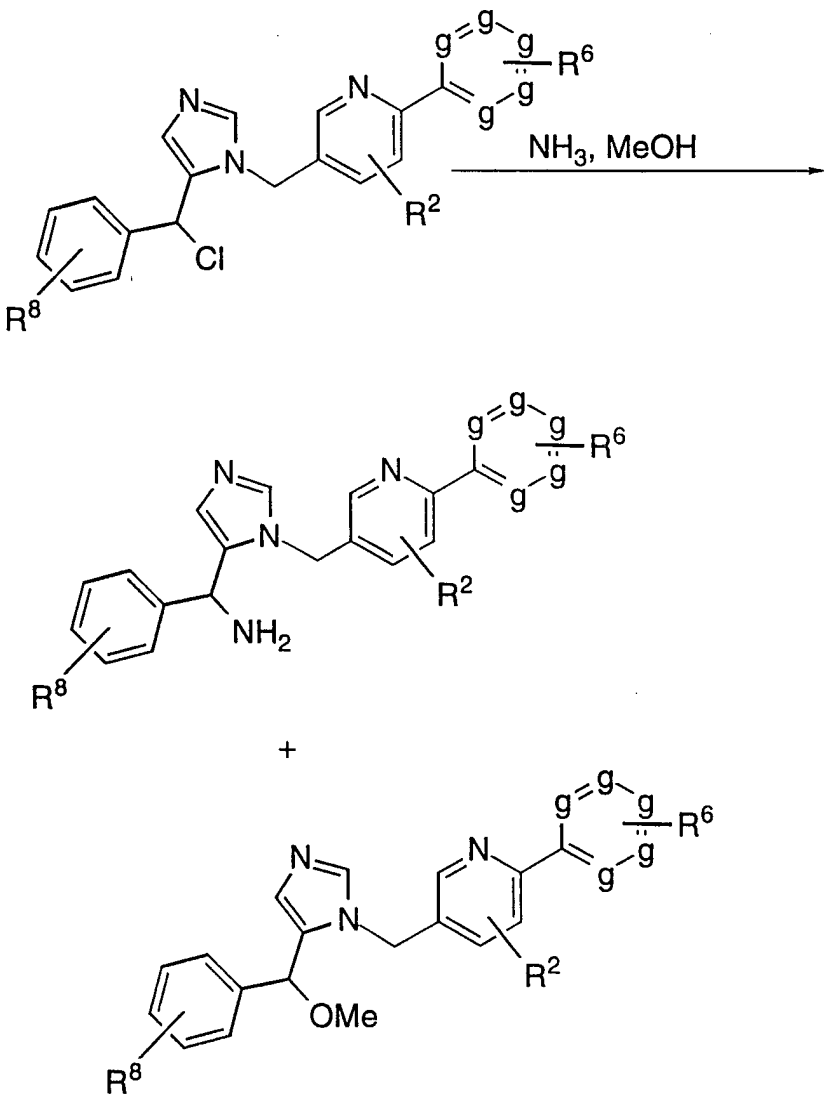
SCHEME 76


i, Na, MeOH
ii. 120°C
TrCl, NEt3
i. -78°C-20°C
ii. MeOH reflux
DMF, Pd(PPh3)4
K3PO4, 80°C
XVII

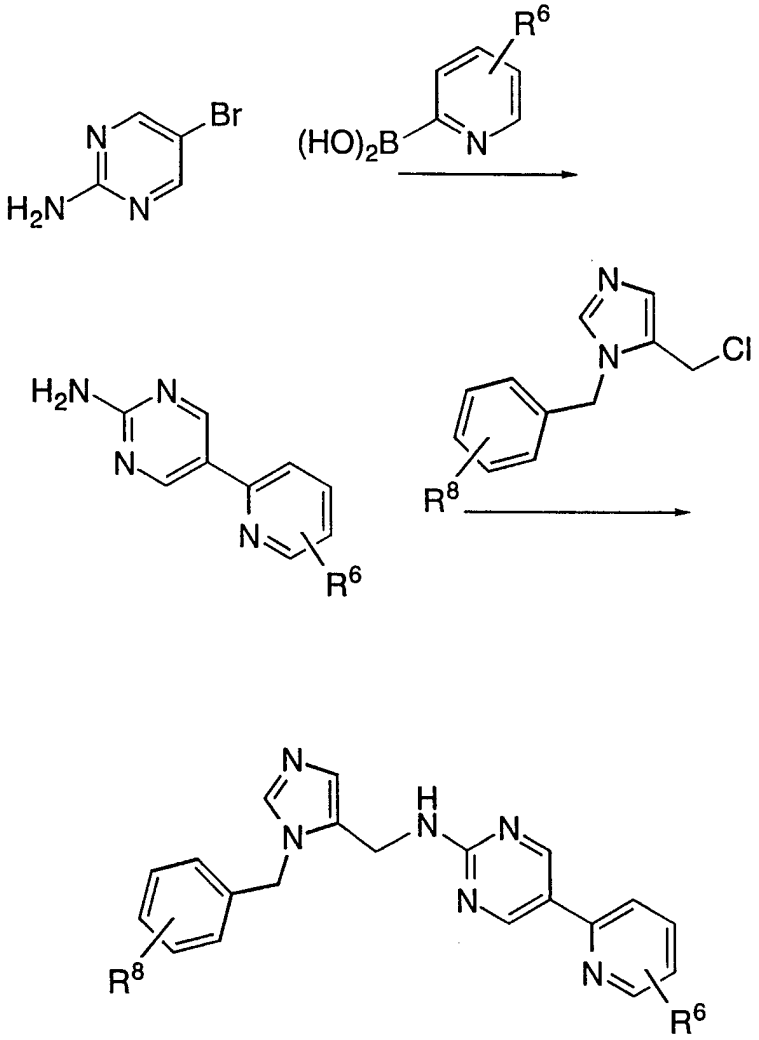
SCHEME 77


Tr
N
N
I
XVIII
EtMgBr
O
R8
OH
XIX
Ac2O, py
OAc
HO
R2
(CF3SO2)2O, -78°C
NEtiPr2,CH2Cl2
R6
LiOH
XX
SOCl2

SCHEME 77 (continued)



SCHEME 78



The farnesyl transferase inhibitors of formula (II-j) can be synthesized in accordance with Schemes 79-88, 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^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents.

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. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 79-88:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 79-88 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl side chain. Thus, in Scheme 79, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinone **1** may be reacted under coupling conditions with a suitably substituted iodobenzyl alcohol to provide the intermediate alcohol **2**. The intermediate alcohol **2** may converted to the corresponding bromide **3**. The bromide **3** may be coupled to a suitably substituted benzylimidazolyl **4** to provide, after deprotection, the instant compound **5**.

Schemes 80-82 illustrate methods of synthesizing related or analogous key alcohol intermediates, which can then be processed as described in Scheme 79. Thus, Scheme 80 illustrates pyridinonyl-pyridyl alcohol forming reactions starting with the suitably substituted iodonicotinate **6**.

Scheme 81 illustrates preparation of the intermediate alcohol **9** wherein the terminal lactam ring is saturated. Acylation of a suitably substituted 4-aminobenzyl alcohol **7** with a suitably substituted brominated acyl chloride provides the bisacylated intermediate **8**. Closure of the lactam ring followed by saponifi-

action of the remaining acyl group provides the intermediate alcohol. Preparation of the homologous saturated lactam **10** is illustrated in Scheme 82.

Scheme 83 illustrates the synthesis of the alcohol intermediate **13** which incorporates a terminal pyrazinone moiety. Thus, the amide of a suitably substituted amino acid **11** is formed and reacted with glyoxal to form the pyrazine **12**, which then undergoes the Ullmann coupling to form intermediate **13**.

Scheme 84 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **14** may be selectively iodinated to provide the 5-iodoimidazole **15**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **16**. Intermediate **16** can then undergo the alkylation reactions that were described hereinabove.

Scheme 85 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the bicyclic moiety via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **17**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **18**. The amine **18** may then react under conditions well known in the art with various activated bicyclic moieties to provide the instant compounds shown.

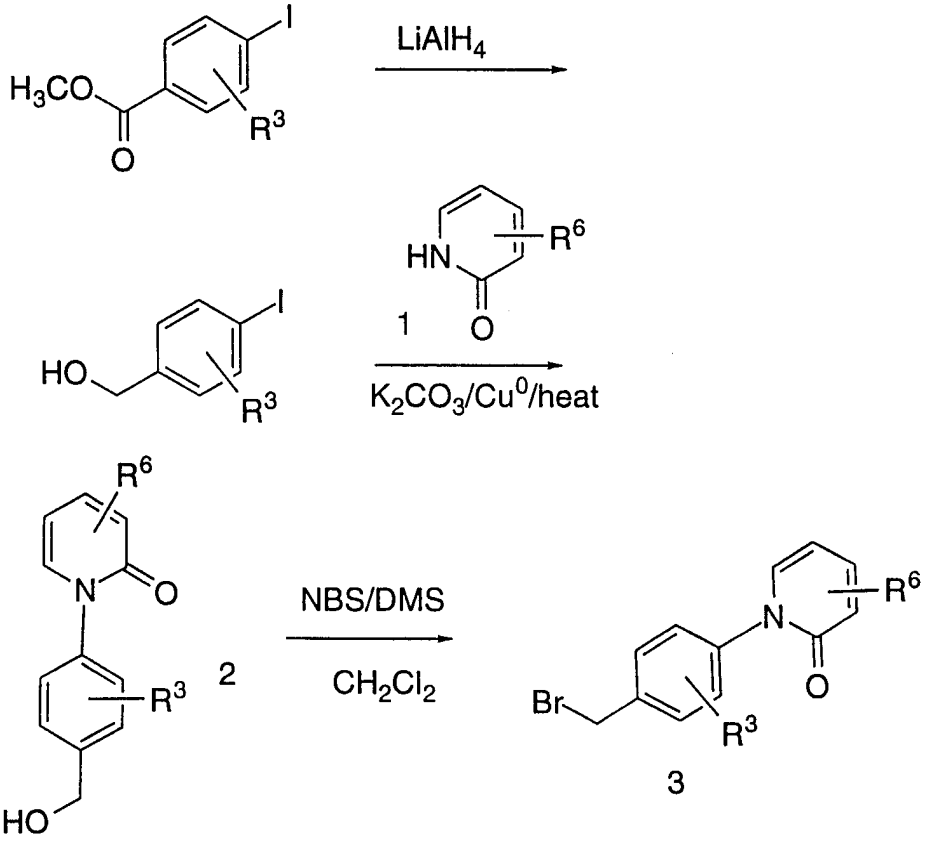
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 86. The suitably substituted phenol **19** may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole **20**. After selective protection of one of the imidazolyl nitrogens, the intermediate **21** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 87. Thus, the N-

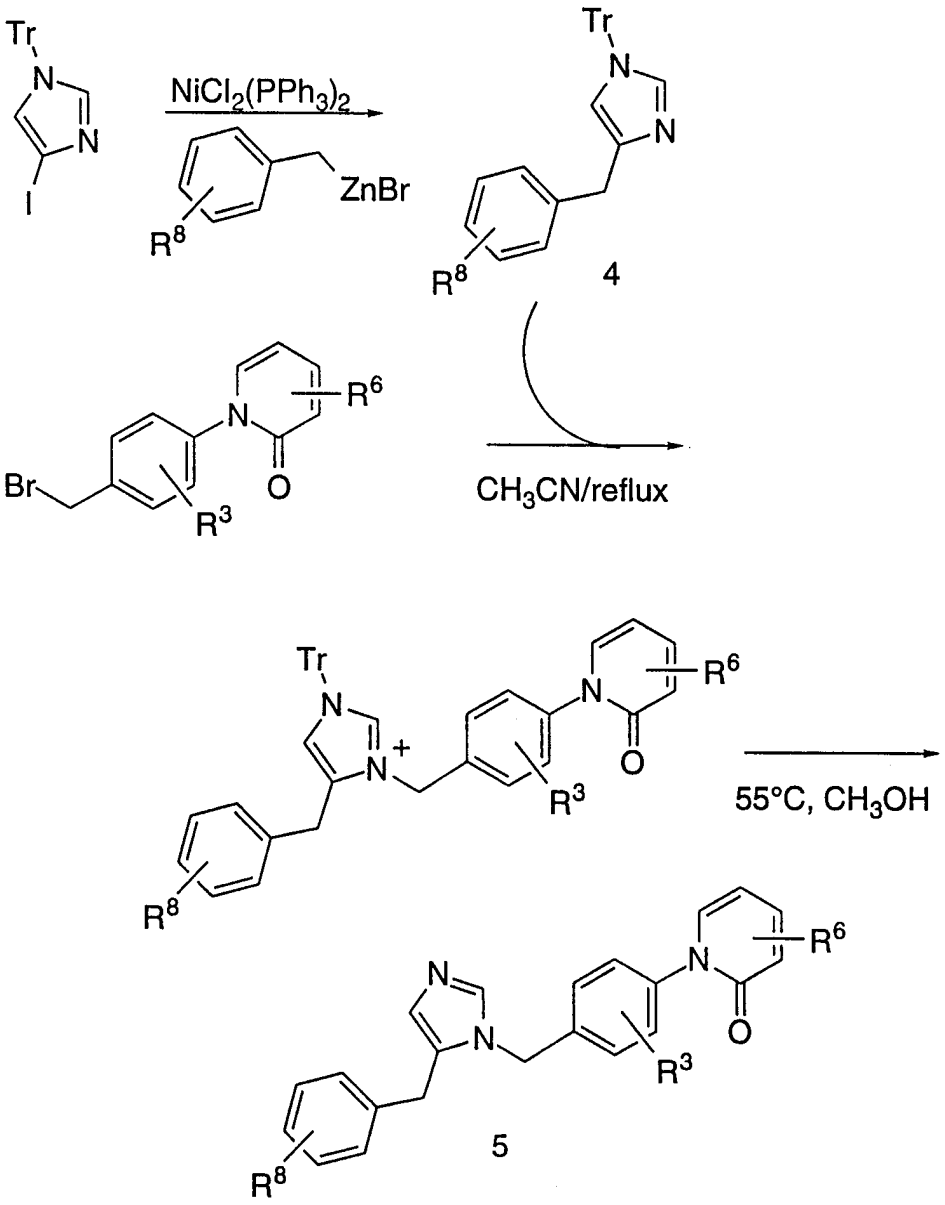
protected imidazolyl iodide **22** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **23**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 79) provides the instant compound **24**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 88 illustrates incorporation of an acetyl moiety as the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds. Thus the readily available methylphenone **25** undergoes the Ullmann reaction and the acetyl is brominated to provide intermediate **26**. Reaction with the imidazolyl reagent **4** provides, after deprotection, the instant compound **27**.

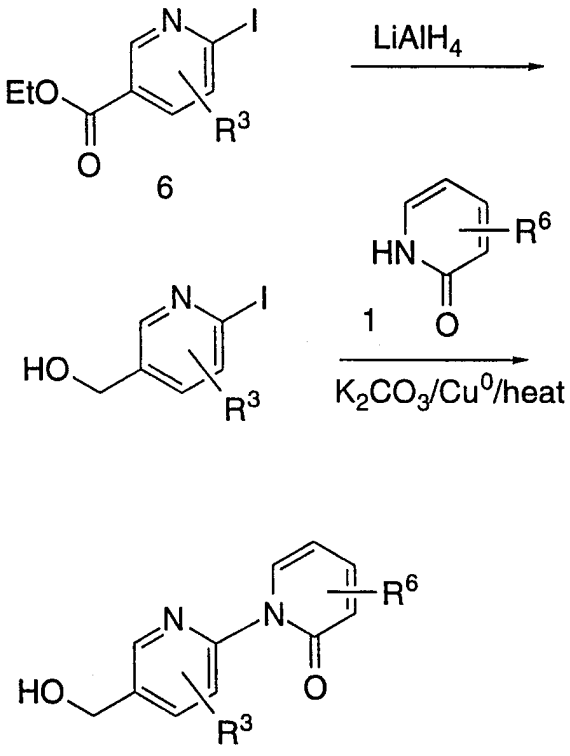
SCHEME 79



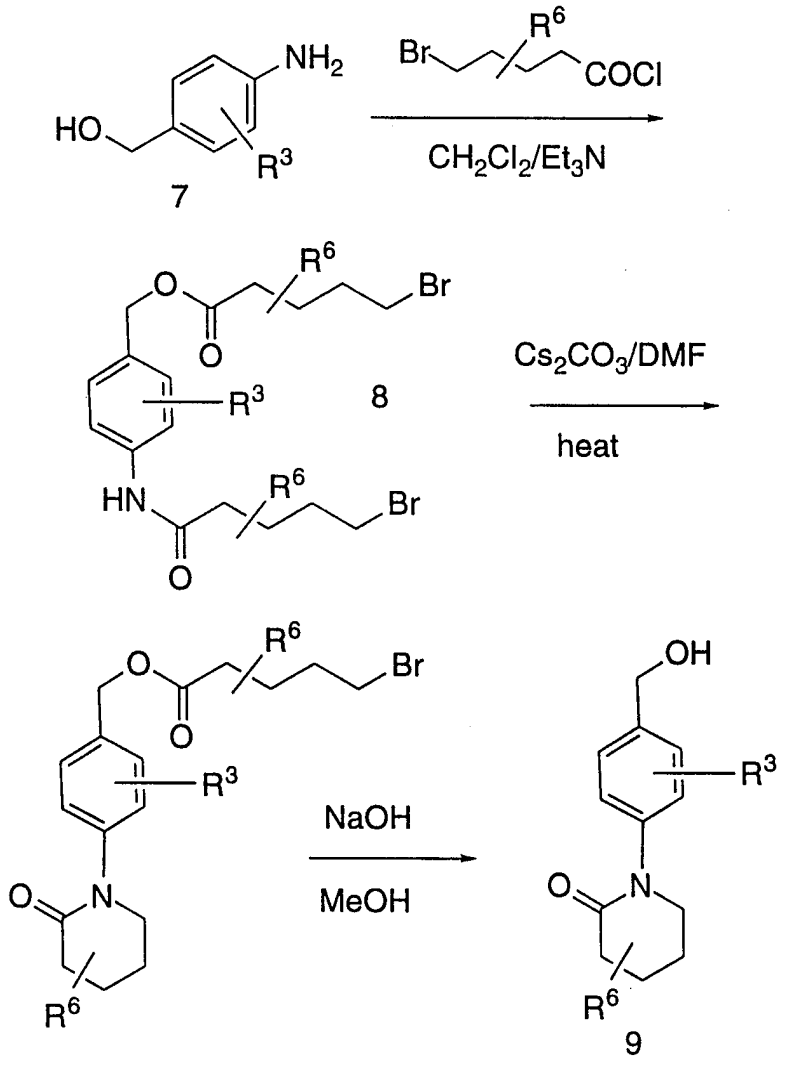
SCHEME 79 (continued)



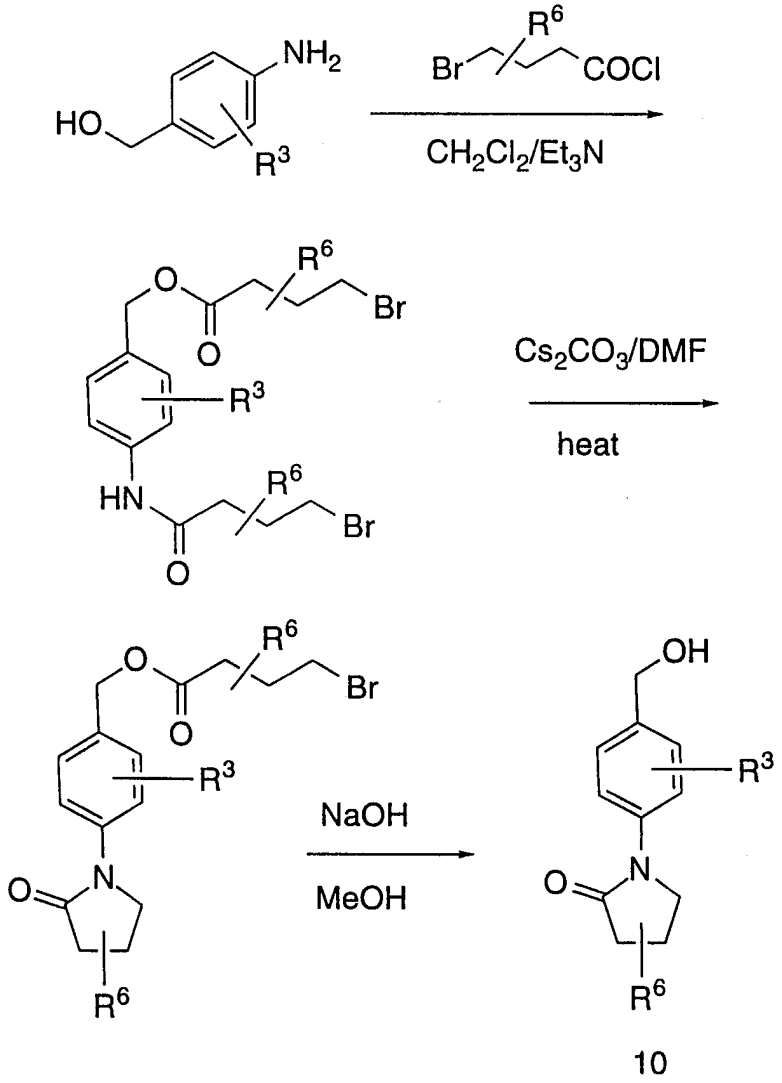
SCHEME 80



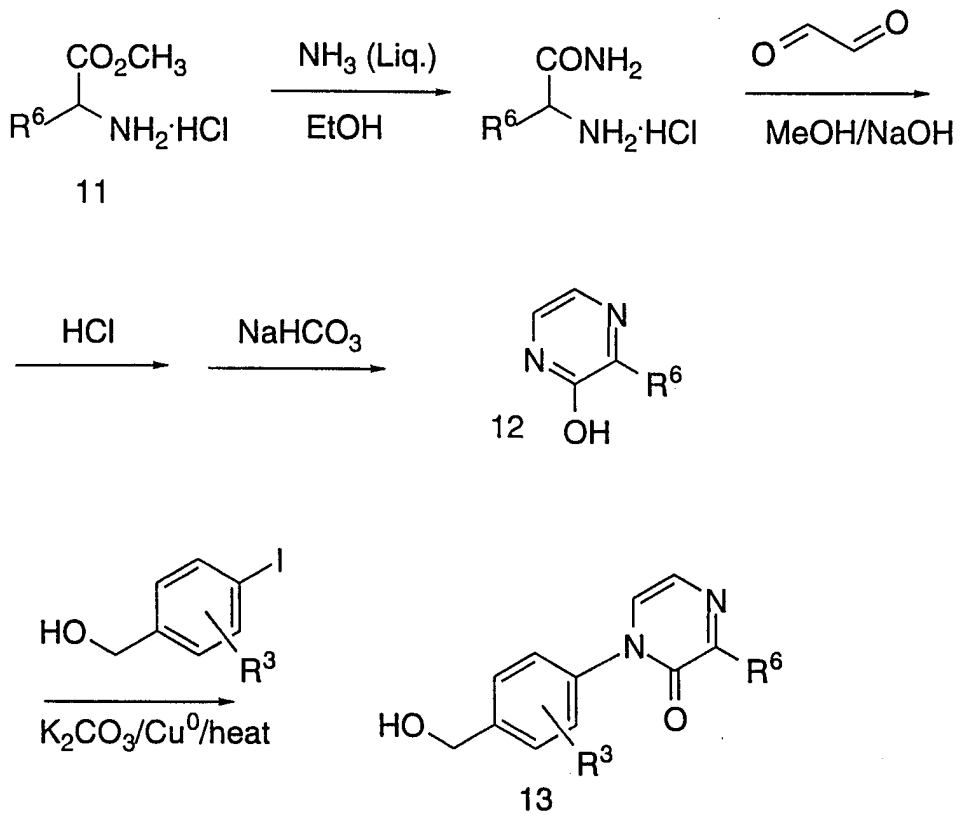
SCHEME 81


NH2
HO
R3
7
R6
Br
COCl
CH2Cl2/Et3N
O
Br
R6
O
R3
8
HN
R6
Br
O
Cs2CO3/DMF
heat
O
Br
R6
O
R3
O
N
R6
NaOH
MeOH
OH
R3
O
N
R6
9

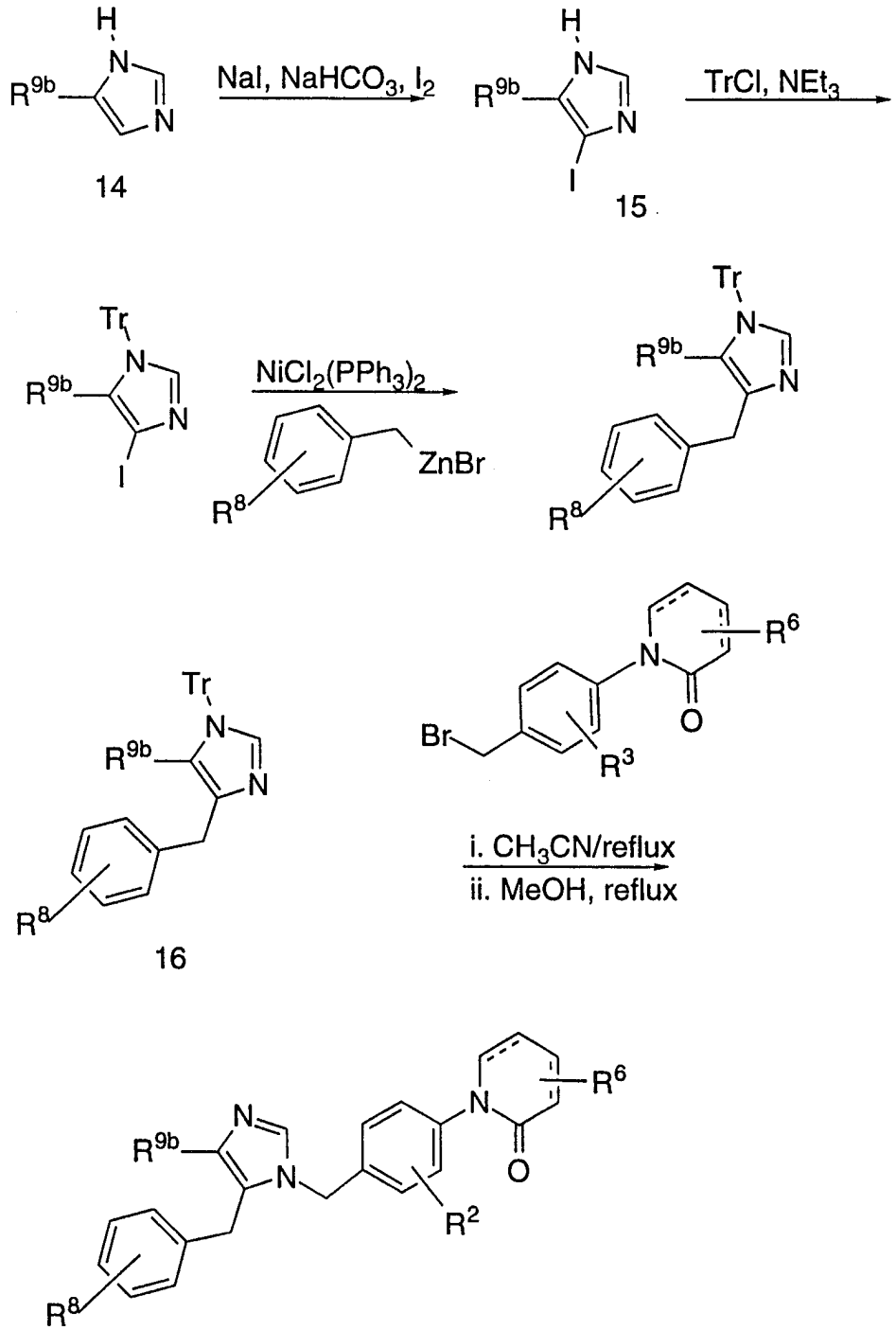
SCHEME 82


NH2
HO
R3
R6
Br
COCl
CH2Cl2/Et3N
O
Br
Cs2CO3/DMF
heat
HN
NaOH
MeOH
OH
N
10

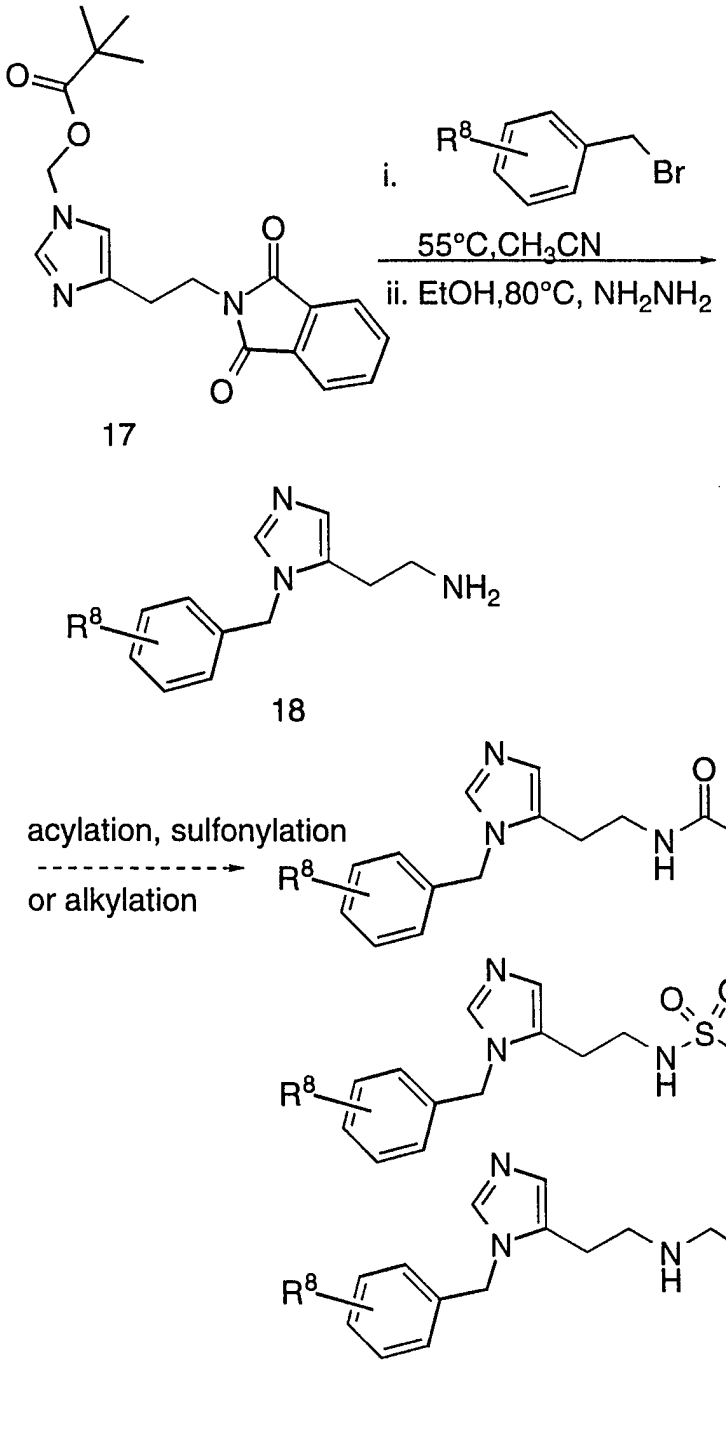
SCHEME 83


CO2CH3
R6
NH2·HCl
11
NH3 (Liq.)
EtOH
CONH2
R6
NH2·HCl
O
O
MeOH/NaOH
HCl
NaHCO3
N
N
R6
12
OH
HO
I
R3
K2CO3/Cu0/heat
HO
N
N
R6
O
R3
13

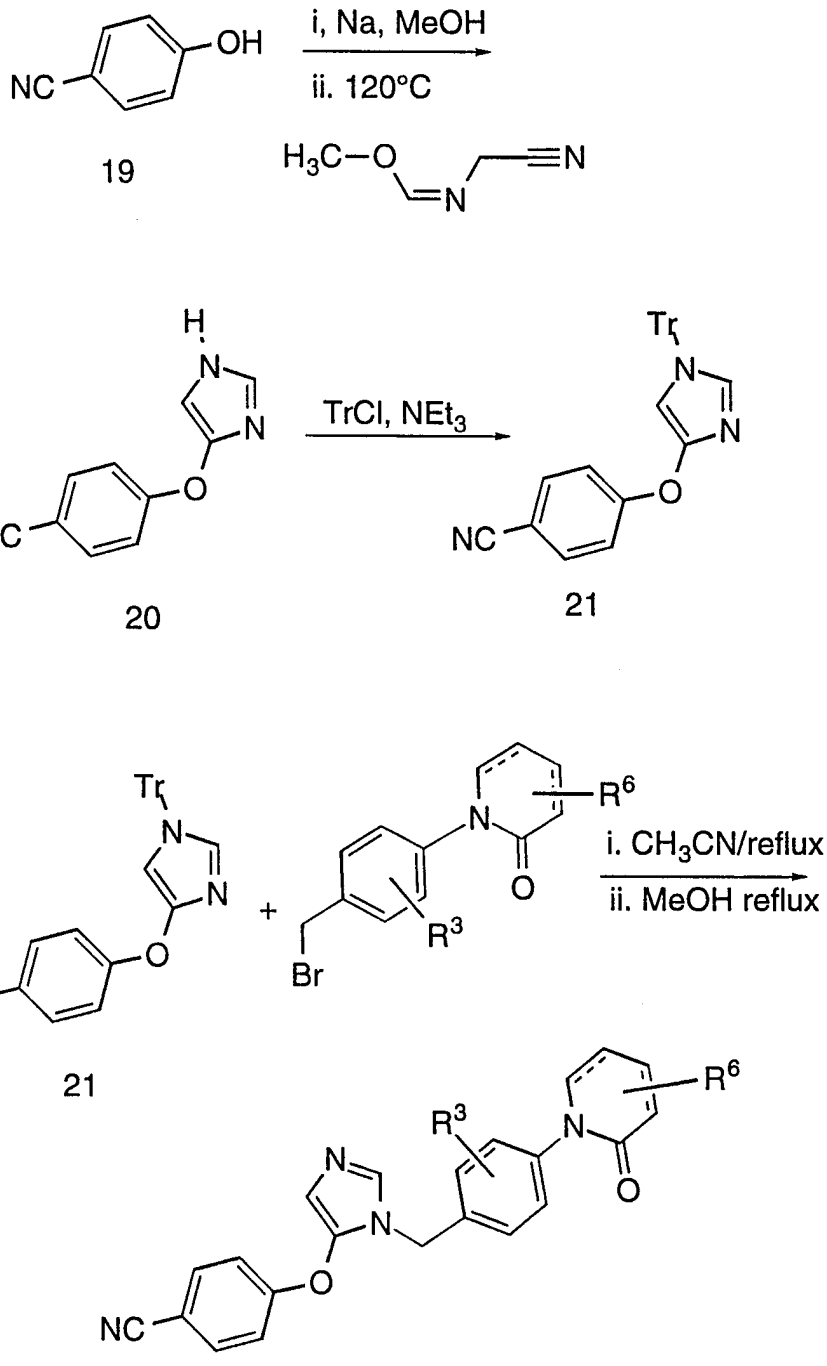
SCHEME 84


NaI, NaHCO3, I2
TrCl, NEt3
NiCl2(PPh3)2
ZnBr
i. CH3CN/reflux
ii. MeOH, reflux

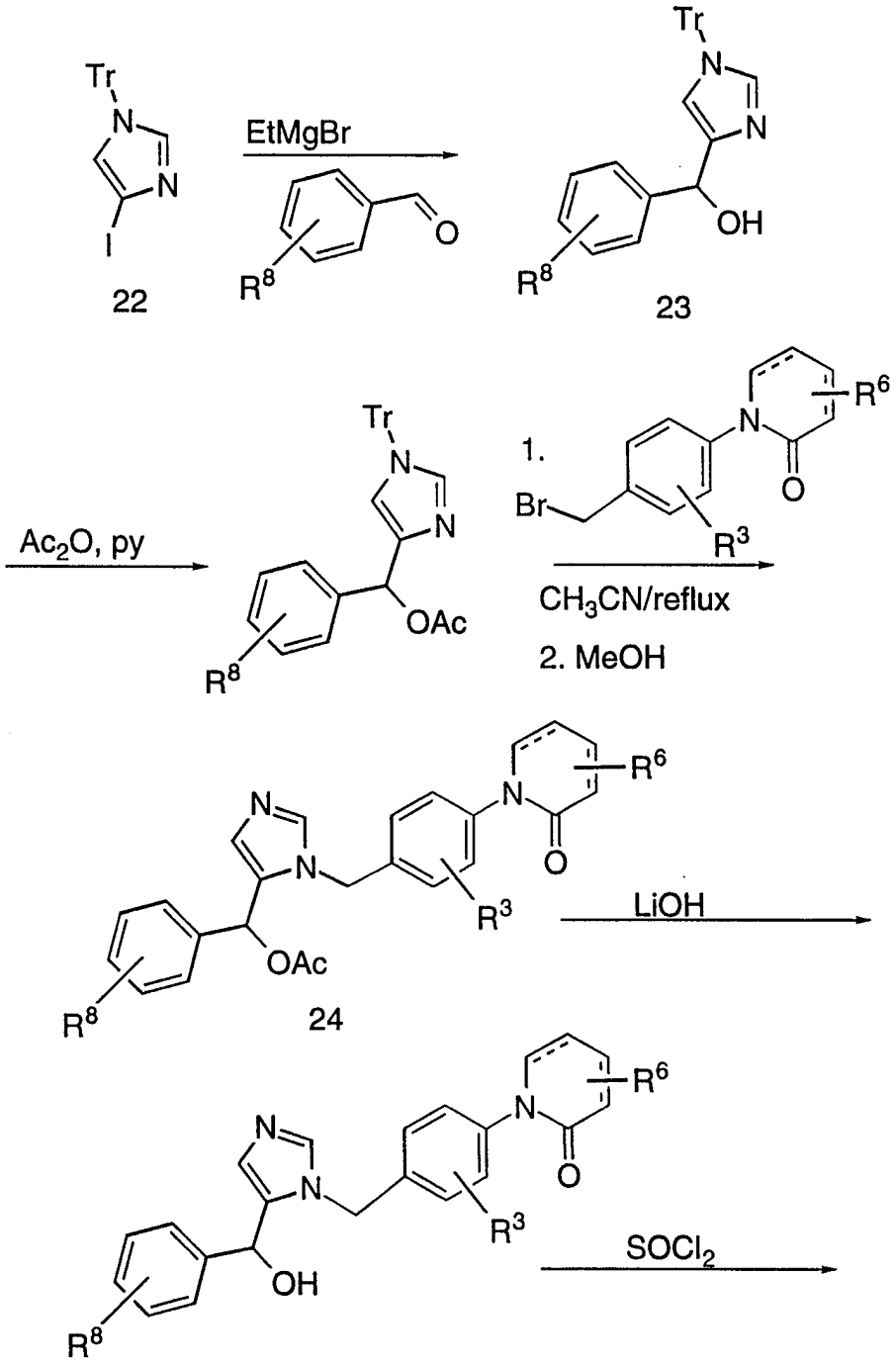
SCHEME 85


i.
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
17
18
acylation, sulfonylation
or alkylation

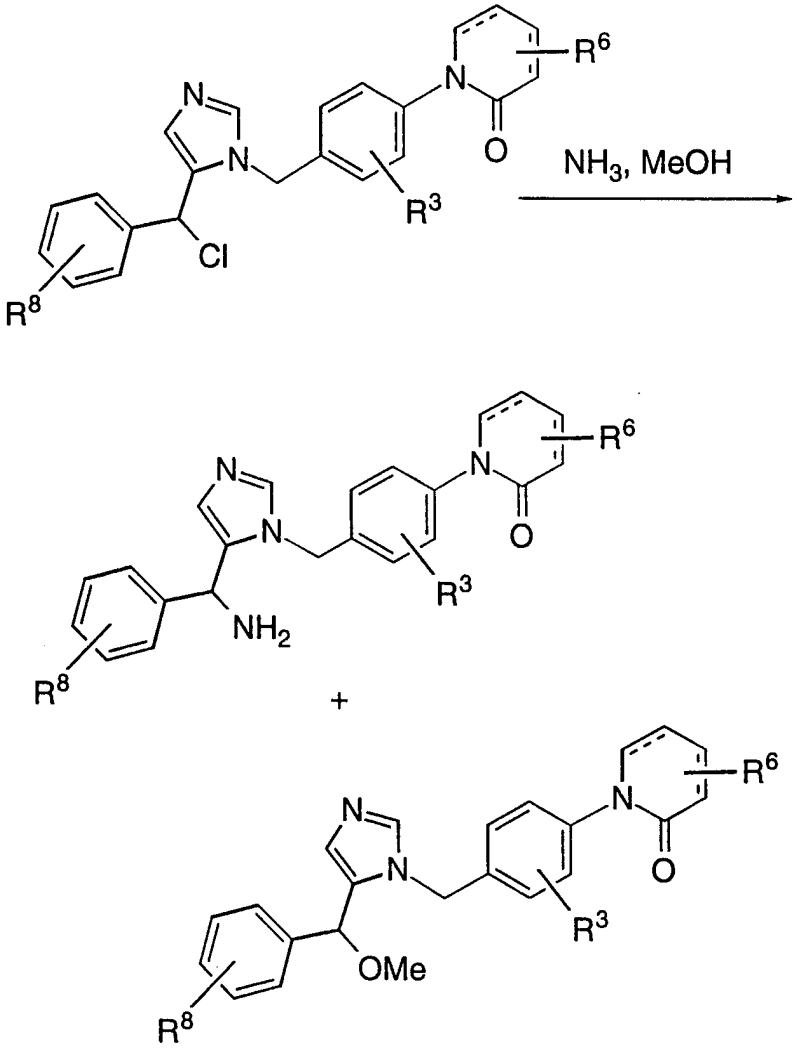
SCHEME 86


OH
NC
i, Na, MeOH
ii. 120°C
19
H3C–O
N
N
H
TrCl, NEt3
Tr
20
21
R6
R3
Br
i. CH3CN/reflux
ii. MeOH reflux

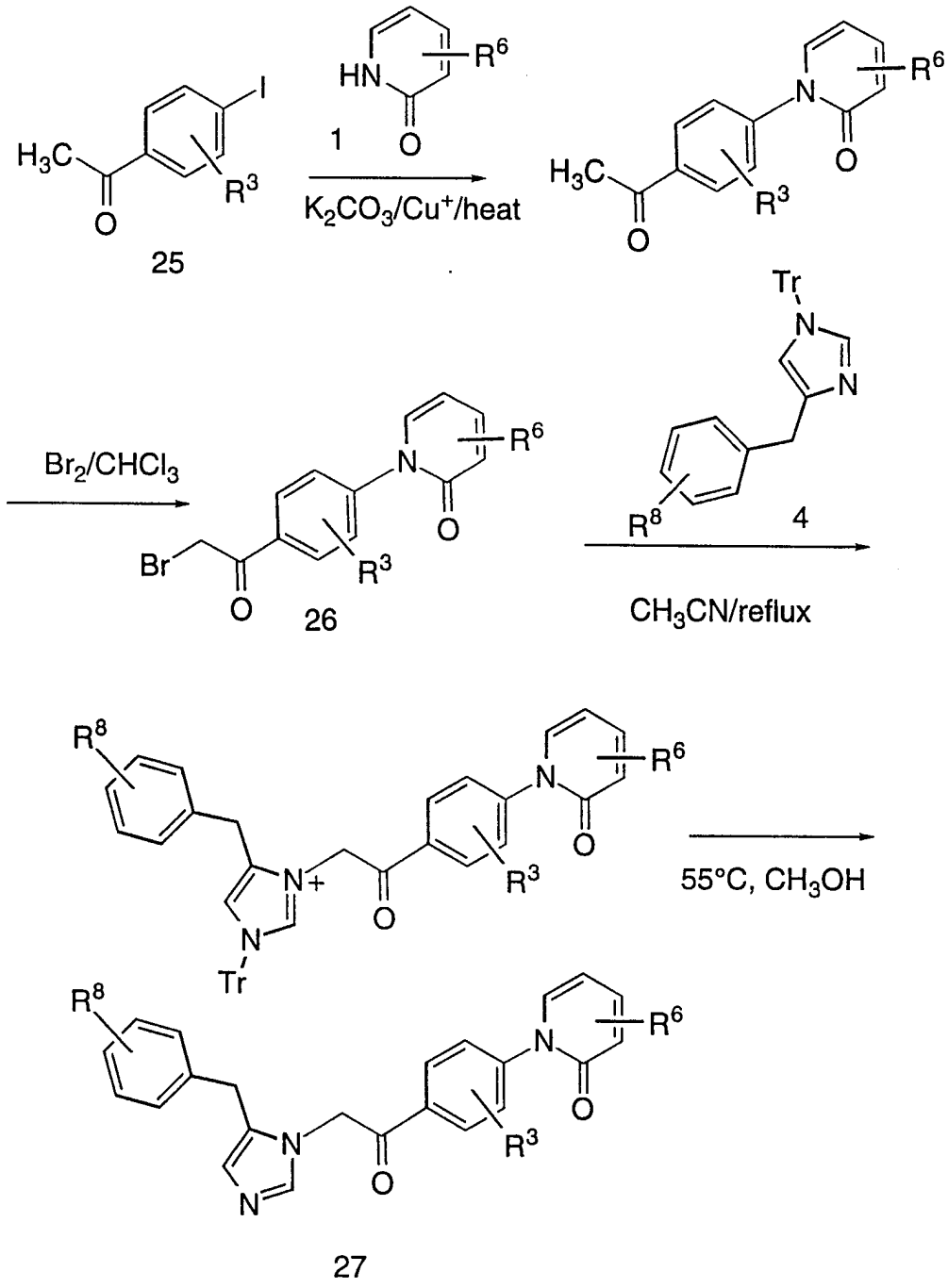
SCHEME 87


Tr
N
N
I
22
EtMgBr
O
R8
Tr
N
N
OH
R8
23
Ac2O, py
Tr
N
N
OAc
R8
1.
Br
R3
R6
N
O
CH3CN/reflux
2. MeOH
R6
N
N
N
O
R3
OAc
R8
24
LiOH
R6
N
N
N
O
R3
OH
R8
SOCl2

SCHEME 87 (continued)



SCHEME 88



27

The farnesyl transferase inhibitors of formula (II-k) can be synthesized in accordance with Schemes 89-97, 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^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents.

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. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 89-97:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 89-96 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl side-chain. Thus, in Scheme 89, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinonyl alcohol **29** may be synthesized starting from the corresponding isonicotinate **28** according to procedures described by Boekelhiede and Lehn (*J. Org. Chem.*, 26:428-430 (1961)). The alcohol is then protected and reacted under Ullmann coupling conditions with a suitably substituted phenyl iodide, to provide the intermediate bicyclic alcohol **30**. The intermediate alcohol **30** may converted to the corresponding bromide **31**. The bromide **31** may be coupled to a suitably substituted benzylimidazolyl **32** to provide, after deprotection, the instant compound **33**.

Schemes 90-92 illustrate methods of synthesizing related or alcohol intermediates, which can then be processed as described in Scheme 89. Thus, Scheme 90 illustrates preparation of a pyridyl-pyridinonyl alcohol and thienylpyridinonyl alcohol starting with the suitably substituted halogenated heterocycles.

Scheme 91 illustrates preparation of the intermediate bromide **36** wherein the preferred pyridinone is replced by a saturated lactam. Acylation of a suitably substituted aniline **34** with a suitably substituted brominated acyl chloride provides the acylated intermediate **35**. Closure of the lactam ring provides the intermediate alcohol, which is converted to the bromide as described above.

Scheme 92 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **37** may be selectively iodinated to provide the 5-iodoimidazole **38**. That imidazole **38** may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **39**. Intermediate **39** can then undergo the alkylation reactions that were described hereinabove.

Scheme 93 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **40**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **41**. The amine **41** may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

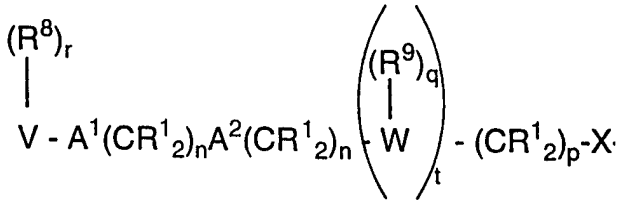
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 94. The suitably substituted phenol **42** may be reacted with methyl

N-(cyano)methanimidate to provide the 4-phenoxyimidazole **43**. After selective protection of one of the imidazolyl nitrogens, the intermediate **44** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 95. Thus, the N-protected imidazolyl iodide **45** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **46**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 89) provides the instant compound **47**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 96 illustrates incorporation of an acetyl moiety as the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds. Thus, the suitably substituted acetyl pyridine **48** is converted to the corresponding pyridinone and undergoes the Ullmann reaction with a suitably substituted phenyl iodide. The acetyl is then brominated to provide intermediate **49**. Reaction with the imidazolyl reagent **32** provides, after deprotection, the instant compound **50**.

Scheme 97 illustrate reactions wherein the moiety

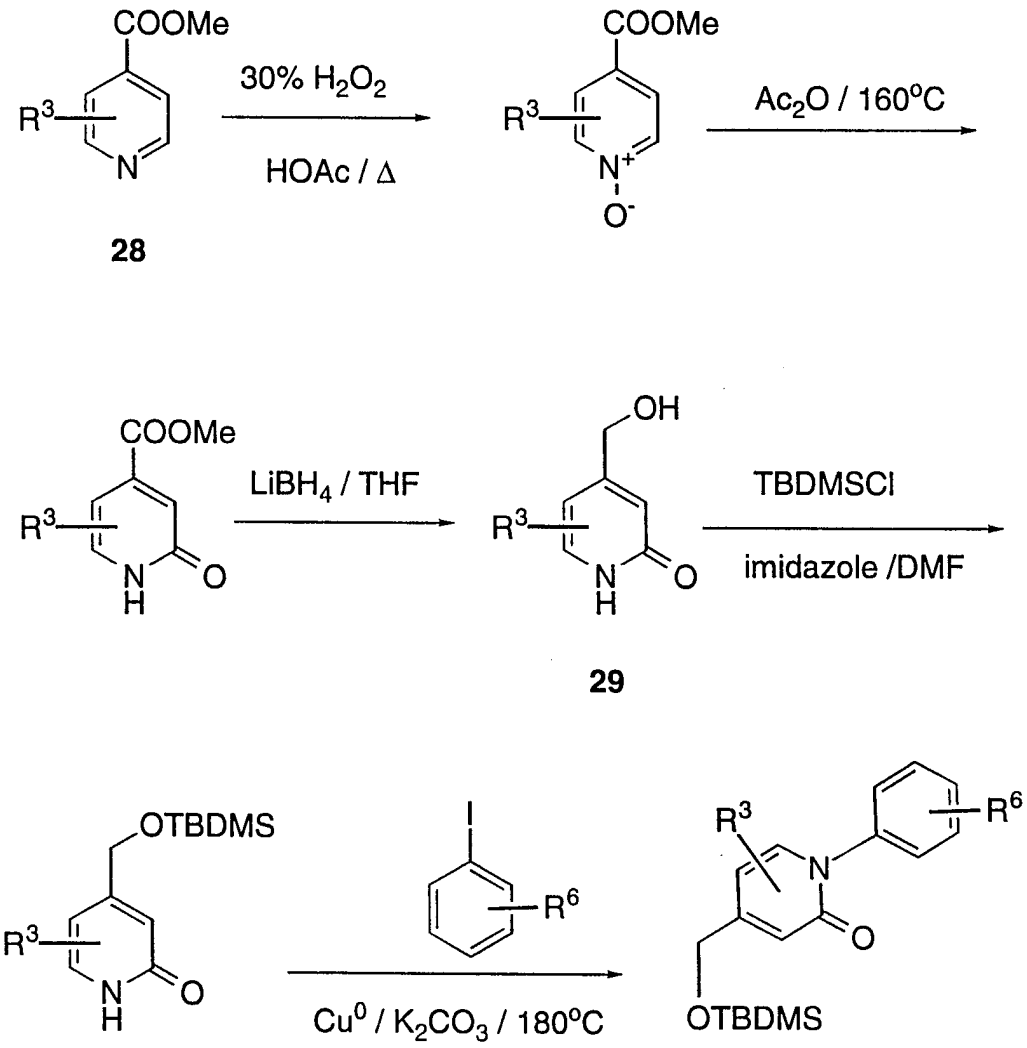


incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

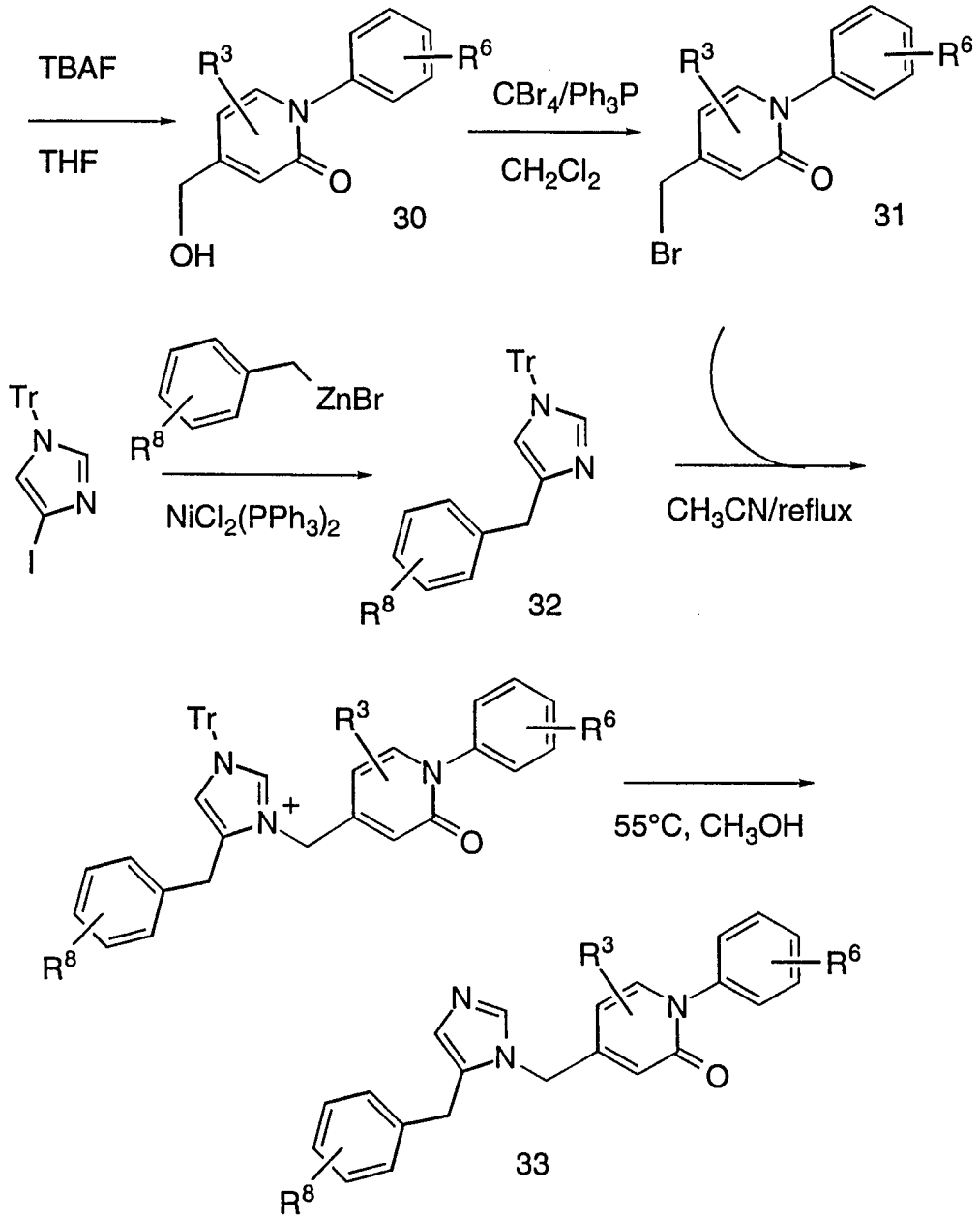
Thus, the intermediates whose synthesis are illustrated in the Schemes, and other pyridinonecarbocyclic and pyridinonehetero-cyclic intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**,

67, 69-75, from the appropriate amino acid. Knochel chemistry may be utilized, as shown in Scheme 97, to incorporate the aryl-pyridinone moiety. Thus, a suitably substituted 4-(bromo)pyridine is converted to the corresponding pyridinone **51** as described above and the pyridinone is coupled to a suitably substituted phenyl iodide as previously described above. The resulting bromide **52** is treated with zinc(0) and the resulting zinc bromide reagent **53** is reacted with an aldehyde to provide the C-alkylated instant compound **54**. Compound **54** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoro-acetic acid in methylene chloride to give the final compound **55**. The compound **55** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **55** can further be selectively protected to obtain **56**, which can subsequently be reductively alkylated with a second aldehyde to obtain compound **57**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **58** can be accomplished by literature procedures.

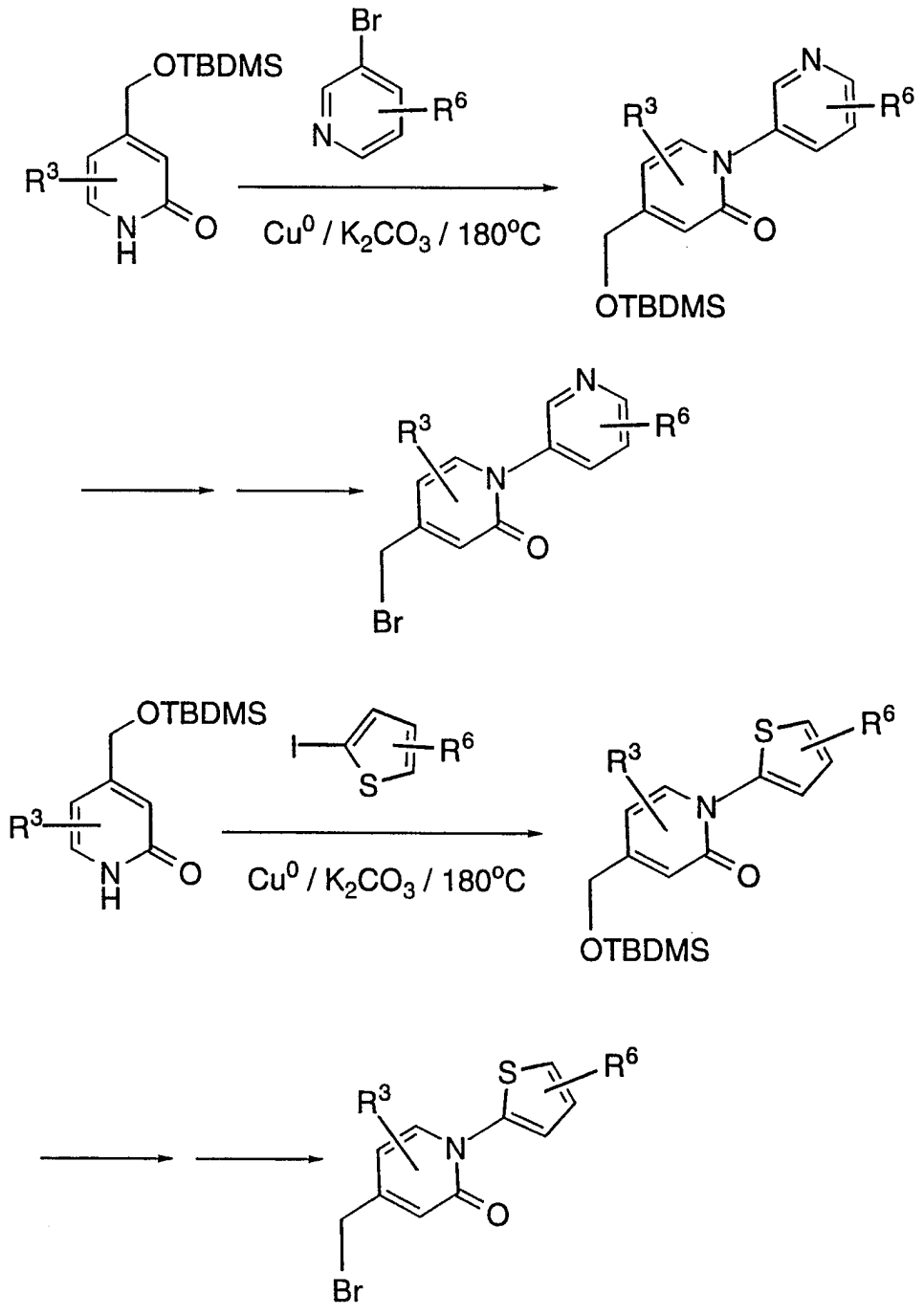
SCHEME 89


COOMe
R3
N
30% H2O2
HOAc / Δ
COOMe
R3
N+
O-
Ac2O / 160°C
28
COOMe
R3
N
H
O
LiBH4 / THF
OH
R3
N
H
O
TBDMSCl
imidazole /DMF
29
OTBDMS
R3
N
H
O
I
R6
Cu0 / K2CO3 / 180°C
R3
N
O
R6
OTBDMS

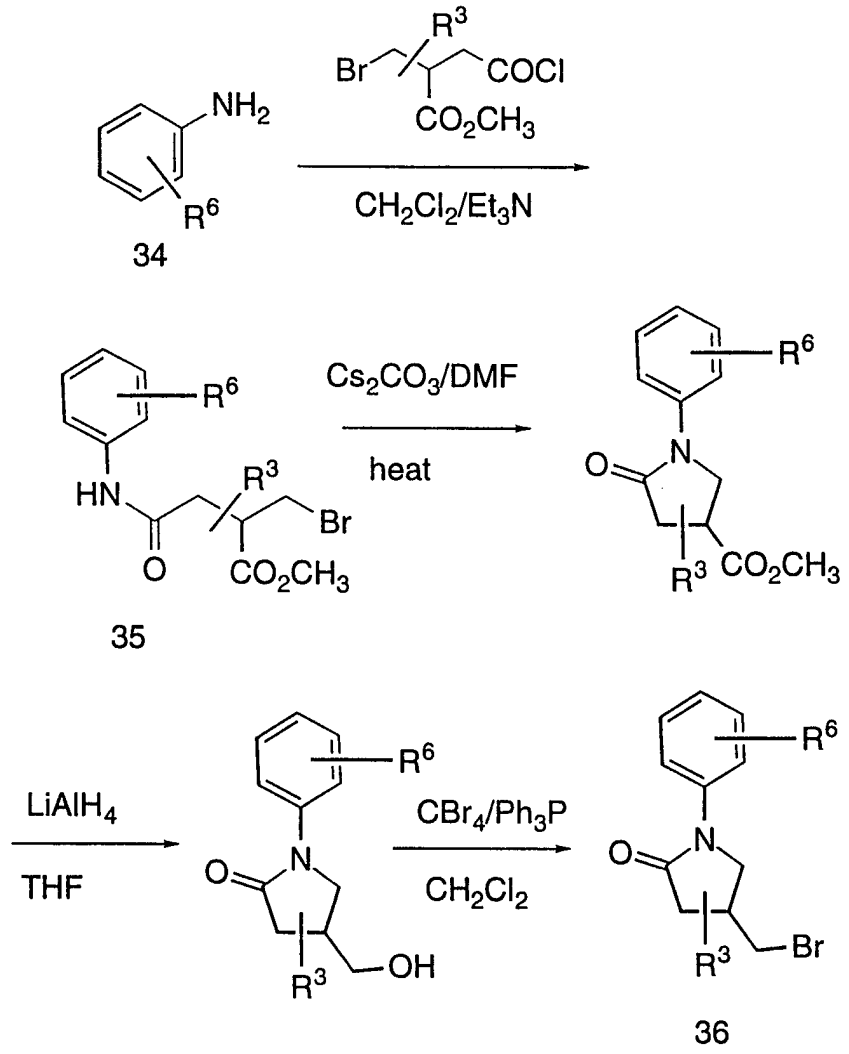
SCHEME 89 (continued)



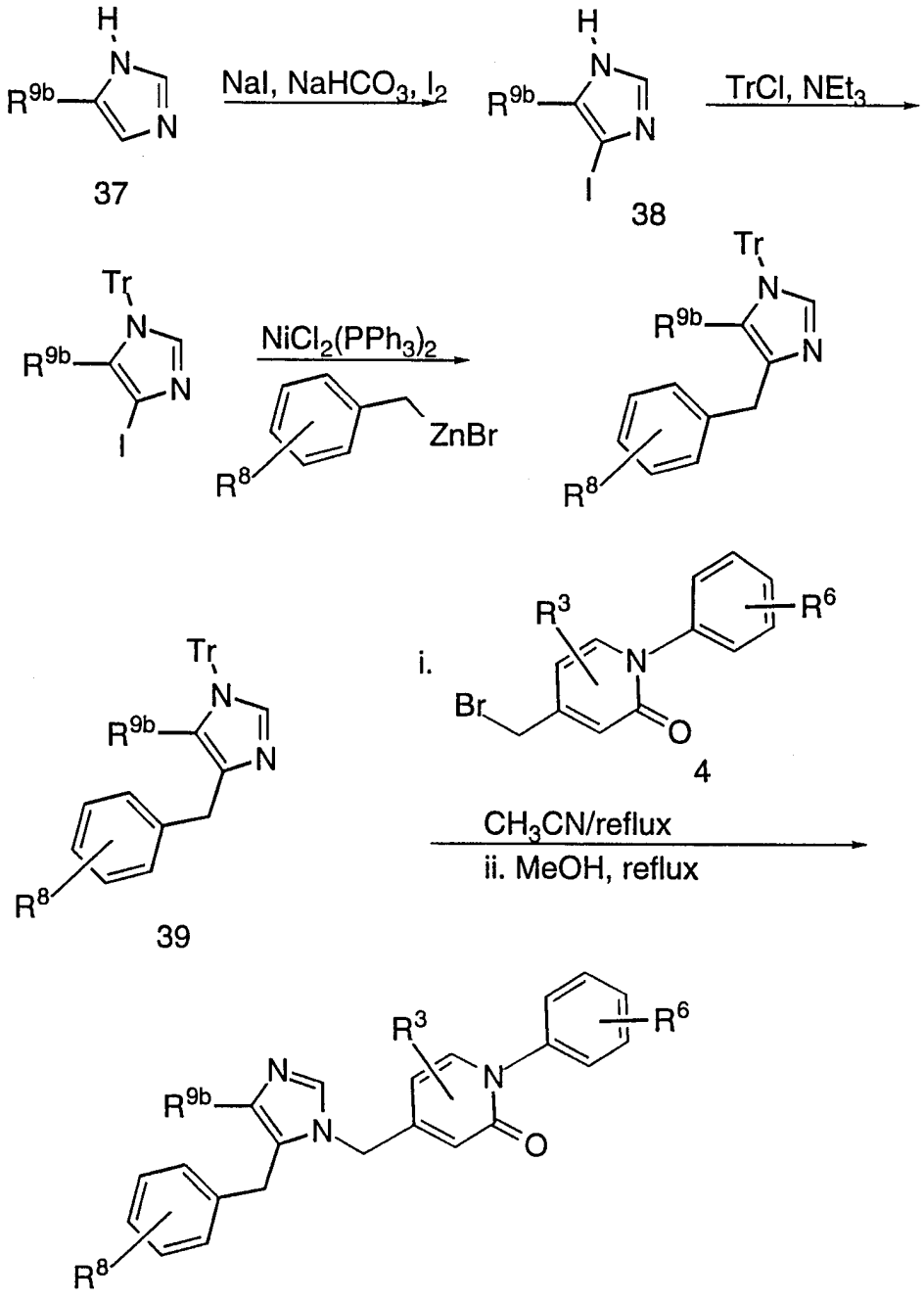
SCHEME 90



SCHEME 91

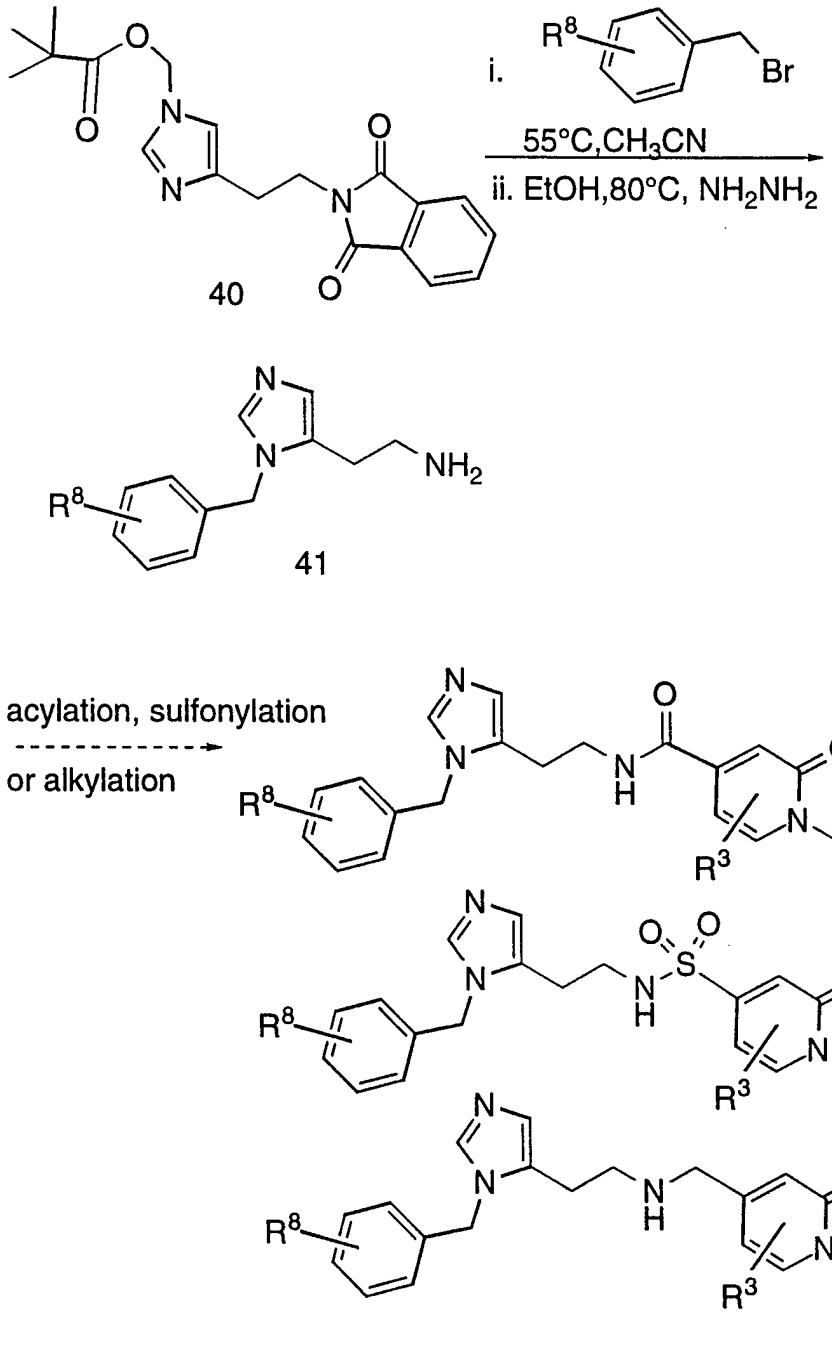

R3
Br
COCl
CO2CH3
NH2
R6
CH2Cl2/Et3N
34
R6
Cs2CO3/DMF
heat
HN
R3
Br
O
CO2CH3
35
R6
N
O
R3
CO2CH3
LiAlH4
THF
R6
N
O
R3
OH
CBr4/Ph3P
CH2Cl2
R6
N
O
R3
Br
36

SCHEME 92

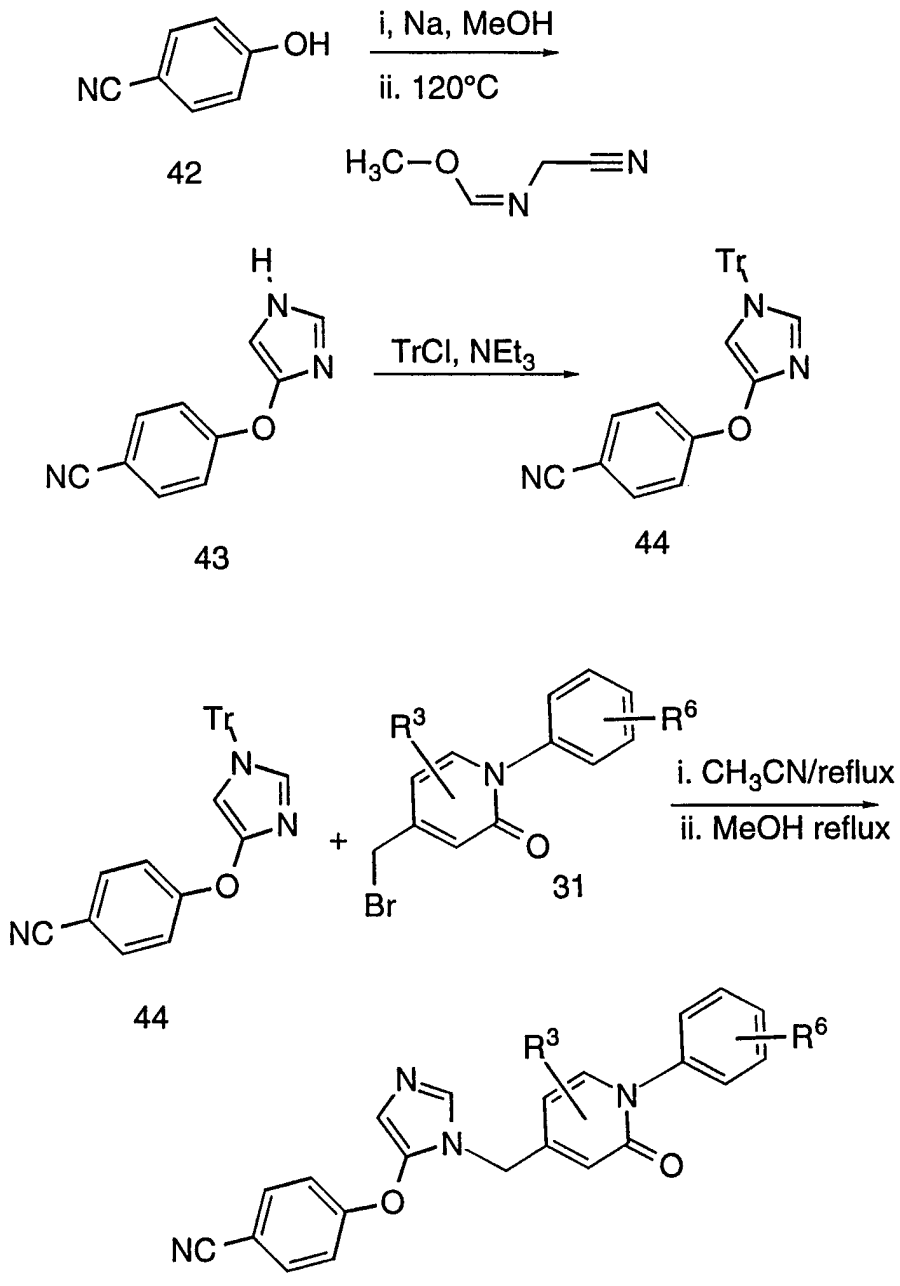


37 38 39 4

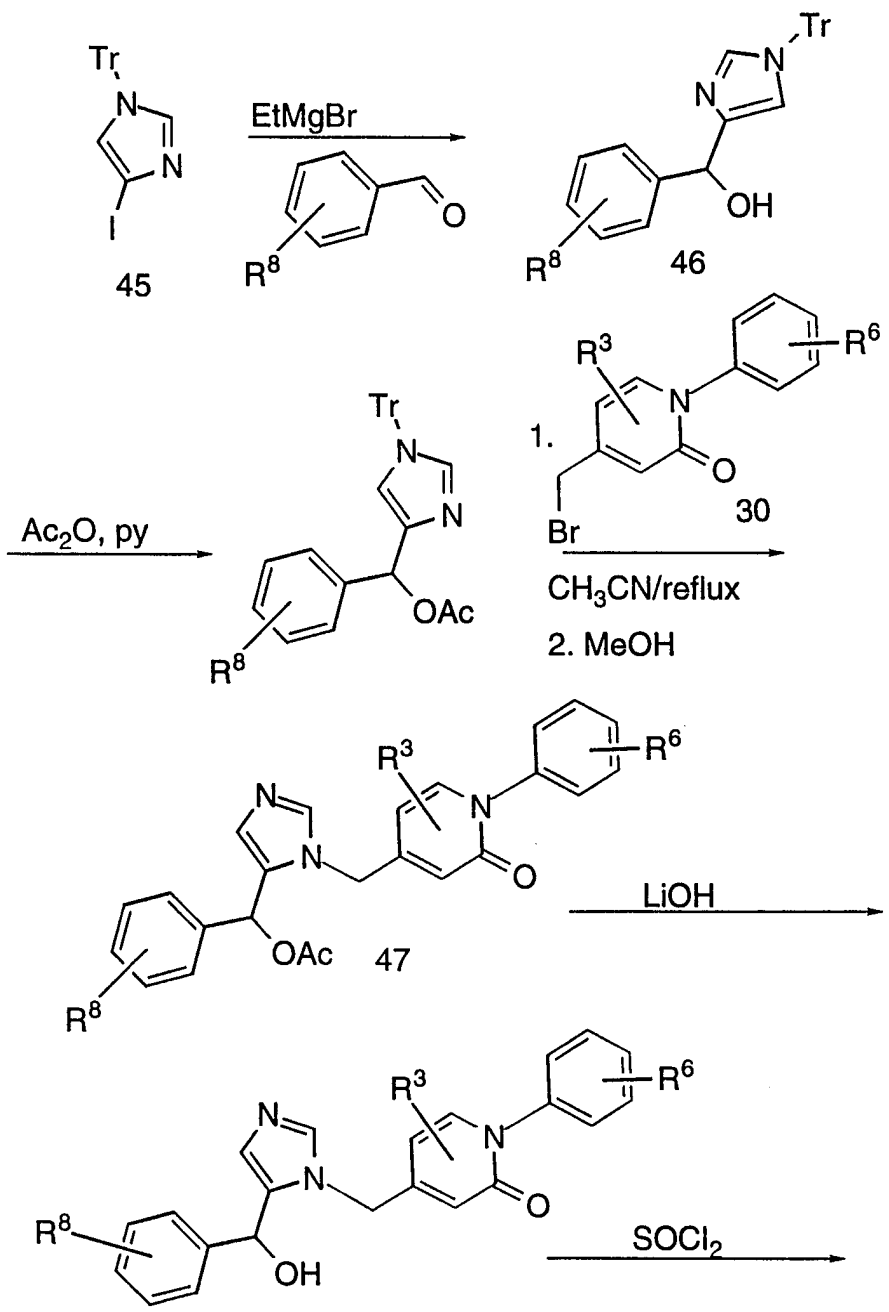
SCHEME 93


i.
Br
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
40
41
acylation, sulfonylation
or alkylation

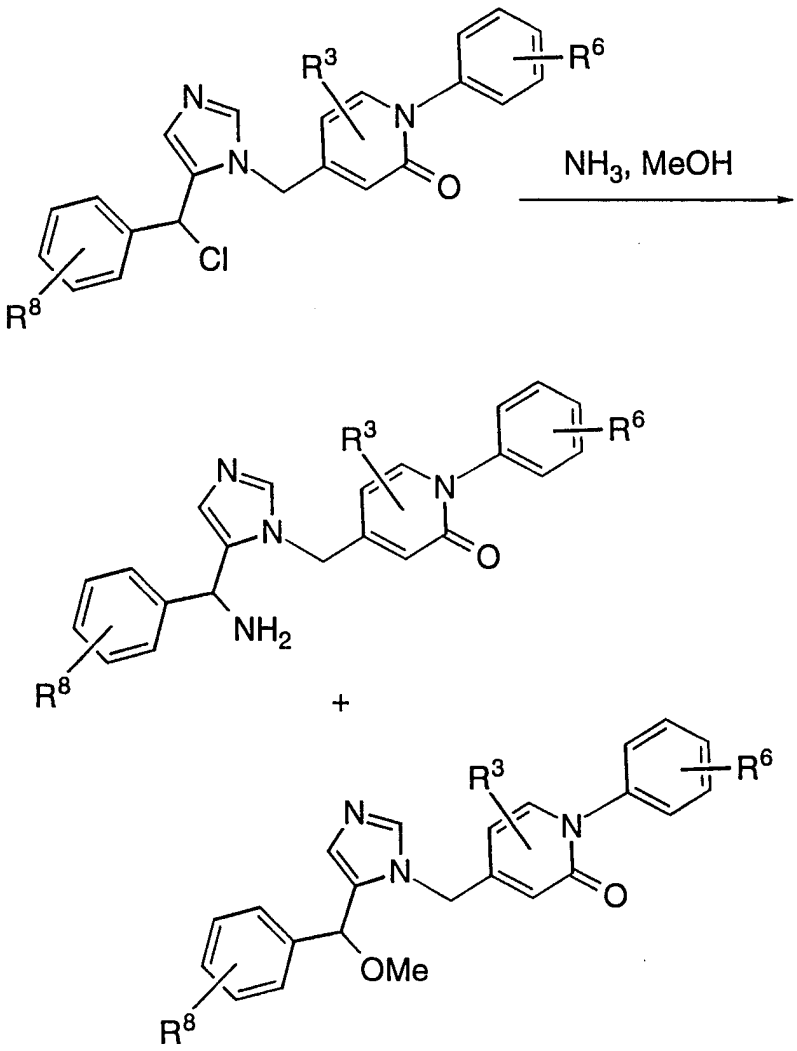
SCHEME 94


i, Na, MeOH
ii. 120°C
42
H_3C-O
N
TrCl, NEt_3
43
44
i. CH_3CN/reflux
ii. MeOH reflux
31
Br
44

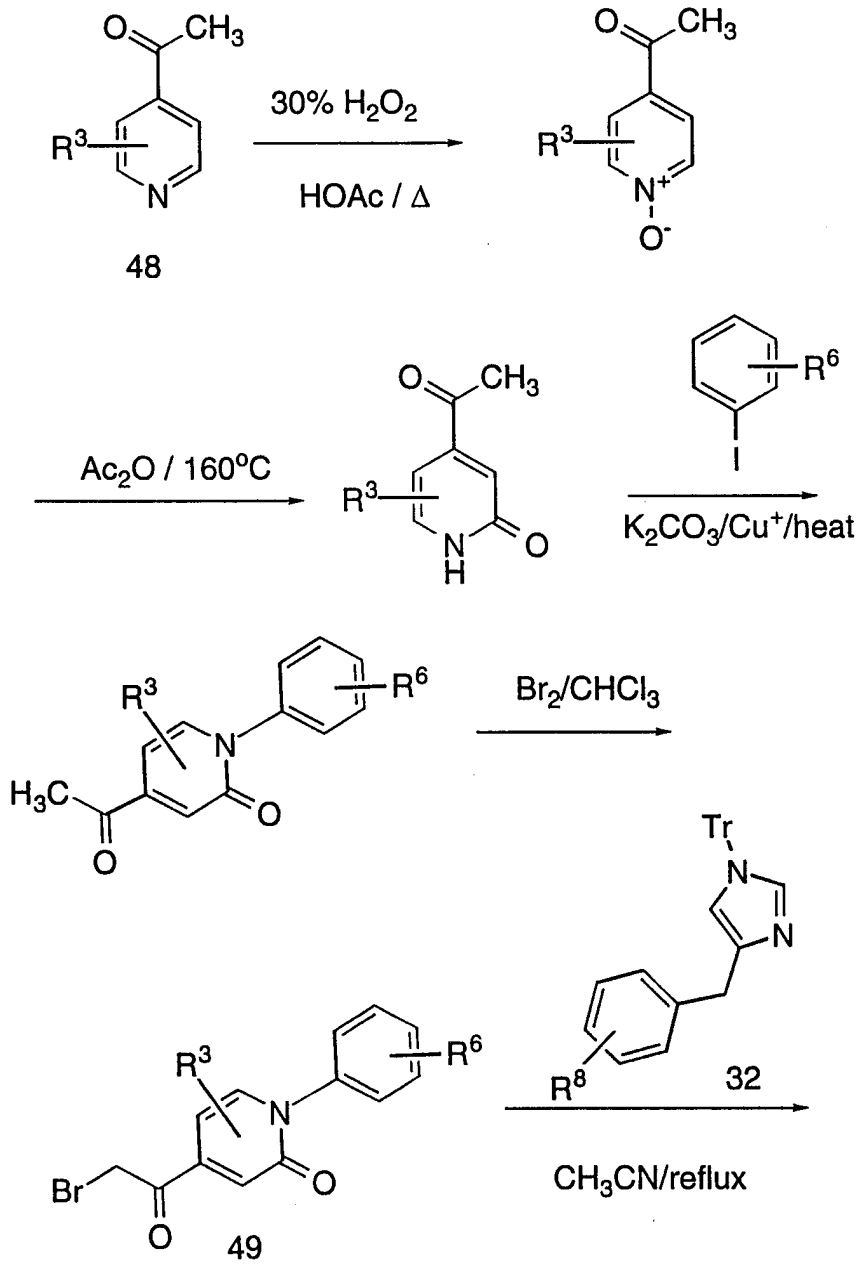
SCHEME 95


Tr
N
N
I
45
EtMgBr
O
R8
Tr
N
N
OH
R8
46
R3
R6
1.
N
O
Br
30
Ac2O, py
Tr
N
N
OAc
R8
CH3CN/reflux
2. MeOH
R3
R6
N
N
N
O
OAc
47
R8
LiOH
R3
R6
N
N
N
O
R8
OH
SOCl2

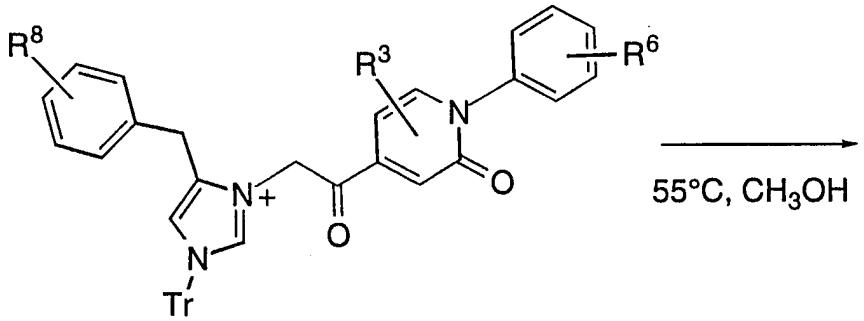
SCHEME 95 (continued)

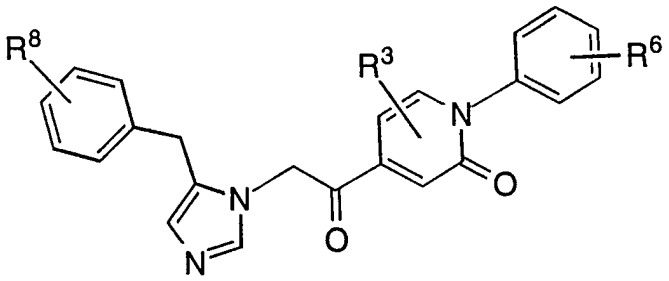


SCHEME 96


30% H_2O_2
HOAc / Δ
48
Ac_2O / 160°C
K_2CO_3/Cu^+/heat
$Br_2/CHCl_3$
32
CH_3CN/reflux
49

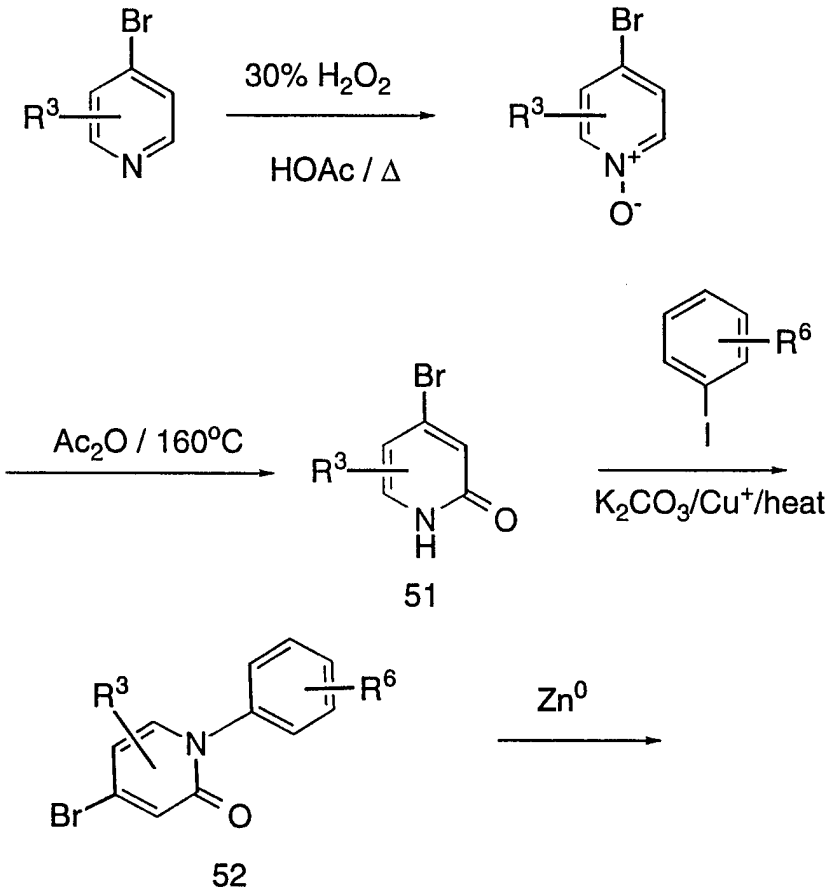
SCHEME 96 (continued)



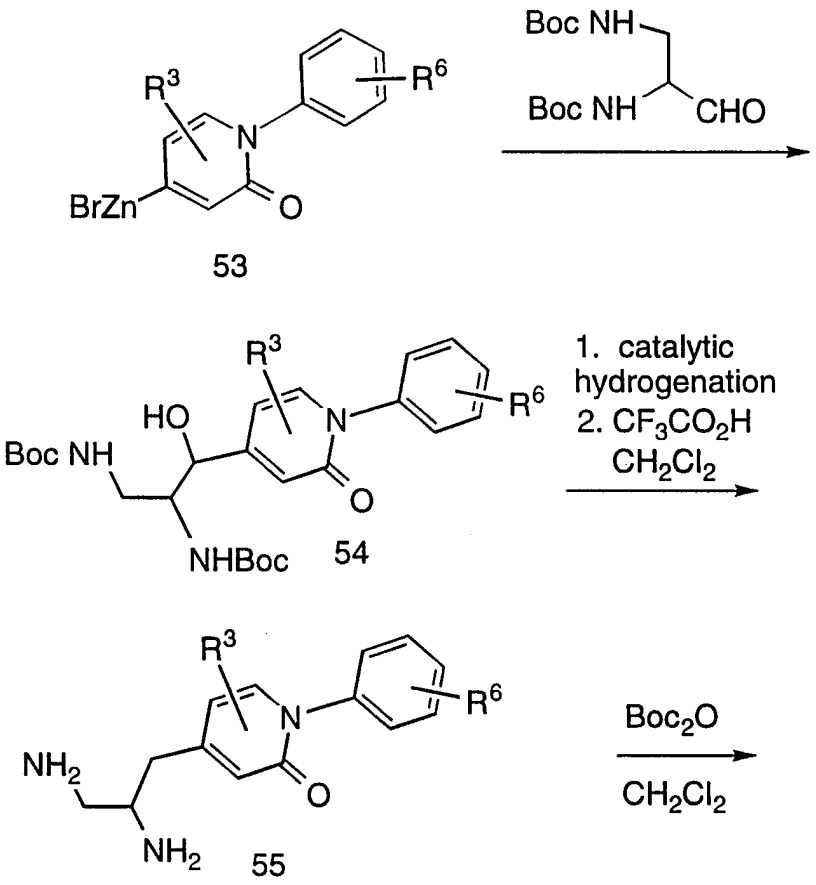


50

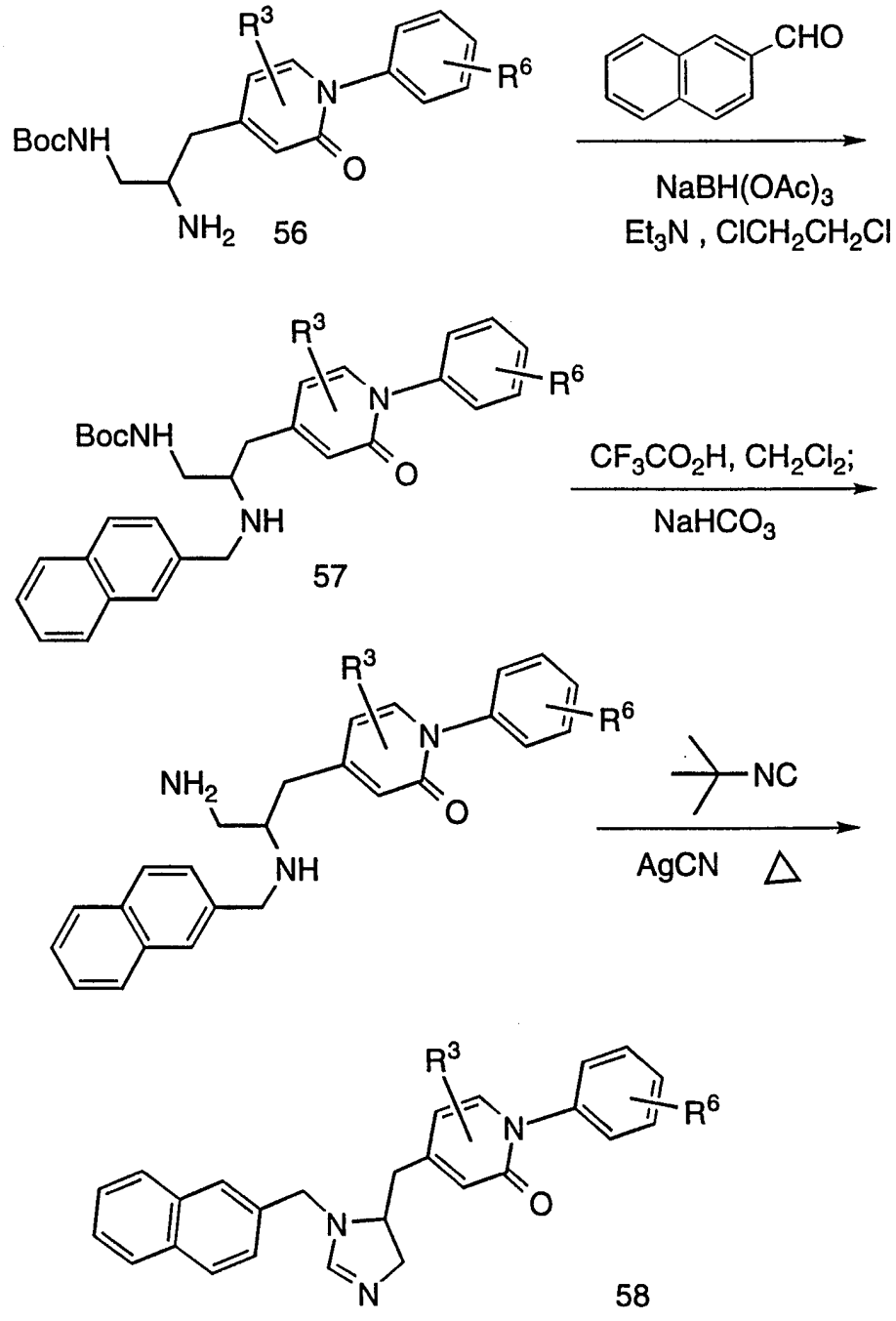
SCHEME 97


Br
R3
N
30% H2O2
HOAc / Δ
Br
R3
N+
O-
R6
I
Ac2O / 160°C
Br
R3
N
H
O
K2CO3/Cu+/heat
51
R3
R6
N
Br
O
Zn0
52

SCHEME 97 (continued)



SCHEME 97 (continued)



5

The farnesyl transferase inhibitors of formula (II-i) can be synthesized in accordance with Reaction Schemes, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key reactions utilized to form the aminodiphenyl moiety of the instant compounds are shown.

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 Reaction Schemes.

Reaction Schemes A-P describe the preparation of appropriately substituted aniline intermediates that may be further functionalized by the methods described in Reaction Schemes Q-Y to provide the compounds of the instant invention.

Reaction Schemes A-D illustrate use of Ullman reactions to provide diphenyl ethers, amines and sulfides from readily available fully substituted phenols/thiophenols/anilines and aryl halides. In such syntheses, the desired amine moiety is typically masked as a nitro group which is subsequently reduced by techniques well known in the art. An alternative synthesis of the diphenyl ethers which employs para-nitro fluorobenzene is shown in Reaction Scheme E.

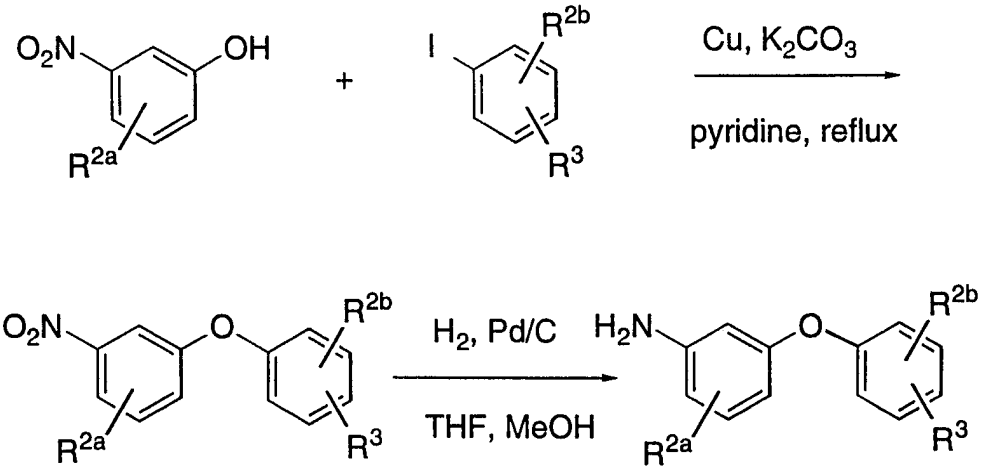
Reaction Scheme F illustrates standard acid-amine coupling to provide the fully substituted N-phenylbenzamides. Reaction Scheme G illustrates formation of the aminomethyl spacer via a reductive amination of a suitably substituted benzaldehyde.

Reaction Scheme H illustrates coupling of suitably substituted anilines with readily available phenylsulfonyl chlorides. Access to aminobenzophenones is illustrated in Reaction Scheme I, which also illustrates the reduction of the carbonyl to provide the unsubstituted methyl spacer. An alternative method of forming the benzophenone intermediates is illustrated in Reaction Scheme J. Also shown in Reaction Scheme J is reductive amination of the resulting carbonyl to provide the amine substituted methyl spacer. Another

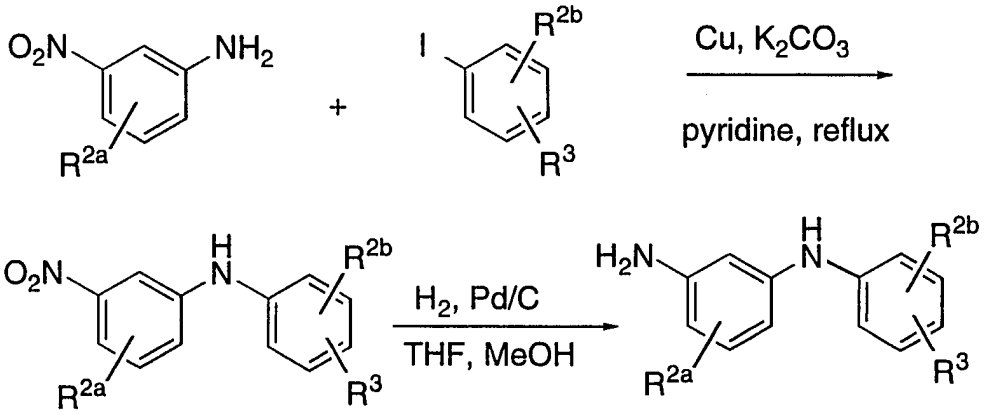
method of forming the benzophenone intermediates, illustrated in Reaction Scheme K, is a Stille reaction with an aryl stannane.

Reaction Schemes L and M illustrate palladium mediated formation of olefin and acetylene spacer units. Reaction Scheme N illustrates formation of an appropriately substituted benzyl ether. Reaction Scheme P illustrates the use of the Claisen rearrangement to provide methyl spacers having substituents such as a vinyl group which can be further functionalized.

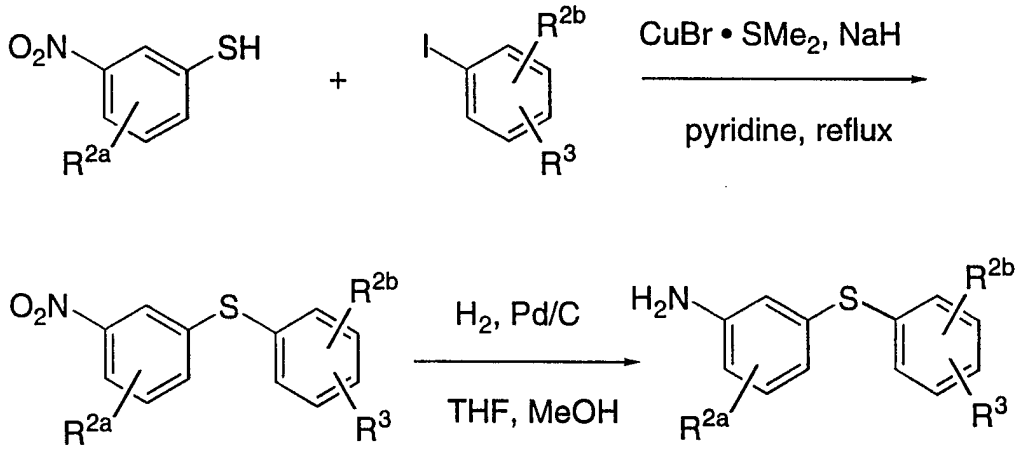
REACTION SCHEME A



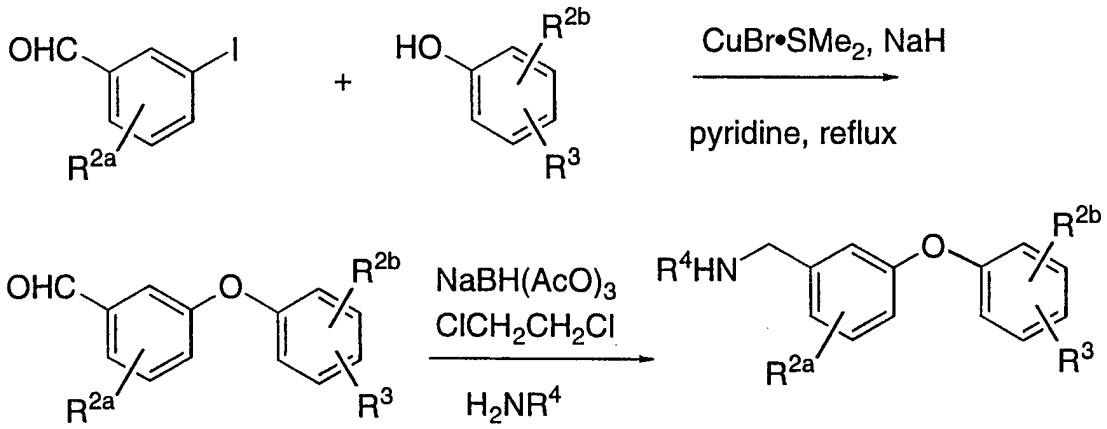
REACTION SCHEME B



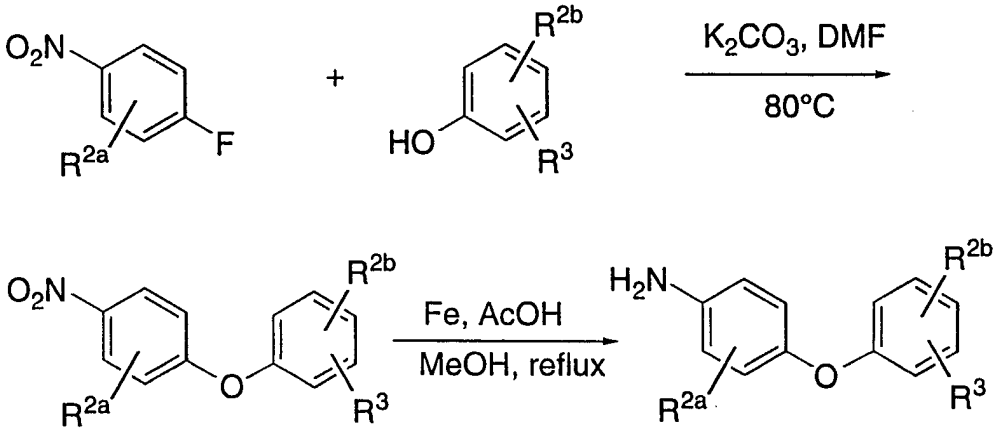
REACTION SCHEME C



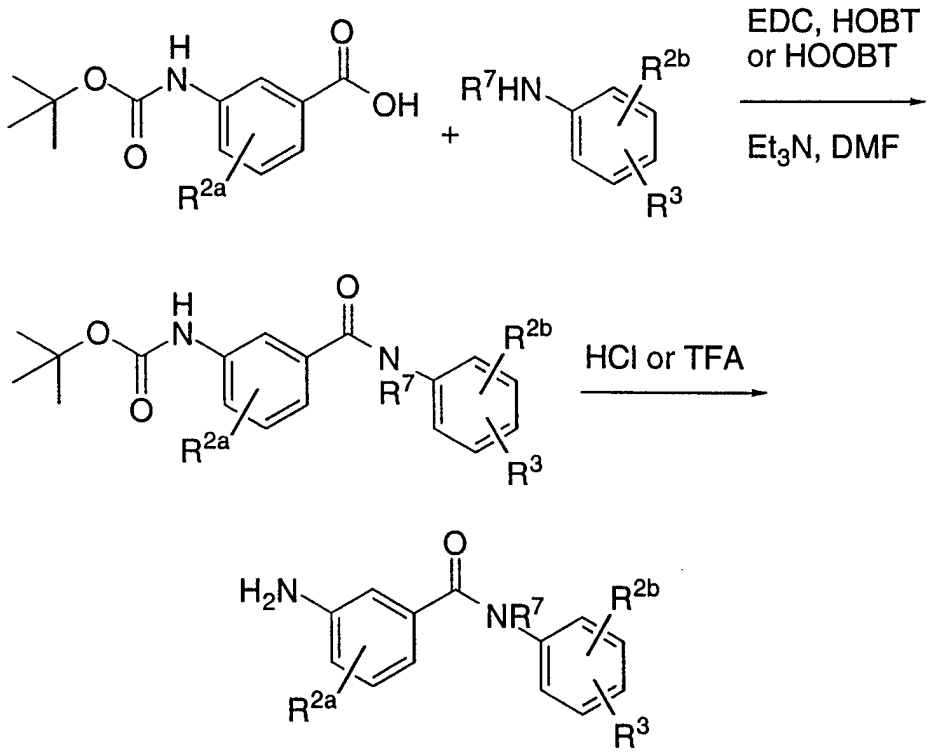
REACTION SCHEME D



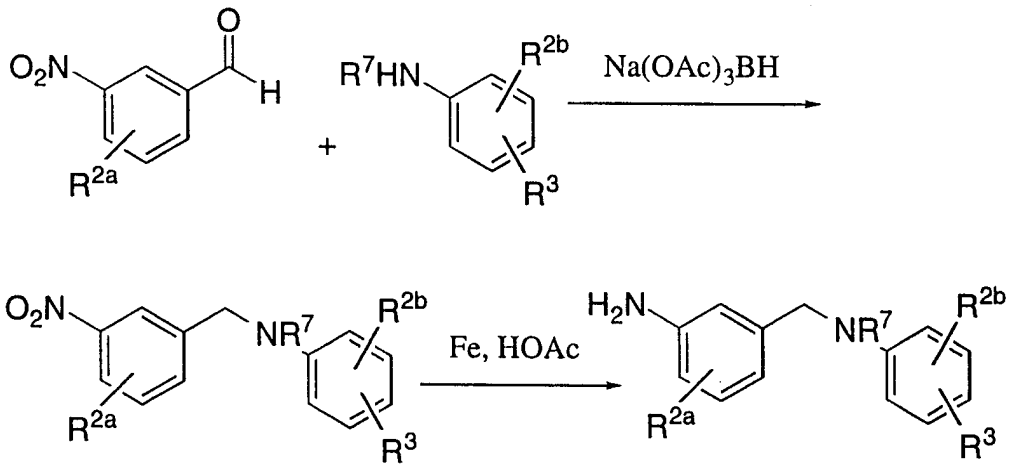
REACTION SCHEME E



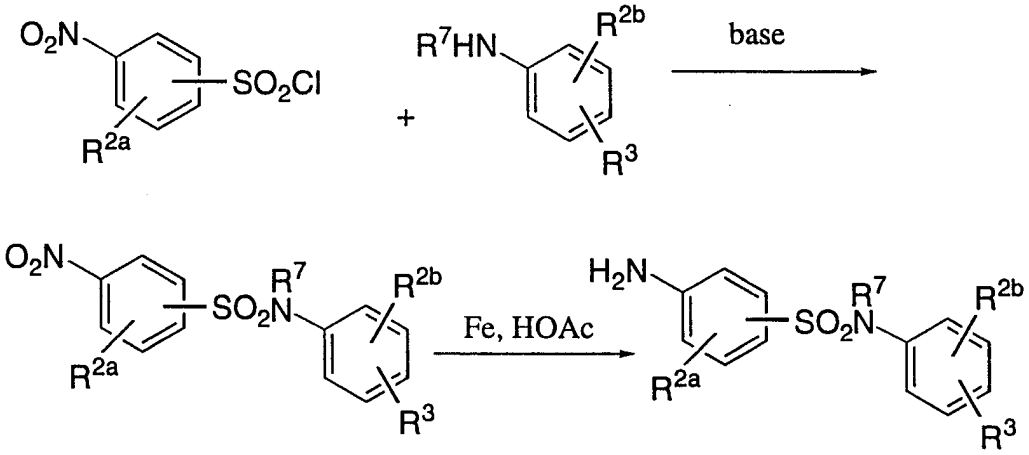
REACTION SCHEME F



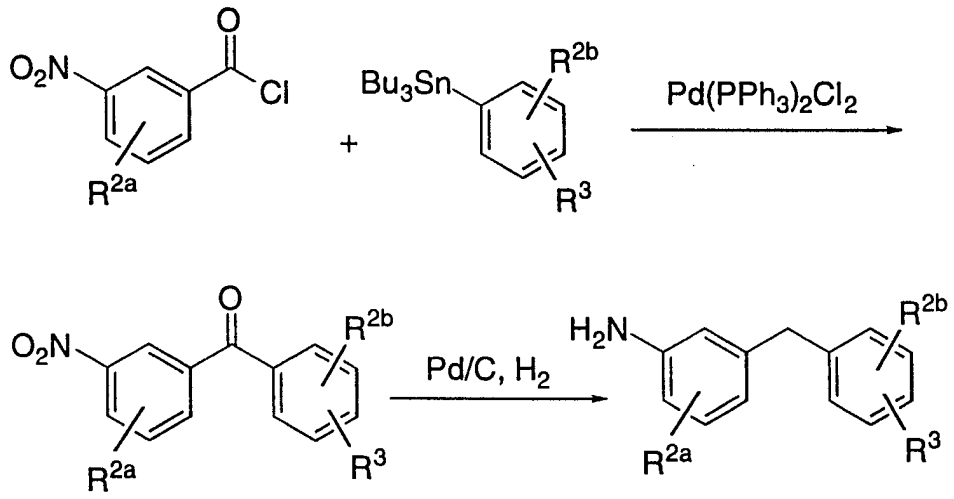
REACTION SCHEME G



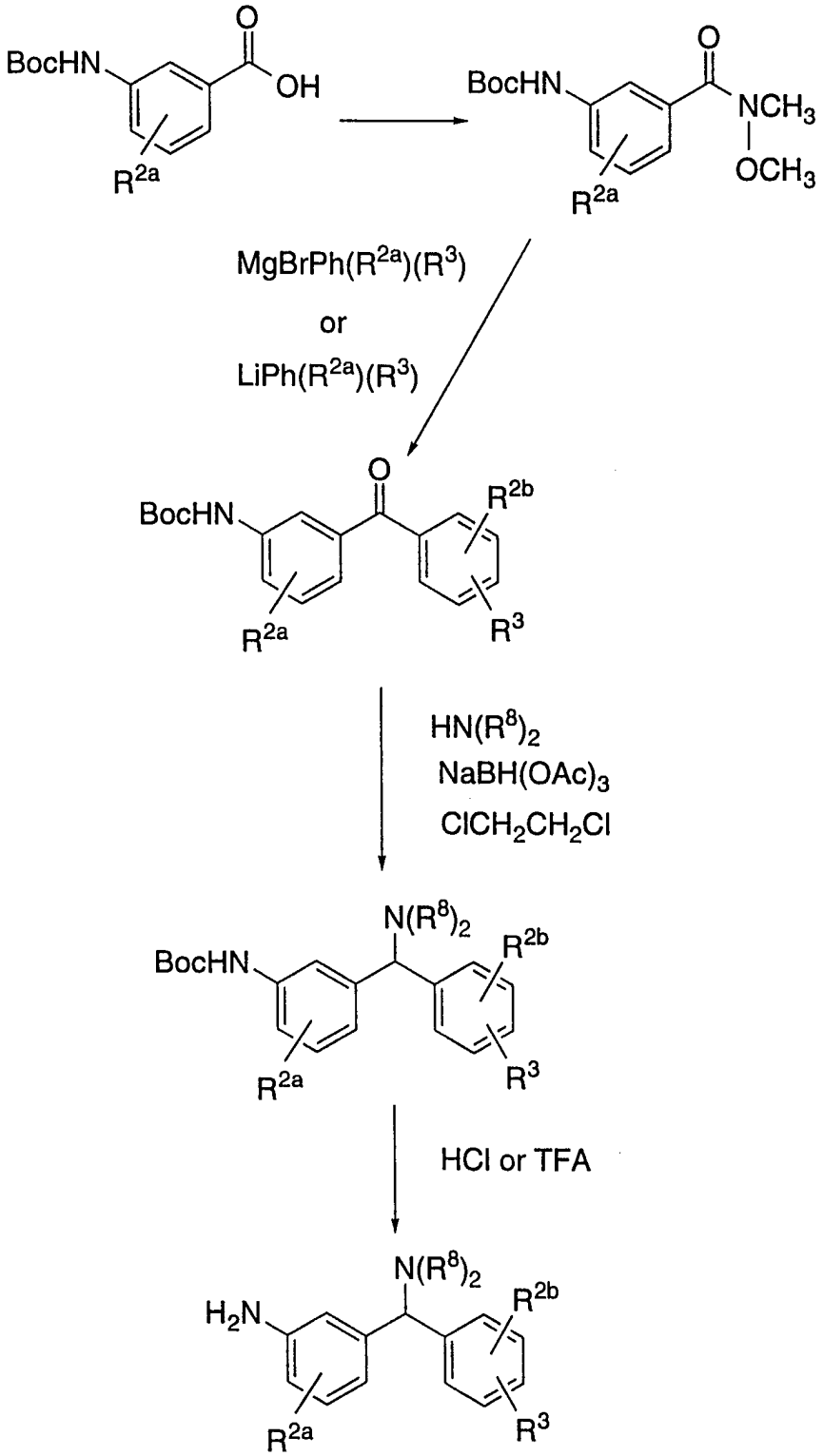
REACTION SCHEME H



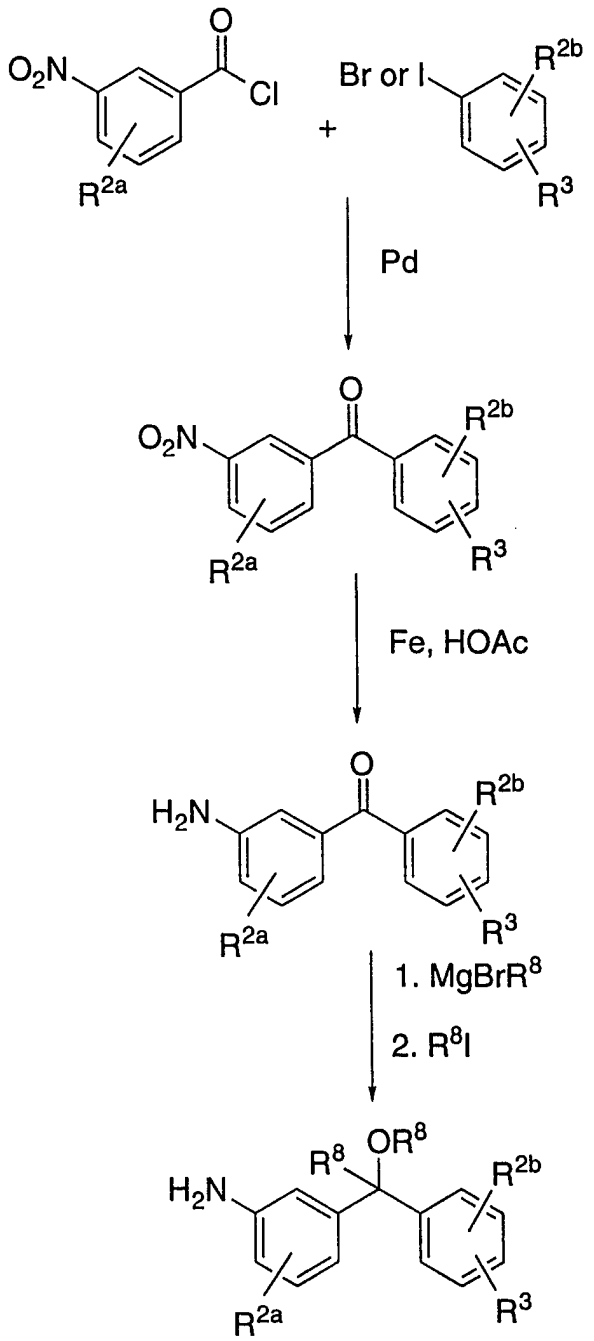
REACTION SCHEME I



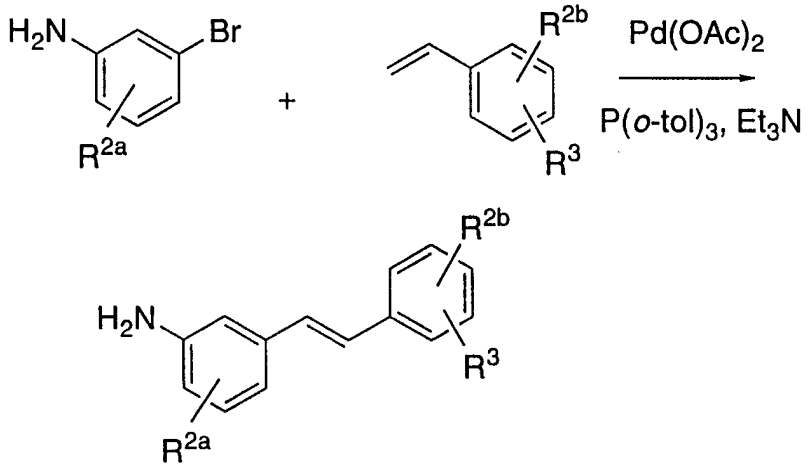
REACTION SCHEME J


BocHN
O
OH
R2a
BocHN
O
NCH3
OCH3
R2a
MgBrPh(R2a)(R3)
or
LiPh(R2a)(R3)
BocHN
O
R2b
R2a
R3
HN(R8)2
NaBH(OAc)3
ClCH2CH2Cl
BocHN
N(R8)2
R2b
R2a
R3
HCl or TFA
H2N
N(R8)2
R2b
R2a
R3

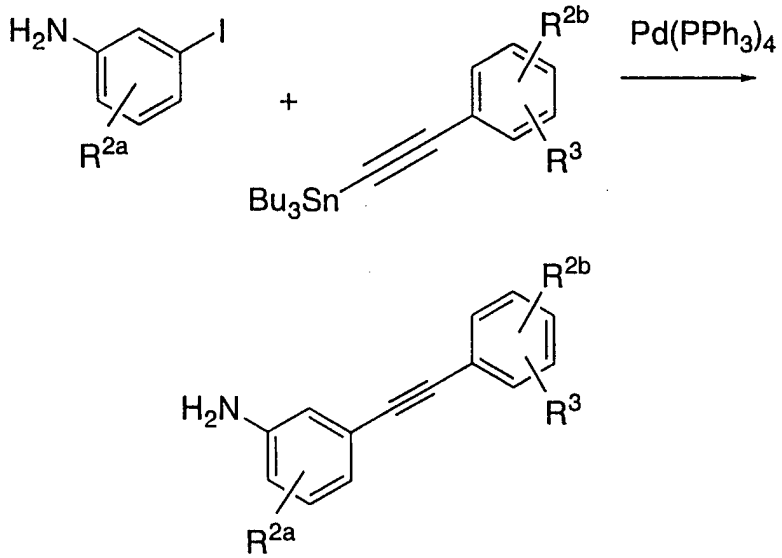
REACTION SCHEME K



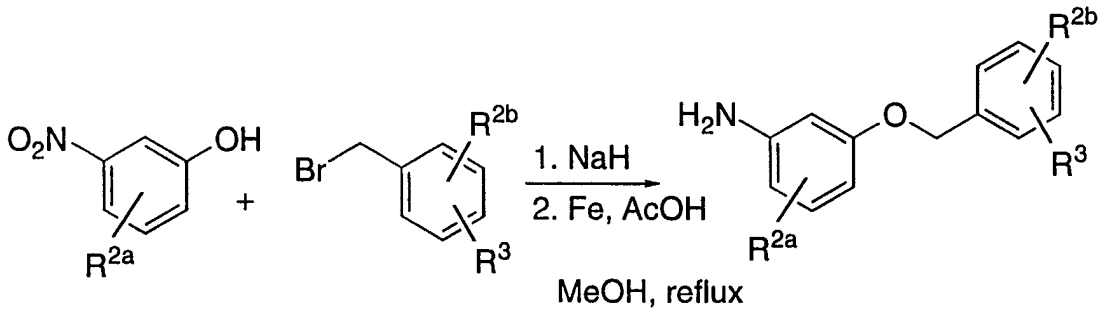
REACTION SCHEME L



REACTION SCHEME M



REACTION SCHEME N



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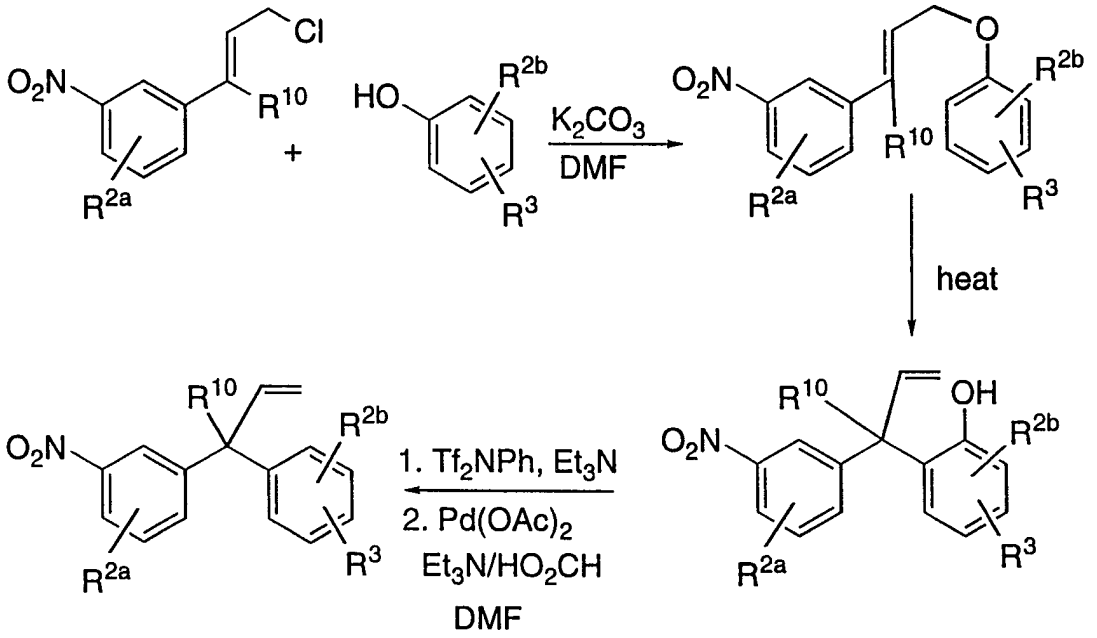
REACTION SCHEME P



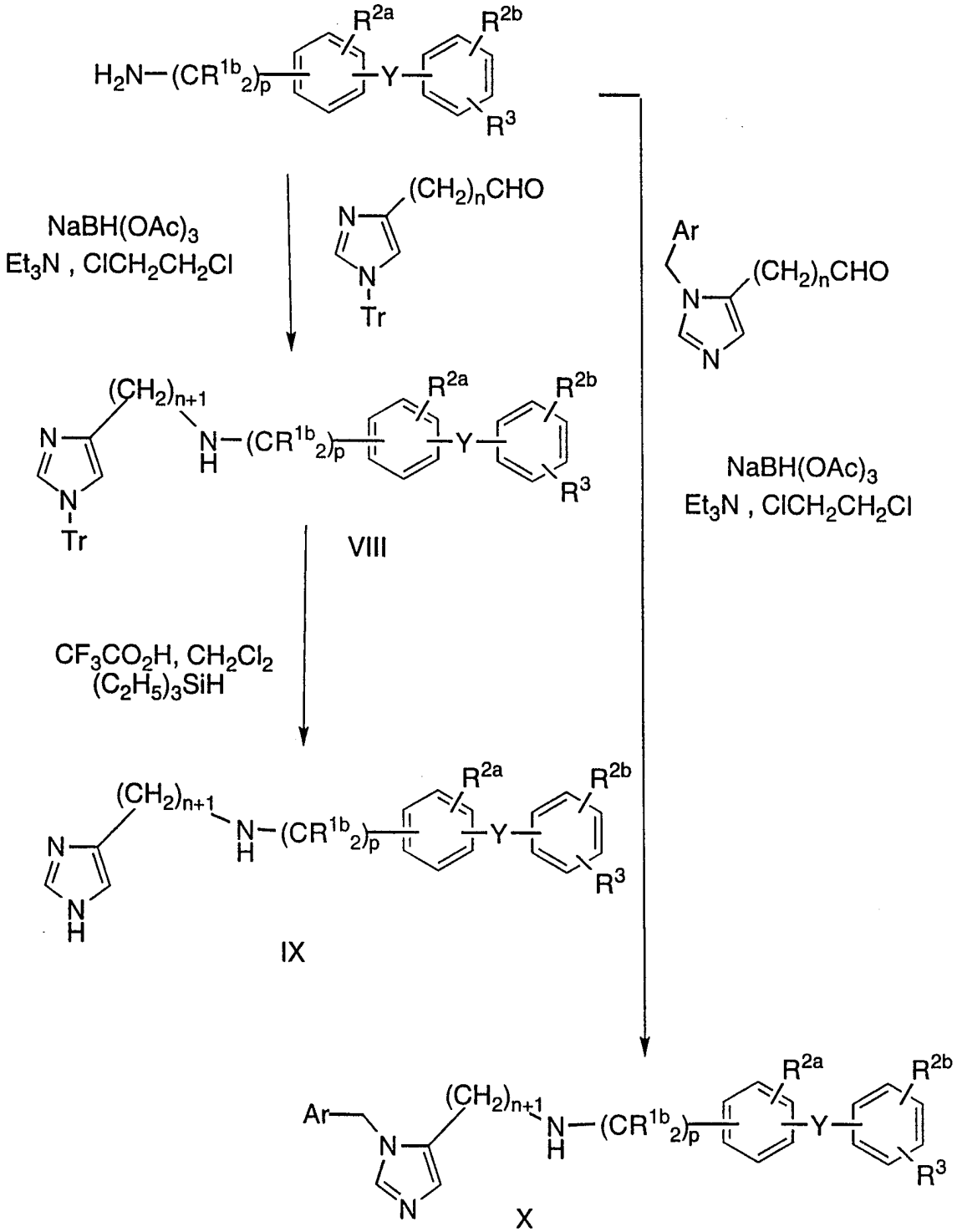
10 Reaction Schemes Q- S illustrate reactions wherein the non-sulfhydryl-containing moiety(ies) of the compounds of the instant invention is attached to the aminodiphenyl subunit to provide the instant compounds.

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

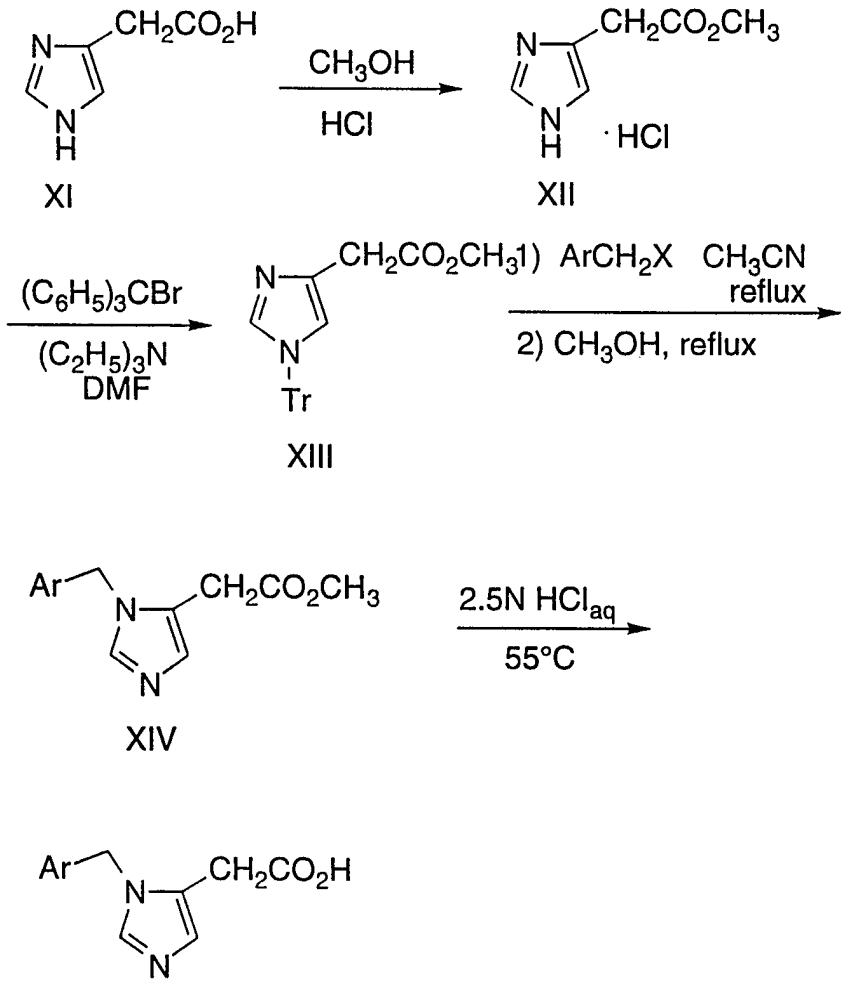
The imidazole acetic acid **XI** can be converted to the acetate **XIII** by standard procedures, and **XIII** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **XIV**. Hydrolysis and reaction with the aminodiphenyl subunit in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as **XV**. Coupling reactions with other suitably substituted aldehydes may be performed as illustrated in Schemes 3 and 6-9 hereinabove.

Reaction Scheme S illustrates a one pot synthesis of an instant compound wherein the N-terminus nitrogen is substituted with two different non-sulfhydryl-containing moieties. Thus, the aminodiphenyl subunit is treated with one equivalent of an appropriate aldehyde and, after the reductive adduct has been formed, the in situ intermediate is treated with an equivalent of a different aldehyde.

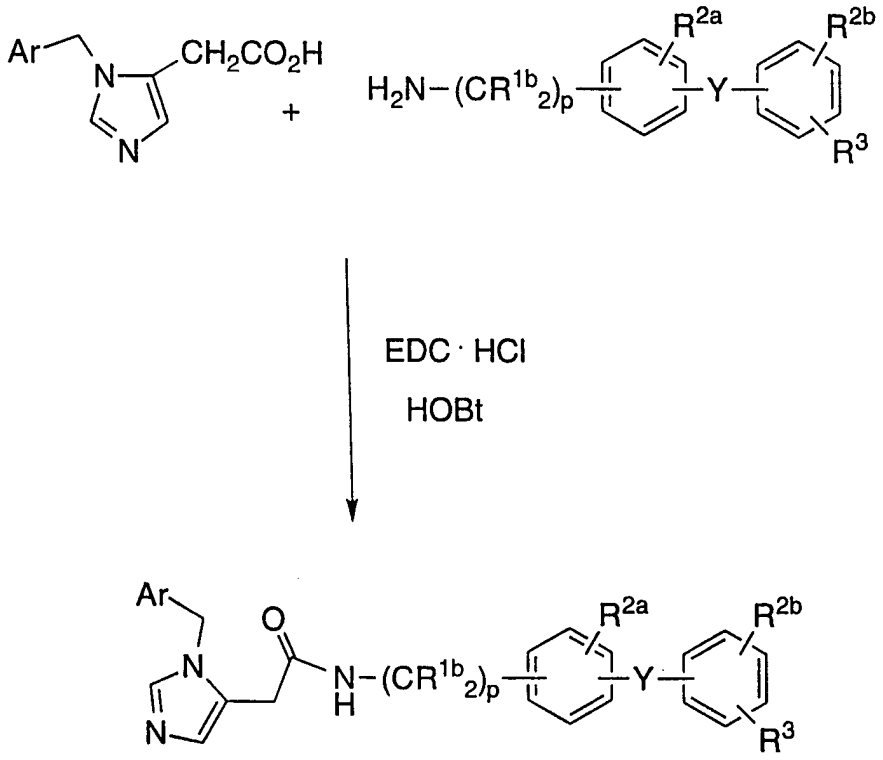
REACTION SCHEME Q



REACTION SCHEME R

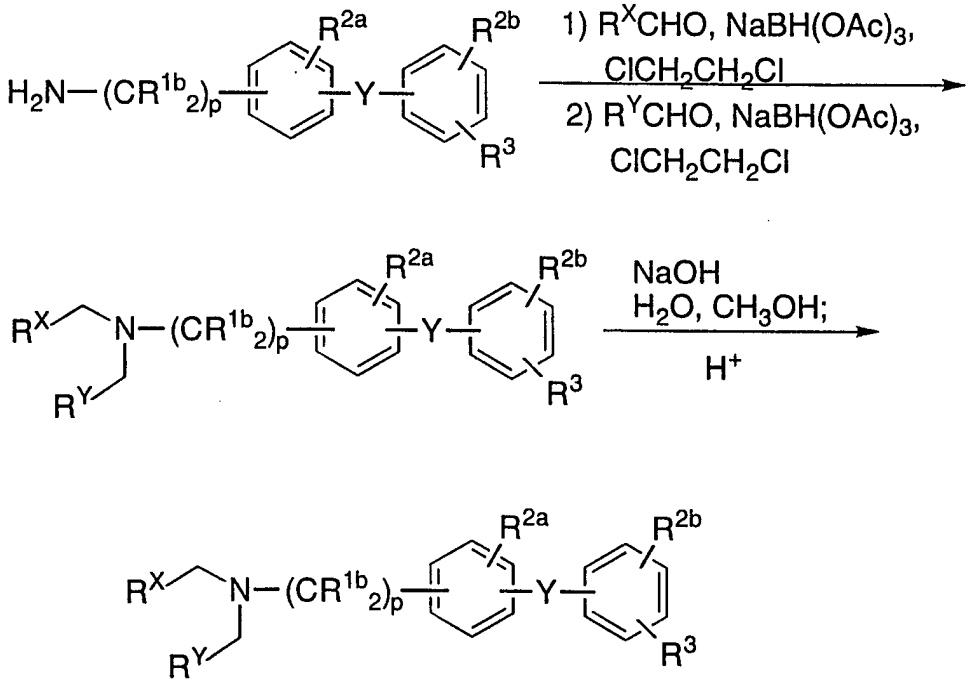


REACTION SCHEME R (continued)



XV

REACTION SCHEME S



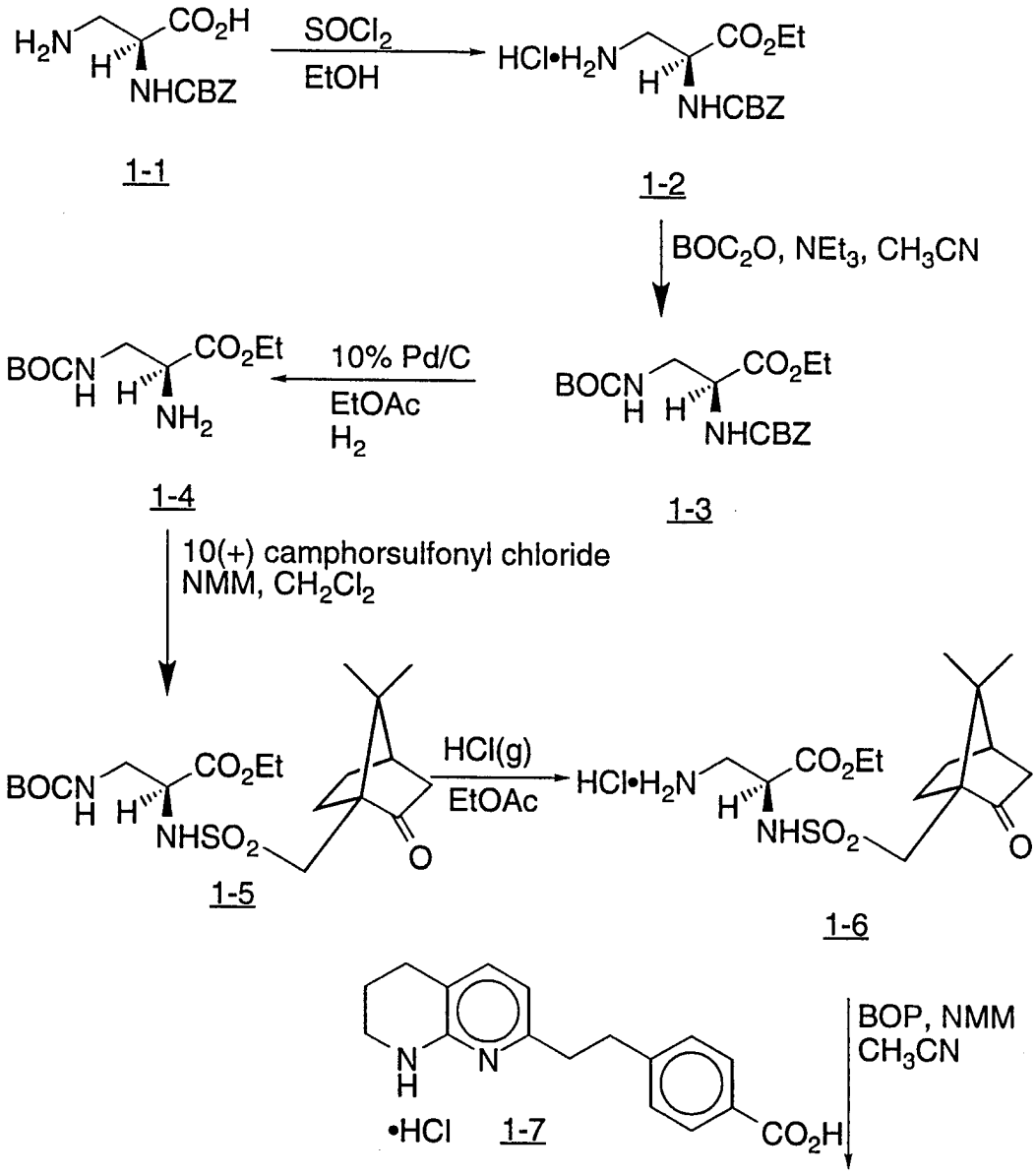
wherein, in the above Reaction Schemes, R' is R^{1a}; R" is $(R^6)_r$-V-A^1-$(CR^{1a})_n$-; R'" is selected such that R'"CH_2- is R^8; and R^x and R^y are selected such that R^x CH_2- and R^yCH_2- are either R^4 or R^5.

EXAMPLES

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

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

EXAMPLE 1


H2N
CO2H
H
NHCBZ
SOCl2
EtOH
HCl•H2N
CO2Et
H
NHCBZ
1-1
1-2
BOC2O, NEt3, CH3CN
BOCN
H
H
CO2Et
NH2
10% Pd/C
EtOAc
H2
BOCN
H
H
CO2Et
NHCBZ
1-4
1-3
10(+) camphorsulfonyl chloride
NMM, CH2Cl2
BOCN
H
H
CO2Et
NHSO2
O
HCl(g)
EtOAc
HCl•H2N
CO2Et
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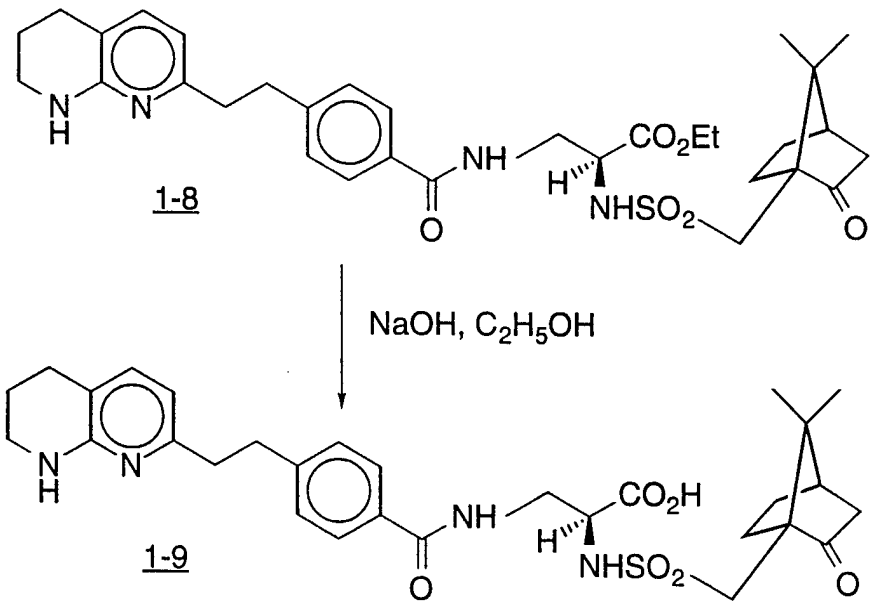
H
N
•HCl
1-7
CO2H
BOP, NMM
CH3CN



Step 1: Ethyl 2(S)-Nα-Cbz-2,3-diaminopropionate hydrochloride (1-2)

1-1 (5 g, 21 mmol) was dissolved in 100 mL EtOH and cooled to 0°C. $SOCl_2$ (9.2 mL, 126 mmol) was added followed by removal of the cooling bath. After 6 hours, the reaction was concentrated to provide 1-2 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 7.35 (m, 5H), 5.14 (s, 2H), 4.44 (m, 1H), 4.22 (q, J=7Hz, 2H), 3.43 (m, 1H), 3.20 (m, 1H), 1.25 (t, J=7Hz, 3H).

Step 2: Ethyl 2(S)-Nα-Cbz-Nβ-Boc-2,3-diaminopropionate (1-3)

1-2 (2 g, 6.6 mmol) was dissolved in 60 mL CH_3CN. NEt_3 (1 mL, 7.2 mmol) was added followed by BOC_2O (1.58 g, 7.3 mmol). After two hours, the reaction was concentrated, diluted with EtOAc, washed with sat. $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$), filtered and concentrated to provide 1-3 as a clear oil.

TLC R_f 0.87 (silica, 80% EtOAc/hex).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.75 (bs, 1H), 5.12 (s, 2H), 4.81 (bs, 1H), 4.39 (m, 1H), 4.19 (m, 2H), 3.56 (m, 2H), 1.42 (s, 9H), 1.29 (q, J=7Hz, 3H).

Step 3: Ethyl 2(S)-Nβ-Boc-2,3-diaminopropionate (1-4)

1-3 (2.4 g, 6.6 mmol) with 10% Pd/C (240 mg) in EtOAc (35 mL) was stirred under a H_2 atmosphere for 20 hours. The reaction was filtered through a celite pad and concentrated to provide 1-4 as a clear oil.
TLC R_f 0.13 (silica, 80% EtOAc/hex).
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (bs, 1H), 4.19 (m, 2H), 3.55 (m, 2H), 3.25 (m, 1H), 1.44 (s, 9H), 1.29 (q, J=7Hz, 3H).

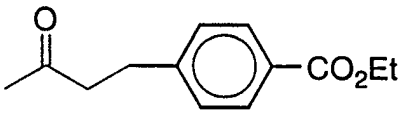
Step 4: Ethyl-2(S)-Nα-(1(S)10-camphorsulfonylamino-Nβ-Boc-2,3-diamino-propionate (1-5)

Amine 1-4 (760 mg, 3.27 mmol) was dissolved in 35 mL CH_2Cl_2 and cooled to 0°C. NMM (755 µL, 6.87 mmol) and 10(+) camphorsulfonyl chloride (1.23 g, 4.9 mmol) were added. After stirring at 0°C for one hour, the reaction was concentrated, then diluted with EtOAc, washed with H_2O, sat. $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$), and concentrated to an oil. Flash chromatography (silica, 25-40% EtOAc/hexanes) provided 1-5 as a clear oil.
TLC R_f 0.66 (silica, 50% EtOAc/hexanes).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.37 (d, J=8Hz, 1H), 4.99 (bt, 1H), 4.32 (m, 1H), 4.23 (q, J=8Hz, 2H), 3.56 (m, 3H), 3.0 (d, J=15 Hz, 1H), 2.4 (m, 1H), 2.05 (m, 4H), 1.43 (s, 9H), 1.30 (t, J=7 Hz, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

Step 5: Ethyl-2(S)-Nα-(1(S)10-camphorsulfonylamino)-2,3-diaminopropionate hydrochloride (1-6)

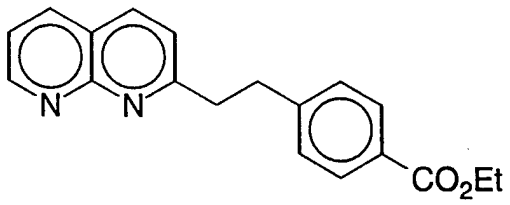
Ester 1-5 (900 mg, 2.18 mmol) was dissolved in 15 mL EtOAc and cooled to 0°C. HCl (g) was bubbled through the reaction mixture for 15 minutes. The reaction was removed from the cooling

bath and purged with Ar (g) for 20 minutes followed by concentration to provide 1-6 as a foamly solid.
TLC R_f 0.05 (silica, 20% MeOH/EtOAc).
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.75 (m, 1H), 4.26 (q, J=7Hz, 2H), 3.50 (m, 4H), 2.40 (m, 3H), 1.98 (m, 4H), 1.30 (t, J=7Hz, 3H), 1.04 (s, 3H), 0.91 (s, 3H).



1-10

Step 6: Ethyl-4-(2-butanene)benzoate (1-10)
3-Buten-2-ol (2.15 mL, 25 mmol), ethyl 4-iodobenzoate (5.52 q, 20 mmol) and NEt_3 (3.5 mL, 25 mmol) were combined in 6 mL of CH_3CN under Ar in a pressure tube. $Pd(OAc)_2$ (19 mg, 0.08 mmol) was added and the reaction heated to 100°C for 3 hours. The reaction was cooled, then diluted with Et_2O, washed with H_2O, 10% $KHSO_4$, sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to a yellow oil. Flash chromatography (silica, 10% EtOAc/hex) provided 1-10 as a clear oil.
TLC R_f 0.23 (silica, 30% EtOAc/hex).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 2H), 4.36 (q, J=7Hz, 2H), 2.95 (t, J=7Hz, 2H), 2.78 (t, J=7Hz, 2H), 2.15 (s, 2H), 1.38 (t, J=7Hz, 3H).



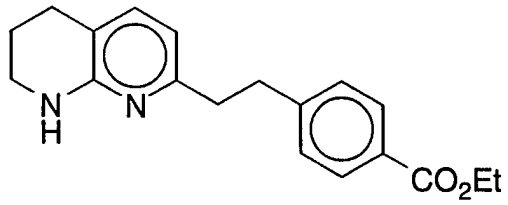
1-11

Step 7: Ethyl 4-[2-(1,8-naphthyridin-7-yl)ethyl]benzoate (1-11)

An ethanol solution of (70 mL) of 1-10 (3.15 g, 14.3 mmol), 2-amino-3-formylpyridine (*Syn. Comm. 17(14)*, 1695(1987) (1.75 g, 14.3 mmol) and 20% KOH (2 mL) was refluxed for 18 hours. The reaction was concentrated to dryness and the residue partitioned between EtOAc and H_2O. The organic layer was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to give a yellow oil. Flash chromatography (silica, 60%-80% EtOAc/hex) provided 1-11 as a yellow solid.

TLC Rf 0.31 (silica, 70% EtOAc/hex).

^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (m, 1H), 8.18 (d, J=8Hz, 1H), 8.08 (d, J=8Hz, 1H), 7.95 (d, J=8Hz, 2H), 7.47 (m, 1H), 7.30 (d, J=8Hz, 2H), 4.35 (q, J=7Hz, 2H), 3.35 (m, 4H), 1.38 (t, J=7Hz, 3H).



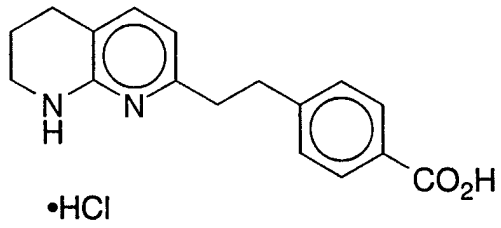
1-12

Step 8: Ethyl 4-[2-(1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoate (1-12)

A mixture of 1-11 (645 mg, 2.11 mmol), 10% Pd/C (65 mg), and ethanol (10 mL) was stirred under a hydrogen atmosphere for 18 hr. Filtration through a celite pad followed by concentration provided by 1-12 as an off white solid.

TLC R_f 0.75 (silica, 70% EtOAc/hex).

^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 2H), 7.03 (d, J=7Hz, 1H), 6.28 (d, J=7Hz, 1H), 4.81 (s, 1H), 4.35 (q, J=7Hz, 2H), 3.40 (m, 2H), 3.03 (m, 2H), 2.84 (m, 2H), 2.69 (t, J=6Hz, 2H), 1.93 (t, J=6Hz, 2H), 1.38 (t, J=7Hz, 3H).



1-7

Step 9: 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoic acid hydrochloride (1-7)

Ester 1-12 (680 mg, 2.11 mmol) in 10 mL 6N HCl was heated to 50°C for 18 hours. Concentration provided 1-7 as a yellow solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.93 (d, J=8Hz, 2H), 7.52 (d, J=8Hz, 1H), 7.31 (d, J=8Hz, 2H), 6.54 (d, J=8Hz, 1H), 3.48 (t, J=5Hz, 2H), 3.03 (m, 4H), 2.79 (t, J=6Hz, 2H), 1.93 (t, J=6Hz, 2H).

Step 10: 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl] benzoyl-2(S)[1(S)10-camphorsulfonylamino] β-alanine ethyl ester (1-8)

1-7 (200 mg, 0.627 mmol), amine 1-6 (240 mg, 0.69 mmol), NMM (345 µL, 3.13 mmol) and BOP reagent (332 mg, 0.75 mmol) were combined in 5 mL CH_3CN. After stirring overnight, the reaction was concentrated, then diluted with EtOAc, washed with H_2O, sat. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography (silica, EtOAc) provided 34-8 as an off-white foamy solid.

TLC R_f 0.13 (silica, EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 2H), 7.03 (d, J=7Hz, 1H), 6.72 (t, J=5Hz, 1H), 6.5 (bm, 1H), 6.28 (d, J=7Hz, 1H), 4.79 (s, 1H), 4.42 (bs, 1H), 4.25 (q, J=7Hz, 2H), 4.04 (m, 1H), 3.85 (m, 1H), 3.55 (d, J=15Hz, 1H), 3.41 (m, 2H), 3.00 (m, 3H), 2.82 (t, J=4Hz, 2H), 2.69 (t, J=6Hz, 2H), 2.04 (m, 8H), 1.58 (bs, 3H), 1.31 (t, J=7Hz, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

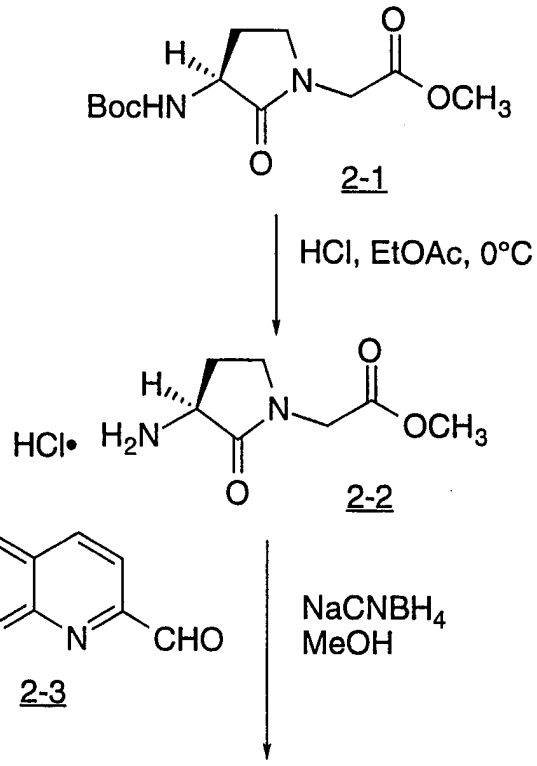
Step 11: 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl] benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-9)

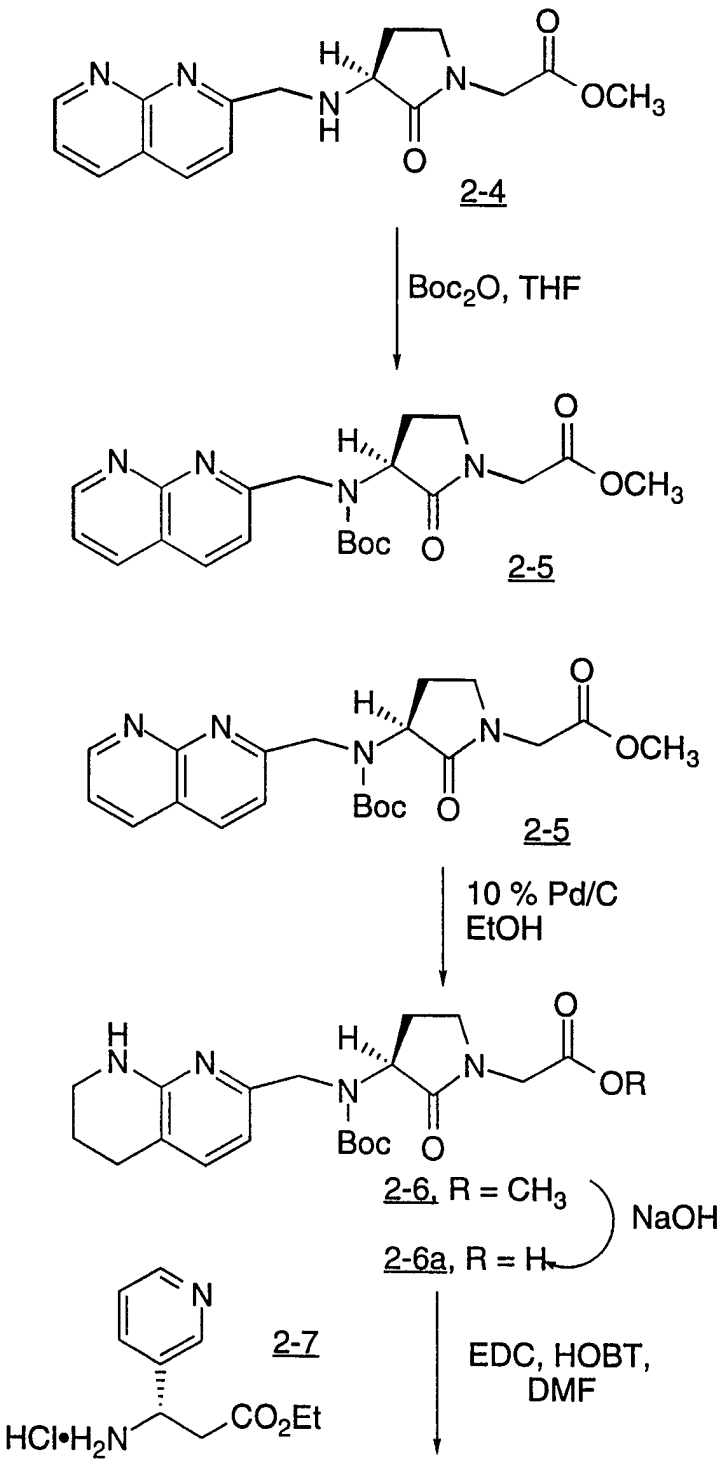
1-8 (250 mg, 0.409 mmol) was dissolved in 4 mL EtOH, 1M NaOH (1.02 mL, 1.02 mmol) was added and the reaction mixture was stirred for two hours. The reaction mixture was neutralized with 1N HCl and then concentrated to a foamy solid. Flash chromatography (silica, 18:10:1:1 EtOAc/EtOH/NH_4OH/H_2O) provided 1-9 as a slightly yellow solid.

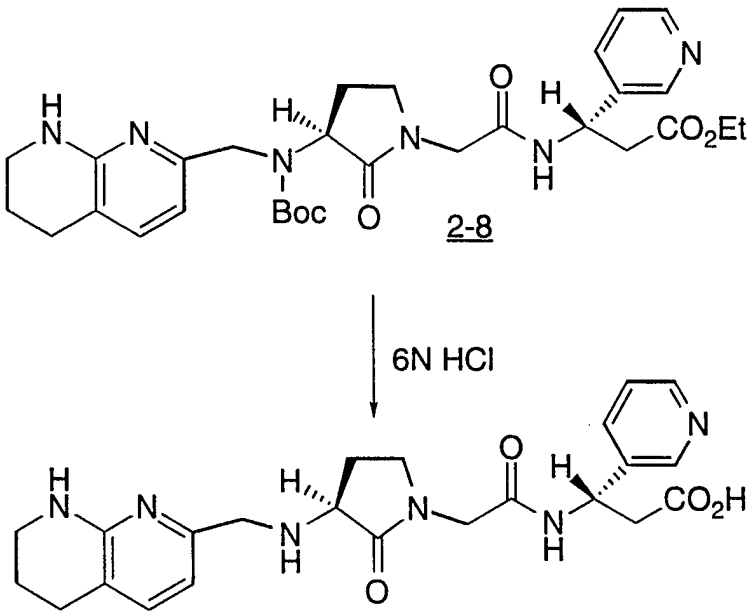
TLC R_f 0.49 (silica, 12:10:1:1 EtOAc/EtOH/NH_4OH/H_2O).

^1H NMR (400 MHz, DMSO) δ 8.48 (bt, 1H), 7.72 (d, J=8Hz, 2H), 7.55 (bs, 1H), 7.28 (d, J=8Hz, 2H), 7.02 (d, J=7Hz, 1H), 6.37 (s, 1H), 6.26 (d, J=7Hz, 1H), 4.13 (s, 1H), 3.54 (m, 3H), 3.37 (m, 2H), 2.94 (m, 3H), 2.73 (t, J=7Hz, 2H), 2.6 (t, J=6Hz, 2H), 2.3 (m, 3H), 2.02 (m, 1H), 1.89 (m, 2H), 1.75 (m, 2H), 1.49 (m, 1H), 1.37 (m, 1H), 1.05 (m, 1H), 0.95 (s, 3H), 0.66 (s, 3H).

EXAMPLE 2




2-4
Boc2O, THF
2-5
2-5
10 % Pd/C
EtOH
2-6, R = CH3
NaOH
2-6a, R = H
2-7
HCl•H2N
CO2Et
EDC, HOBT,
DMF



2-8

2-9

Step 1: (S)-(3-amino-2-oxo-pyrrolidin-1-yl)-acetic acid (2-2)

A solution of 2-1 (0.50 g, 1.84 mmol) (prepared as described by Freidinger, R. M.; Perlow, D. S.; Veber, D. F.; *J. Org. Chem.*, 1982, *26*, 104) in anhydrous ethyl acetate (50 mL) was cooled to 0°C and saturated with HCl gas, then stirred at 0°C for 2 h. The resulting colorless solution was concentrated at reduced pressure and the residue triturated with anhydrous diethyl ether giving 2-2 as a hygroscopic white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 4.16 (d, 2H); 4.2 (m, 1H); 3.68 (s, 3H); 3.53 (m, 2H); 2.58 (m, 1H); 2.09 (m, 1H).

Step 2: 2-oxo-3-(S)-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl]-acetic acid (2-4)

A solution of 2-2 (232 mg, 1.11 mmol) and [1,8]naphthyridin-2-ylcarboxaldehyde (176 mg, 1.11 mmol) (prepared as reported by Weissenfels, M.; Ulrici, B.; *Z. Chem.* 1978, *18*, 20.) in anhydrous methanol (10 mL) was treated with NaOAc (91 mg, 1.11 mmol) , $NaBH_3CN$ (70 mg, 1.11 mmol) and powdered 4 Å molecular sieves (450 mg). The resulting mixture was stirred at 0° for 3.5 h, then

concentrated and the residue subjected to flash chromatography on silica gel (95:4.5:0.5 CH_2Cl_2/MeOH/NH_4OH) to afford 2-4 as a colorless glass.

FAB MS (315, M^{+1});

^1H NMR (300 MHz, CD_3OD) δ 9.04 (d, 1H); 8.41 (dd, 1H); 8.38(d, 1H); 7.72 (d, 1H); 7.62 (dd, 1H); 4.31 (d, 2H); 4.21 (m, 2H); 3.68 (s, 3H);3.63 (m, 1H); 3.53 (m, 2H); 2.52 (m, 1H); 1.95 (m, 1H).

Step 3: Methyl-[3-(S)-[*tert*-butoxycarbonyl-[1,8]naphthyridin-2-ylmethyl)-amino]-2-oxo-pyrrolidin-1-yl]-acetic acid (2-5)

A solution of amine 2-4 (69 mg, 0.22 mmol) in THF (5 mL) was treated with Boc_2O (83 mg, 0.24 mmol) and stirred at room temperature for 18 h. The solvent was removed in vacuo and the resulting residue isolated by chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford 2-5 as a yellow glass.

FAB MS (415, M^{+1});

^1H NMR (300 MHz, CD_3OD) δ 9.04 (d, 1H); 8.20 (m, 2H); 7.88 (d, 0.5H (rotamer a)); 7.82 (d, 0.5H (rotamer b)); 7.46(m, 1H); 5.1-4.3 (m, 5H); 3.81 (m, 2H); 3.72 (s, 3H); 3.41 (m, 2H); 2.36 (m, 2H); 1.47 (s, 4.5 H (rotamer a)); 1.30 (s, 4.5 H , (rotamer b)).

Step 4: Methyl-3-(S)-[*tert*-butoxycarbonyl-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-2-oxo-pyrrolidin-1-yl]-acetic acid (2-6)

A solution of 2-5 (40 mg, 0.097mmol) in EtOH (5 mL) was treated with 10% Pd on C (8 mg) and then stirred under a H_2 filled balloon for 16 h. The catalyst was removed by filtration through celite and the filtrate concentrated to afford 2-6 as a colorless glass.

^1H NMR (300 MHz, CD_3OD) δ 7.10 (d, 1H) 6.78 (d, 0.5H (rotamer a)); 6.62 (d, 0.5H (rotamer b)); 4.8-3.9 (m, 5H); 3.81 (m, 2H); 3.72 (s, 3H); 3.38 (m, 2H); 2.36 (m, 2H); 1.21(s, 4.5 H (rotamer a)); 1.15 (s, 4.5 H , (rotamer b)).

Step 5: 3-(S)-[*tert*-butoxycarbonyl-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-2-oxo-pyrrolidin-1-yl]-acetic acid (2-6a)

A solution of 2-6 (38 mg, 0.091 mmol) in 50 % aqueous THF (2 mL) was treated with 1.0 N NaOH (95 mL, 0.095 mmol) and stirred at room temperature for 2 h. The reaction was nuetralized with 1N HCl, evaporated, and the residue dissolved in MeOH (2.5 mL), filtered and evaporated to afford 2-6a as a colorless glass.
^{1}H NMR (300 MHz, CD_3OD) δ 7.31 (d, 1H) 6.78 (br, d, 1H); 4.8-3.9 (m, 5H); 3.81 (m, 2H); 3.38 (m, 2H); 2.36 (m, 2H); 1.21(s, 4.5 H (rotamer a)); 1.15 (s, 4.5 H , (rotamer b)).

Step 6: Ethyl -3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(R)-pyridin-3-yl-propionic acid (2-8)

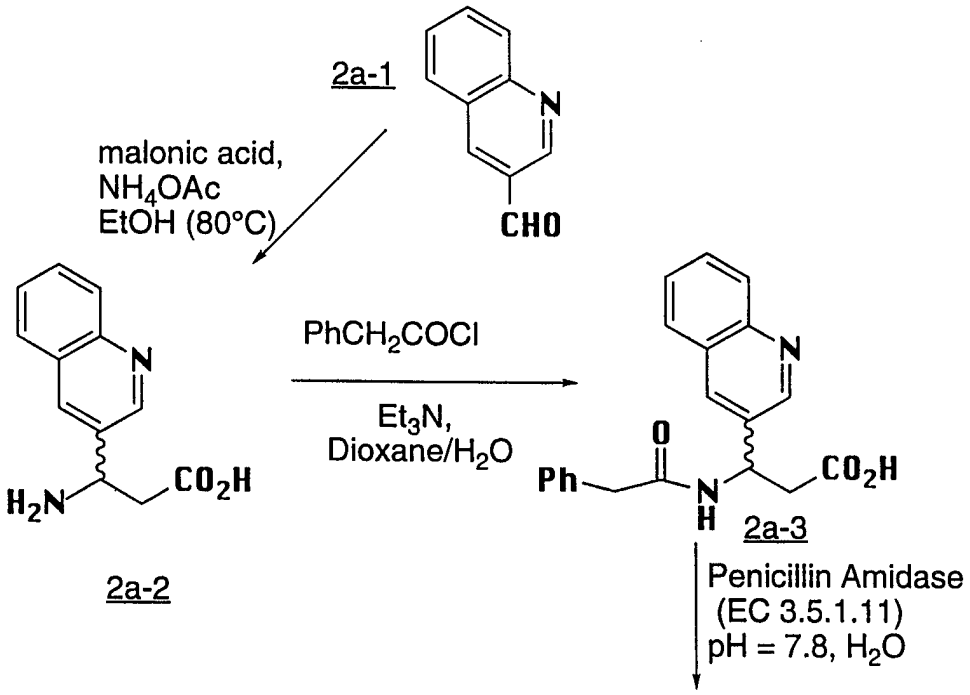
2-6a (43 mg, 0.093 mmol), protected amino acid 2-7 (Zablocki *et al.*, *J. Med. Chem.*, 1995, *38*, 2378), (25 mg, 0093 mmol), EDC (18 mg, 0.093 mmol), HOBT (13 mg, 0.093 mmol), and N-methyl morpholine (31 mL, 0.28 mmol) in anhydrous DMF (5 mL) was stirred at room temperature for 18 h, then concentrated in vacuuo and the residue chromatographed on silica gel using 5% MeOH/CH_2Cl_2 as eluent affording 2-8 as a colorless glass.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H); 8.45 (d, 1H); 8.00 (m, 1H); 7.68, (d, 1H); 7.21 (m, 1H); 7.17 (d, 1H); 5.56 (m, 1H); 4.75 (s, 2H); 4.45 (m, 2H); 4.05 (q, 2H); 3.95 (m, 1H); 3.5-3.3 (m, 4H); 2.92 (m, 1H); 2.87 (m, 1H); 2.74 (m, 2H); 2.35 (m, 2H); 1.92 (m, 2H); 1.36 (s, 9H); 1.21 (t, 3H).

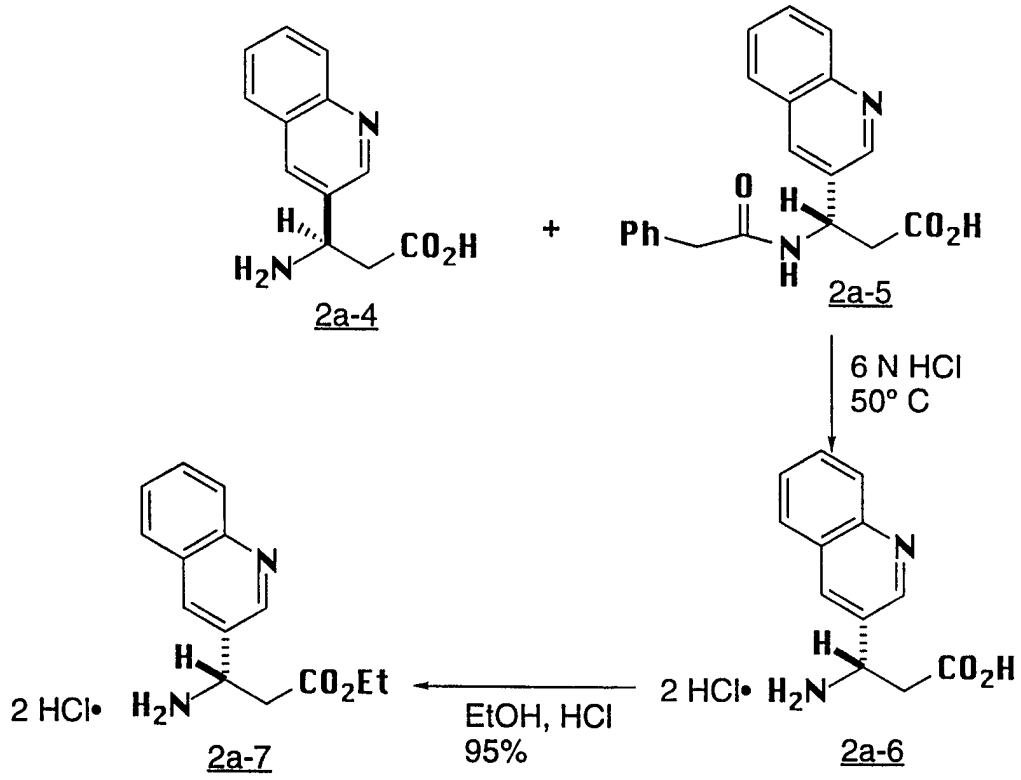
Step 7: 3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(R)-pyridin-3-yl-propionic acid (2-9)

2-8 (25 mg, 0.043 mmol) was dissolved in 6 N HCl (2 mL) and stirred at room temperature for 16 h, then evaporated to afford 2-9 as a pale yellow solid.

FAB MS (453, M^{+1});
^1H NMR (300 MHz, CD_3OD) δ 9.00 (s, 1H); 8.81 (d, 1H); 8.79(m, 1H); 8.10 (m, 1H); 7.71 (d, 1H); 7.01 (m, 1H); 5.56 (m, 1H); 4.75 (s, 2H); 4.61 (m, 1H); 4.50 (m, 1H); 4.35 (m, 1H); 4.10 (s, 2H); 3.62 (m, 4H); 3.4 -3.0 (m, 2H); 2.8 (m, 2H); 2.70 (m, 1H); 2.45 (m 1H); 1.98 (m, 2H).

EXAMPLE 2a





3-quinolin-3-yl-propionic acid (2a-2).

A solution containing quinoline-3-carboxaldehyde 2a-1 (5 g, 31.8 mmol), malonic acid (3.6 g, 35.0 mmol), and ammonium acetate (5.0 g, 63.6 mmol) in anhydrous ethanol (125 mL) was heated at reflux for 12 h. After cooling to room temperature, the resulting white solid was collected by filtration and washed with cold ethanol (150 mL) and then dried under vacuum to provide 2a-2 as a white solid.

^{1}H NMR (300 MHz, D_2O): δ 8.91 (d, J = 2 Hz 1H), 8.21 (d, J = 2 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.84 (d, J = 7 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.54
(t, J = 7 Hz, 1,H), 4.72 (m, 1H), 2.73 (m, 2H).

3-Phenylacetylamino-3-quinolin-3-yl-propionic (2a-3)

A 0° solution of 2a-2 (3.5 g, 16.2 mmol) and $NaHCO_3$ (2.7 g, 32.4 mmol) in 50% aqueous dioxane (100 mL) was treated dropwise with a solution of phenylacetyl chloride (3.00 g, 19.4 mmol) in 25 mL of dioxane. The resulting solution was stirred at 0° for 2.5h

then warmed to room temperature, diluted with H_2O (50 mL) and washed with ether (2 x 100 mL). The aqueous layer was adjusted to pH = 3 with 3N HCl and then extracted with CH_2Cl_2 (3 x 150 mL). The pooled organic extracts were dried, filtered and concentrated to afford 2a-3 as an off white solid.

^1H NMR (300 MHz, CD_3OD): δ 8.85 (d, J = 2 Hz 1H), 8.20 (d, J = 2 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 7.86 (d, J = 7 Hz, 1H), 7.76 (t, J = 7 Hz, 1H), 7.52 (t, J = 7 Hz, 1,H), 7.28 (m, 6H), 5.53 (t, J = 6.8 Hz, 1H), 3.57 (s, 2H), 2. 96 (m, 2H).

3-(S)-Quinolin-3-yl-propionic acid dihydrochloride (2a-6)

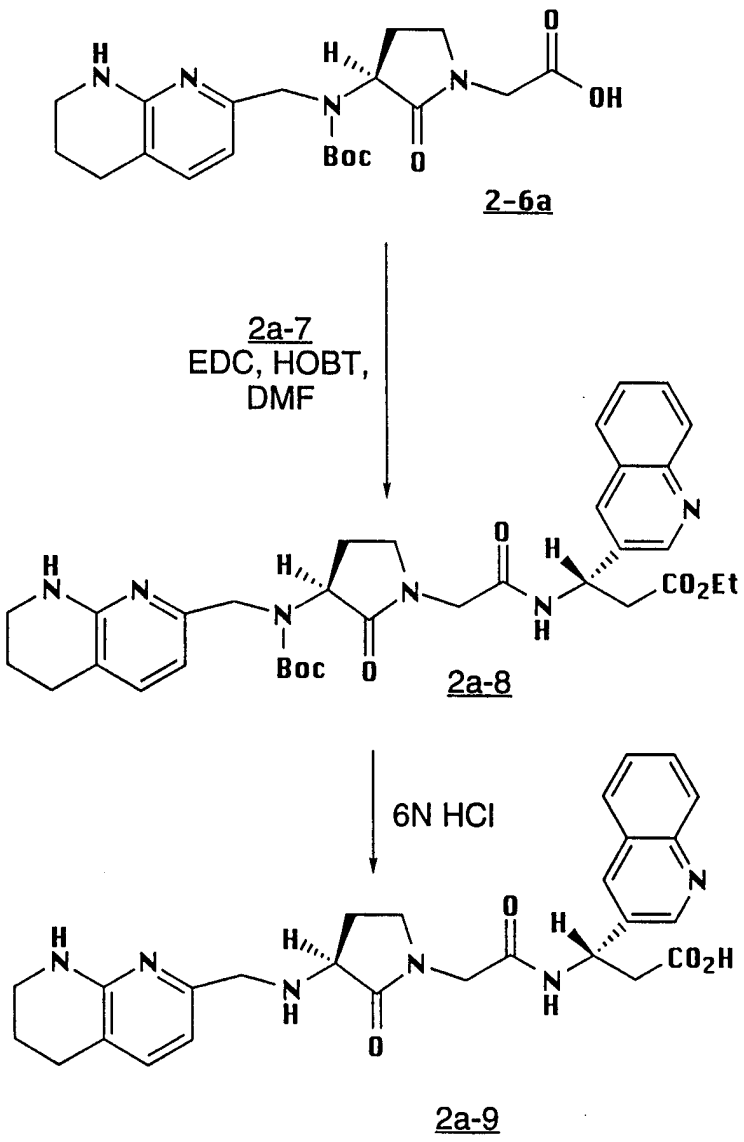
Acid 2a-3 (5.0 g, 15 mmol) was suspended in water (3.5 L) then treated with 1N NaOH (15 mL) to afford a clear solution. Penicillin amidase (Sigma, EC 3.5.1.11, 10,000 U) in 0.1 M phosphate buffer was added. The pH of the mixture was adjusted to 7.8 with 1N NaOH and the solution was stirred at room temperature for 4 days. The reaction was monitored periodically by hplc and the reaction stopped once the 50% conversion was reached. Next, the reaction solution was cooled to 0°C and adjusted to pH = 3 with 3N HCl. An oily yellow precipitate formed and was collected by filtration then washed with water to afford crude 2a-5 (1.8 g, 5.3 mmol). The filtrate was extracted with CH_2Cl_2 (3 x 500 mL) to afford additional 2a-5 contaminated by phenylacetic acid. Both batches of crude 2a-5 were combined and stirred in 3 N HCl (200 mL) at 50° for 12 h then cooled, washed with ether (2 x 100 mL) and evaporated to afford 2a-6.

3-(S)-Quinolin-3-yl-propionic acid ethyl ester dihydrochloride (2a-7).

The resolved acid 2a-6 was converted to 2a-7 by refluxing in ethanolic HCl.

^1H NMR (300 MHz, CD_3OD): δ 9.25 (d, J = 2 Hz 1H), 8.31 (d, J = 2 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 7.84 (d, J =7 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.54 (t, J = 7 Hz, 1,H), 4.72 (m, 1H), 4.15 (q, J = 6 Hz, 2H), 2.73 (m, 2H) 1.18 (t, J= 6 Hz, 3H).

EXAMPLE 2a (continued)



Ethyl -3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)- *tert*-butoxycarbonyl amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-quinolin-3-yl-propionic acid (2a-8)

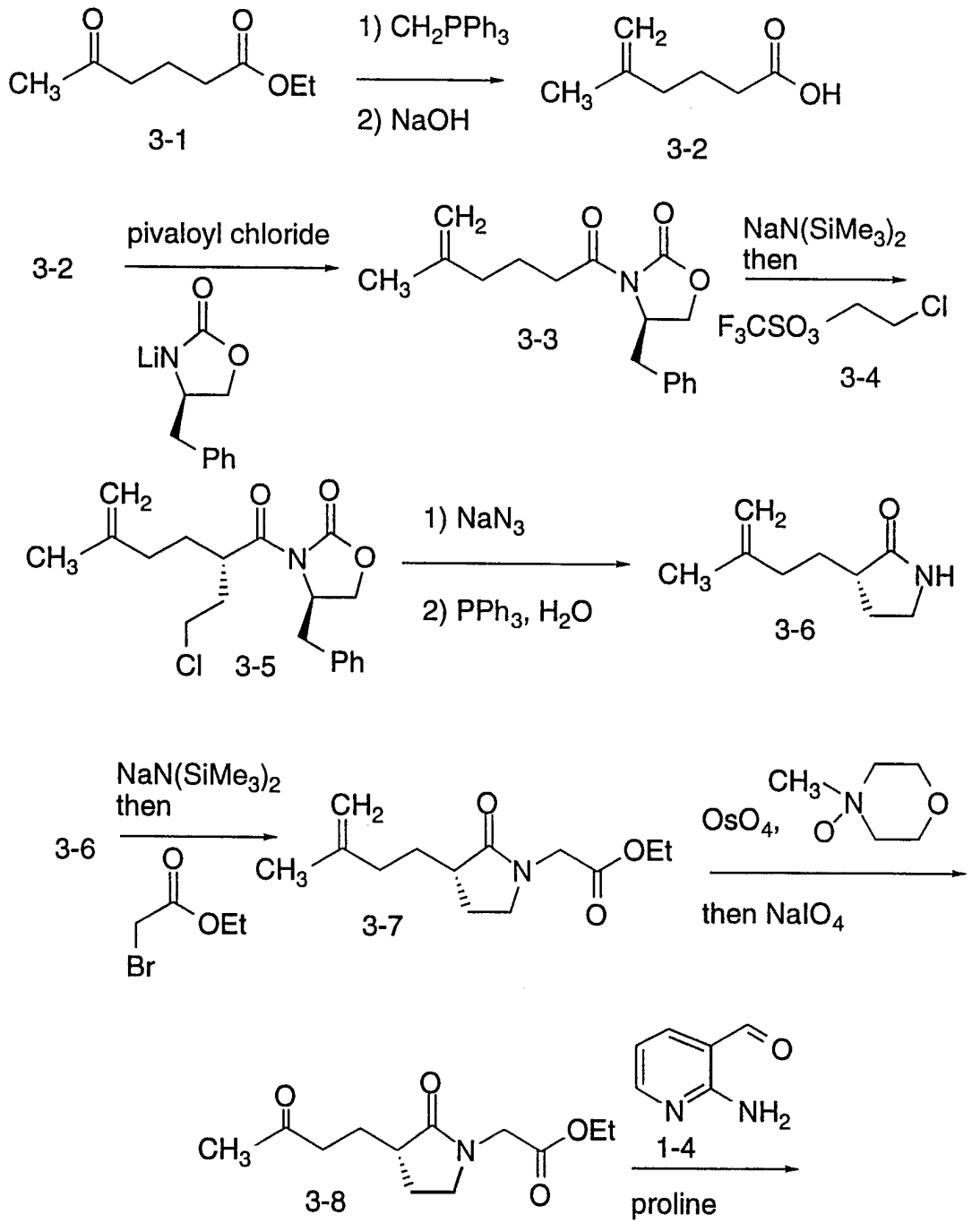
2-6a (100 mg, 0.216 mmol) from Example 2, Step 5, 2a-7 (53 mg, 0.216 mmol), EDC (41 mg, 0.216 mmol), HOBT (30 mg, 0.216 mmol), and N-methyl morpholine (66 μL, 0.48 mmol) in anhydrousous DMF (10 mL) was stirred at room temperature for 18 h, then concentrated in vacuo and the residue chromatographed on silica gel using 5% MeOH/CH_2Cl_2 as eluent affording 2a-8 as a colorless glass.

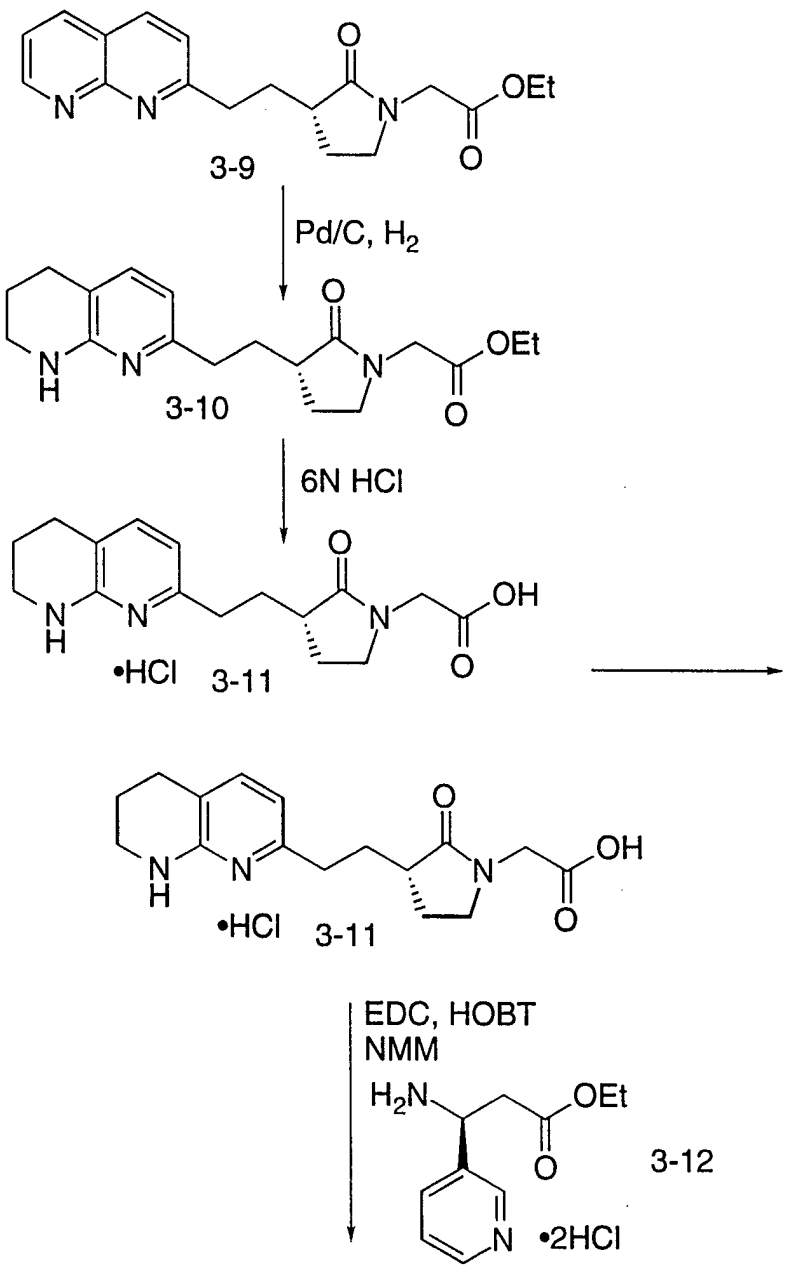
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H); 8.13 (d, 1H); 8.08 (s, 1H); 7.91, (d, 1H); 7.63 (m, 1H); 7.58 (m, 1H); 7.53 (t, 1H); 7.05 (d, 1H); 6.45 (s, 1H); 5.63 (m, 1H); 5.05 (br, s, 1H); 4.75 (s, 2H); 4.45 (m, 2H); 4.05 (q, 2H); 3.95 (m, 1H); 3.5-3.3 (m, 4H); 2.92 (m, 1H); 2.87 (m, 1H); 2.74 (m, 2H); 2.35 (m, 2H); 1.92 (m, 2H); 1.34 (s, 9H); 1.20 (t, 3H).

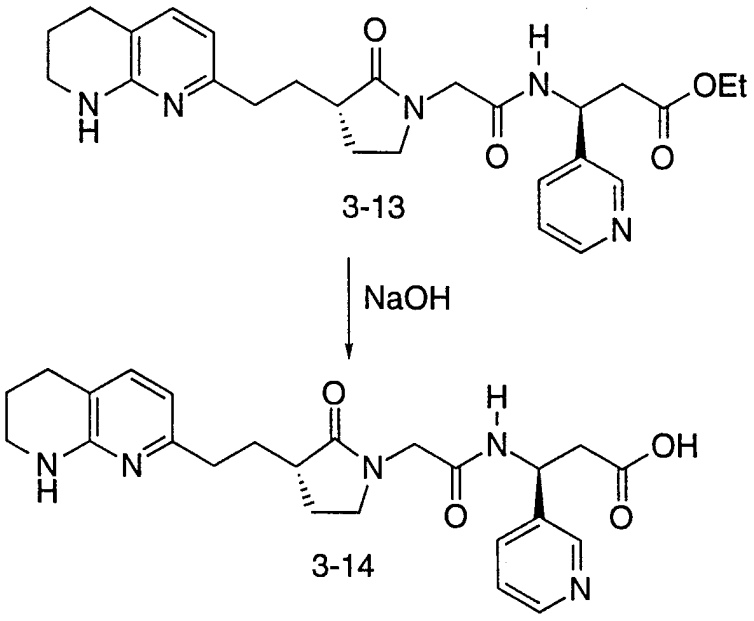
3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-quinolin-3-yl-propionic acid (2a-9).

2a-8 (125 mg, 0.24 mmol) was dissolved in 6 N HCl (2 mL) and stirred at room temperature for 14 h, then evaporated to afford 2a-9 as a pale yellow solid which was purified by preparative reverse phase hplc (C_{18}, 0.1% aqueous TFA/CH_3CN).
FAB MS (503, M^{+1});
^{1}H NMR (300 MHz, CD_3OD) δ 9.01 (s, 1H); 8.93 (s, 1H); 8.09 (d, 1H); 8.0 5 (d, 1H); 7.91 (t, 1H); 7.81 (t, 1H); 7.38 (d, 1H); 6.82 (d, 2H); 5.58 (m, 1H); 4.45 (m, 1H); 4.3 (m, 1H); 4.20 (m, 1H); 4.35 (m, 1H); 4.10 (s, 2H); 3.62 (m, 4H); 3.4 -3.0 (m, 2H); 2.8 (m, 2H); 2.70 (m, 1H); 2.45 (m 1H); 2.05 (m, 1H); 1.98 (m, 2H).

EXAMPLE 3


1) CH_2PPh_3
2) NaOH
3-1
3-2
pivaloyl chloride
LiN
Ph
3-3
$NaN(SiMe_3)_2$
then
F_3CSO_3
Cl
3-4
1) NaN_3
2) PPh_3, H_2O
3-5
3-6
$NaN(SiMe_3)_2$
then
Br
3-7
OsO_4,
then $NaIO_4$
3-8
1-4
proline


3-9
Pd/C, H2
3-10
6N HCl
•HCl 3-11
•HCl 3-11
EDC, HOBT
NMM
3-12
•2HCl



Step 1: 4-(Propyl-2-ene)butyric acid (3-2)

To a stirred suspension of methyltriphenylphosphonium bromide (67.7 g, 190 mmol) in 1 L THF at 0° C was added a solution of sodium bis(trimethylsilyl)amide (190 mL, 190 mmol, 1M THF) . After an additional 30 minutes, ethyl 4-acetylbutyrate 3-1 (Aldrich Chemical Co.)(25.0 g, 158 mmol) was added, and the mixture stirred for 18 h. The mixture was filtered, and the filtrate concentrated. The residue was triturated with hexanes, and then filtered. Following evaporative removal of the solvent, the residue was chromatographed on silica gel, eluting with 10% ethyl acetate/hexanes to give the olefin as a colorless oil. TLC Rf = 0.52 (10% ethyl acetate/hexanes).

^{1}H NMR (300 MHz, $CHCl_3$) δ 4.71 (d, 2H, J=13 Hz), 4.13 (q, 2H, J=7 Hz), 2.29 (t, 2H, J=7 Hz), 2.05 (t, 2H, J= 8 Hz), 1.77 (m, 2H), 1.72 (s, 3H), 1.26 (t, 3H, J=7Hz).

A solution of the above olefin (15.4 g, 98.6 mmol), 1 N NaOH (150 mL), and EtOH (300 mL) was stirred at ambient temperature for 2 h. Following acidification with 1 N HCl, the mixture was extracted with ether. The ether layer was washed with brine, dried over magnesium sulfate, and concentrated to give 3-2 as a colorless oil.

^{1}H NMR (300 MHz, $CHCl_3$) δ 4.70 (d, 2H, J=13 Hz), 2.27 (t, 2H, J=7 Hz), 2.06 (t, 2H, J= 7 Hz), 1.72 (m, 5H).

Step 2: (4-(Propyl-2-ene)butanoyl)-4(R)-benzyl-2-oxazolidinone (3-3)

To a solution of 3-2 (6.0 g , 46.8 mmol) in THF (200 ml) at -78° C was added triethylamine (7.19 mL , 51.5 mmol) followed by pivaloyl chloride (6.35 mL , 51.5 mmol). The mixture was warmed to 0°C for 1 h, then recooled to -78° C. In a separate flask, of (R)-(+)-4-benzyl-2-oxazolidinone (9.15 g, 51.5 mmol) was dissolved in THF (100 mL), cooled to -78° C, and n-BuLi (32.3 mL, 51.5 mmol; 1.6 M hexanes) was added dropwise. After 10 minutes, the lithium oxazolidinone was added to the pivalic anhydride. After 10 minutes, the mixture was warmed to 0° C for 1.5 h. The mixture was then poured into ethyl acetate, washed with aqueous sodium bicarbonate, and dried over magnesium sulfate. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, dichloromethane) to give 3-3 as a slightly yellow oil.
TLC Rf = 0.8 (CH_2Cl_2).
^{1}H NMR (300 MHz, $CHCl_3$) δ 7.40-7.18 (m, 5H), 4.80-4.60 (m, 3H), 4.18 (m, 2H), 3.30 (dd, 1H, J=3.2, 13.2 Hz), 2.95 (m, 2H), 2.76 (dd, 1H, J=9.5, 13.1 Hz), 2.11 (t, 2H, J=7.5 Hz), 1.87 (m, 2H), 1.74 (s, 3H).

Step 3: 2-Chloroethyltriflate (3-4)

To a solution of 1.67 mL (24.8 mmol) of 2-chloroethanol and 3.47 mL (29.8 mmol) of 2,6-lutidine in 20 mL of dichloromethane at 0° C was added 4.59 mL (27.3 mmol) of triflic anhydride. After 1 h, the mixture was diluted with hexanes, washed with ice-cold 1N HCl, and dried over sodium sulfate. The solvents were evaporated to give 3-4 as a pink oil.
^{1}H NMR (300 MHz, $CHCl_3$) δ 4.69 (t, 2H, J=5.3 Hz), 3.78 (t, 2H, J=5.6 Hz).

Step 4: 2(S)-Chloroethyl-4-(propyl-2-ene)butanoyl-(4(R)-benzyl-2-oxazolidinone) (3-5)

To a solution of 3-3 (11.0 g, 38.3 mmol) in THF (60 mL) at -78°C was added a solution of sodium bis(trimethylsilyl)amide (42.1 mL, 42.1 mmol; 1M/THF). After 20 min, 3-4 (16.2 ml, 115 mmol) was added over 5 min, and the resulting mixture stirred for 1.5 h at -78°C, then 2 h at -15°C. The mixture was diluted with hexanes, washed with sat. ammonium chloride, and dried over sodium sulfate. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 14% ethyl acetate/hexanes) to give 3-5 as a colorless oil. TLC Rf = 0.5 (20% ethyl acetate/hexanes).

^{1}H NMR (300 MHz, $CHCl_3$) δ 7.30-7.18 (m, 5H), 4.67 (m, 3H), 4.19 (m, 2H), 3.99 (m, 1H), 3.58 (m, 2H), 3.33 (dd, 1H, J=3.2, 12.0 Hz), 2.75 (dd, 1H, J=9.7, 13.5 Hz), 2.23 (m, 1H), 2.18-1.82 (m, 4H), 1.77-1.60 (m, 1H), 1.71 (s, 3H).

Step 5: Ethyl 2-oxo-3(S)-(3-methylenebutyl)pyrrolidine (3-6)

A mixture of 3-5 (8.15 g, 23.3 mmol) and NaN_3 (4.54 g, 69.8 mmol) in DMSO (120 mL) was heated at 75° C for 2 h. After cooling, the mixture was diluted with ether and hexanes, washed with water, and dried over sodium sulfate. Evaporative removal of the solvent gave the azide as a colorless oil.

TLC Rf = 0.5 (20% ethyl acetate/hexanes).

^{1}H NMR (300 MHz, $CHCl_3$) δ 7.30-7.22 (m, 5H), 4.69 (m, 3H), 4.17 (d, 2H, J=5.1 Hz), 3.89 (m, 1H), 3.38 (m, 3H), 2.74 (m, 1H), 2.13-1.63 (m, 6H), 1.71 (s, 3H).

To a solution of of this azide (8.0 g , 22.4 mmol) in THF (250 mL) and water (40 mL) was added triphenylphosphine (8.24 g , 31.4 mmol) in 4 portions over 5 minutes. This mixture was heated at reflux for 2 h, cooled, and evaporated. The residue was chromatographed (silica gel, 10% chloroform/ethyl acetate) to give 3-6 as a colorless oil.

TLC Rf = 0.40 (20% chloroform/ethyl acetate).
^{1}H NMR (300 MHz, $CHCl_3$) δ 6.47 (br s, 1H), 4.73 (m, 2H), 3.31 (m, 2H), 2.33 (m, 2H), 2.08 (m, 3H), 1.81 (m, 1H), 1.74 (s, 3H), 1.44 (s, 1H).

Step 6: Ethyl 2-oxo-3(S)-(3-methylenebutyl)pyrrolidin-1-yl)acetate (3-7)

To a solution of 3-6 (2.50 g, 16.3 mmol) in THF (40 mL) at -78° C was added sodium bis(trimethylsilyl)amide (17.1 mL, 17.1 mmol; 1M/ THF) dropwise. After an additional 20 min, ethyl bromoacetate (2.17 mL, 19.6 mmol) was added dropwise over 3 min. After an additional 20 min, 20 mL sat. aqueous NH_4Cl was added, and the cooling bath removed. The layers were separated, the aqueous layer washed with ether, and the combined organic extracts were dried over sodium sulfate. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 40% ethyl acetate/hexanes) to give 3-7 as a colorless oil.
TLC Rf = 0.85 (50% chloroform/ethyl acetate).
^{1}H NMR (300 MHz, $CHCl_3$) δ 4.73 (m, 2H), 4.18 (q, 2H, J=7.1Hz), 4.06 (dd, 2H, J=17.6, 20.8 Hz), 3.42 (m, 2H), 2.44 (m, 1H), 2.27 (m, 1H), 2.12 (m, 3H), 1.75 (m, 1H), 1.74 (s, 3H), 1.50 (m, 1H), 1.28 (t, 3H, J=7.3 Hz).

Step 7: Ethyl 2-oxo-3(S)-(3-oxo-butyl)pyrrolidin-1-yl)acetate (3-8)

To a solution of 3-7 (3.35 g,14.0 mmol) and N-methylmorpholine-N-oxide (3.27 g, 28.0 mmol) in THF (10 mL) and water (1 mL) was added OsO_4 (5.7 mL, 0.56 mmol; 2.5 % t-butanol). After 1 h, $NaIO_4$ (5.99 g , 28 mmol) in warm water (30 mL) was added over 2 min, and the resulting mixture stirred for 1 h. Water was then added, and the aqueous layer washed with ether and ethyl acetate, and the combined organic extracts were dried over sodium sulfate. Evaporative removal of the solvent gave 3-8 as a dark oil containing residual OsO_4.

TLC Rf = 0.78 (70:20:10 chloroform/ethyl acetate/MeOH).
^{1}H NMR (300 MHz, $CHCl_3$) δ 4.19 (m, 2H, J=7.2 Hz), 4.03 (s, 2H), 3.41 (m, 2H), 2.68 (t, 2H, J=9.4 Hz) 2.45 (m, 1H), 2.27 (m, 1H), 2.17 (s, 3H), 1.97 (m, 1H), 1.78 (m, 2H), 1.28 (t, 3H, J=7.2 Hz).

Step 8: Ethyl 2-oxo-3(S)-[2-([1,8]-naphthyridin-2-yl)ethyl] pyrrolidin-1-yl)acetate (3-9)

A mixture of 3-8 (3.25 g, 13.5 mmol), 2-amino-3-formyl-pyridine (2.2 g, 18.2 mmol; for preparation see *Synth. Commun.* 1987, 17, 1695) and proline (0.62 g, 5.39 mmol) in absolute ethanol (45 mL) was heated at reflux for 15 h. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:25:5 chloroform/ethyl acetate/MeOH to give 3-9 as a colorless oil.
TLC Rf = 0.24 (70:25:5 chloroform/ethyl acetate/MeOH).
^{1}H NMR (300 MHz, $CHCl_3$) δ 9.08 (m, 1H), 8.16 (m, 2H), 7.47 (m, 2H), 4.17 (m, 4H), 3.42 (m, 2H), 3.21 (t, 2H, J=6.0 Hz), 2.56 (m, 1H), 2.39 (m, 2H), 2.08 (m, 1H), 1.87 (m, 1H), 1.27 (t, 3H, J=7.1 Hz).

Step 9: Ethyl 2-oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetate (3-10)

A mixture of 3-9 (3.33 g, 10.2 mmol) and 10% Pd/carbon (1.5 g) in EtOH (50 mL) was stirred under a balloon of hydrogen for 13 h. Following filtration and evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:20:10 chloroform/ethyl acetate/MeOH to give 3-10 as a colorless oil.
TLC Rf = 0.20 (70:20:10 chloroform/ethyl acetate/MeOH).
^{1}H NMR (300 MHz, $CHCl_3$) δ 7.05 (d, 1H, J=7.3 Hz), 6.38 (d, 1H, J=7.3 Hz), 4.88 (br s, 1H), 4.17 (dd, 2H, J=7.0, 14.4 Hz), 4.04 (dd, 2H, J=17.6, 27.3 Hz), 3.40 (m, 4H), 2.69 (m, 4H), 2.51 (m, 1H), 2.28 (m, 2H), 1.90 (m, 2H), 1.78 (m, 2H), 1.27 (t, 3H, J=6.9 Hz).

Step 10: 2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetic acid (3-11)

A mixture of 3-10 (0.60 g, 1.81 mmol) and 6N HCl (25 mL) was heated at 60° C for 1 h. Evaporative removal of the solvent gave 3-11 as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d6) δ 8.4 (br s, 1H), 7.60 (d, 1H, J=7.3 Hz), 6.63 (d, 1H, J=7.3 Hz), 3.92 (dd, 2H, J=17.6, 25.9 Hz), 3.43 (m, 2H), 3.35 (m, 2H), 2.74 (m, 4H), 2.28 (m, 2H), 2.03 (m, 1H), 1.82 (m, 2H), 1.67 (m, 2H).

Step 11: 2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]-pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester (3-13)

A mixture of 3-11 (0.30 g, 0.882 mmol), amino acid ester 3-12 (Rico *et al., J. Org. Chem.*, 1993, *58*, 7948), (0.354 g, 1.32 mmol), EDC (0.220 g (1.15 mmol), HOBT (0.143 g, 1.05 mmol) and NMM (0.680 mL (6.18 mmol) in CH_3CN (5 mL) and DMF (3 mL) at 0° C was stirred for 10 min, then allowed to warm and stir for 20 h. The mixture was diluted with ethyl acetate, washed with water, brine, and dried over sodium sulfate. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:20:10 chloroform/ethyl acetate/MeOH to give 3-13 as a colorless foam.

TLC Rf = 0.31 (70:20:10 chloroform/ethyl acetate/MeOH).

^{1}H NMR (300 MHz, $CHCl_3$) δ 8.55 (d, 1H, J=2.2 Hz), 8.50 (dd, 1H, J= 1.5, 4.6 Hz), 7.64 (m, 2H), 7.23 (m, 1H), 7.05 (d, 1H, J=7.3 Hz), 6.38 (d, 1H, J=7.3 Hz), 5.40 (m, 1H), 4.98 (br s, 1H), 4.01 (m, 4H), 3.39 (m, 4H), 2.85 (m, 2H), 2.68 (m, 4H), 2.49 (m, 1H), 2.25 (m, 2H), 1.83 (m, 4H), 1.16 (t, 3H, J=7.2 Hz).

Step 14: 2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine (3-14)

To a solution of 3-13 (0.049 g, 0.102 mmol) in THF (1 mL) and water (0.3 mL) at 0°C was added 1M LiOH (0.112 ml, 0.112

mmol). After warming to ambient temperature and stirring for 2 h, the solvents were evaporated and the residue was chromatographed (silica gel, 25:10:1:1 ethyl acetate/EtOH/water/NH_4OH to give 3-14 as a colorless foam.

TLC Rf = 0.15 (25:10:1:1 ethyl acetate/EtOH/water/NH_4OH).

^1H NMR (300 MHz, DMSO-d_6) δ 8.74 (d, 1H, J=8.3 Hz), 8.51 (m, 1H), 8.42 (m, 2H), 7.70 (d, 1H, J=8.1 Hz), 7.33 (m, 1H), 7.21 (d, 1H, J=7.3 Hz), 6.36 (d, 1H, J=7.3 Hz), 5.14 (m, 1H), 4.00 (d, 1H, J=16.8 Hz), 3.70 (d, 1H, J=16.6 Hz), 3.30 (m, 4H), 2.68 (m, 7H), 2.20 (m, 3H), 1.71 (m, 4H).

EXAMPLE 4

(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride

Step A: 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.

Step B: 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. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was

isolated as a white powder which was sufficiently pure for use in the next reaction.

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

A solution of the product from Step B (85.8 g, 225 mmol) and α-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 which was used in the next step without further purification.

Step D: 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 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. $NaHCO_3$ 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 E: 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). 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 as a white powder which was sufficiently pure for use in the next step without further purification.

Step F: (S)-2-(*tert*-butoxycarbonylamino)-*N*-methoxy-*N*-methyl-4-(methylthio)butanamide

L-*N*-Boc-methionine (30.0 g, 0.120 mol), *N,O*-dimethylhydroxylamine hydrochloride (14.1 g, 0.144 mol), EDC hydrochloride (27.7 g, 0.144 mol) and HOBT (19.5 g, 0.144 mol) were stirred in dry DMF (300 mL) at 20°C under nitrogen. More *N,O*-dimethylhydroxylamine hydrochloride (2.3 g, 23 mmol) was added to obtain pH 7-8. The reaction was stirred overnight, the DMF distilled to half the original volume under high vacuum, and the residue partitioned between ethyl acetate and sat. $NaHCO_3$ soln. The organic phase was washed with saturated sodium bicarbonate, water, 10% citric acid, and brine, and dried with sodium sulfate. The solvent was removed *in vacuo* to give the title compound.

Step G: (S)-2-(*tert*-butoxycarbonylamino)-4-(methylthio)butanal

A suspension of lithium aluminum hydride (5.02 g, 0.132 mol) in ether (500 mL) was stirred at room temperature for one hour. The solution was cooled to -50°C under nitrogen, and a solution of the product from Step F (39.8 g, ca. 0.120 mol) in ether (200 mL) was added over 30 min, maintaining the temperature below -40°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. Analysis by tlc revealed incomplete reaction. The solution was rewarmed to 5 °C, stirred for 30 minutes, then cooled to

-50°C. A solution of potassium hydrogen sulfate (72 g, 0.529 mol) in 200 mL water was slowly added, maintaining the temperature below -20°C. The mixture was wasmed to 5°C, filtered through Celite, and concentrated *in vacuo* to provide the title aldehyde.

Step H: (S)-2-(*tert*-butoxycarbonylamino)-*N*-(3-chlorophenyl)-4-(methylthio)butanamine

To a solution of 3-chloroaniline (10.3 mL, 97.4 mmol), the product from Step G (23.9 g, 97.4 mmol), and acetic acid (27.8 mL, 487 mmol) in dichloroethane (250 mL) under nitrogen was added sodium triacetoxyborohydride (41.3 g, 195 mmol). The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The solution was diluted with $CHCl_3$, and the organic phase was washed with water, 10% citric acid and brine. The solution was dried over sodium sulfate and concentrated *in vacuo* to provide the crude product (34.8 g) which was chromatographed on silica gel with 20% ethyl acetate in hexane to obtain the title compound .

Step I: (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methylthio)ethyl]piperazin-2-one

A solution of the product from Step H (22.0 g, 63.8 mmol) in ethyl acetate (150 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (150 mL). Chloroacetyl chloride (5.6 mL, 70.2 mmol) was added dropwise, and the reaction stirred at 0°C for 2h. The layers were separated, and the ethyl acetate phase was washed with 10% citric acid and saturated brine, and dried over sodium sulfate. After concentration *in vacuo*, the resulting crude product (27.6 g) was dissolved in DMF (300 mL) and cooled to 0°C under argon. Cesium carbonate (63.9 g, 196 mmol) was added, and the reaction was stirred for two days, allowing it to warm to room temperature. Another portion of cesium carbonate (10 g, 30 mmol) was added, and the reaction was stirred for 16 hours. The DMF was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with saturated brine, and dried over sodium sulfate.

The crude product was chromatographed on silica gel with 20-25% ethyl acetate in hexane to obtain the title compound.

Step J: (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one

A solution of the product from Step I (14.2 g, 37 mmol) in methanol (300 mL) was cooled to 0°C, and a solution of magnesium monoperoxyphthalate (54.9 g, 111 mmol) in 210 mL MeOH was added over 20 minutes. The ice bath was removed, and the solution was allowed to warm to room temperature. After 45 minutes, the reaction was concentrated *in vacuo* to half the original volume, then quenched by the addition of 2N $Na_2S_2O_3$ soln. The solution was poured into EtOAc and sat $NaHCO_3$ solution, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude sulfone. This material was chromatographed on silica gel with 60-100% ethyl acetate in hexane to obtain the titled compound.

Step K: (S)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl] piperazin-2-one

Through a solution of Boc-protected piperazinone from Step J (1.39 g, 3.33 mmol) in 30 mL of EtOAc at 0°C was bubbled anhydrous HCl gas. The saturated solution was stirred for 35 minutes, then concentrated *in vacuo* to provide the hydrochloride salt as a white powder. This material was suspended in EtOAc and treated with dilute aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the combined organic mixture was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting amine was reconcentrated from toluene to provide the titled material suitable for use in the next step.

Step L: (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-5-[2-(methanesulfonyl)-ethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step K (898 mg, 2.83 mmol) and imidazole carboxaldehyde from Step E (897 mg, 4.25 mmol) in 15 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (1.21 g, 5.7 mmol). The reaction was stirred for 23 hours, then quenched at 0°C with sat. $NaHCO_3$ solution. The solution was poured into $CHCl_3$, and the aqueous layer was back-extracted with $CHCl_3$. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (95:5:0.5-90:10:0 EtOAc:MeOH:NH_4Cl), and the resultant product was taken up in EtOAc/methanol and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 5

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-piperazinone dihydrochloride

Step A: N-(3-chlorophenyl)ethylenediamine hydrochloride

To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). 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, 282 mmol) 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 crude diamine hydrochloride salt as a pale brown solid.

Step B: *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl) ethylenediamine

The amine hydrochloride from Step A (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. $NaHCO_3$ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled carbamate as a brown oil which was used in the next step without further purification.

Step C: *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)-2-chloroacetamide

A solution of the product from Step B (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH_2Cl_2 was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and washed with water, sat. aq. NH_4Cl soln, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step D: 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

To a solution of the chloroacetamide from Step C (*ca.* 282 mmol) in 700 mL of dry DMF was added K_2CO_3 (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hours, cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield

pure product, along with a sample of product (ca. 65% pure by HPLC) containing a less polar impurity.

Step E: 1-(3-chlorophenyl)-2-piperazinone

Through a solution of Boc-protected piperazinone from Step D (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to 0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder. This material was taken up in 300 mL of CH_2Cl_2 and treated with dilute aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (8 x 300 mL) until tlc analysis indicated complete extraction. The combined organic mixture was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled free amine as a pale brown oil.

Step F: 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step E (55.4 mmol, prepared above) in 200 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (10 g), followed by sodium triacetoxyborohydride (17.7 g, 83.3 mmol). The imidazole carboxaldehyde from Step E of Example 4 (11.9 g, 56.4 mmol) was added, and the reaction was stirred at 0°C. After 26 hours, the reaction was poured into EtOAc, washed with dilute aq. $NaHCO_3$, and the aqueous layer was back-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 500 mL of 5:1 benzene:CH_2Cl_2, and propylamine (20 mL) was added. The mixture was stirred for 12 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (2-7% MeOH/CH_2Cl_2), and the resultant white foam was taken up in CH_2Cl_2 and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*,

the product dihydrochloride was isolated as a white powder.

EXAMPLE 6

Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine methyl ester (Compound 6-1)

Step A. Preparation of N-(2(R)-t-butoxycarbonyl-amino-3-triphenyl-methylmercaptopropyl)-valyl-isoleucyl-leucine methyl ester

The tripeptide ester valyl-isoleucyl-leucine methyl ester was synthesized using conventional solution phase peptide synthesis methods. The trifluoroacetate salt of this tripeptide (360 mg, 0.77 mmol) was dissolved in 5 mL of methanol with 147 mg (1.5 mmol) of potassium acetate and 670 mg (1.5 mmol) of N-Boc-S-tritylcysteinal (prepared using the procedure of Goel, Krolls, Stier, and Kesten Org. Syn. **67:** 69-74 (1988) for the preparation of N-Boc-leucinal) was added. Sodium cyanoborohydride (47 mg, 0.75 mmol) was added and the mixture was stirred overnight. The mixture was diluted with ether and washed with water, 5% ammonium hydroxide and brine. The solution was dried (sodium sulfate) and evaporated to give a white foam which was purified by chromatography (1-15% acetone in methylene chloride). The title compound was obtained as an oily material.

Step B. Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine methyl ester

A sample of the protected pseudopeptide prepared as described in Step A (728 mg, 0.92 mmol) was dissolved in 100 mL of methylene chloride, 50 mL of TFA was added and the resulting yellow solution was treated immediately with 0.80 mL (5 mmol) of triethyl-silane. After 45 min, the solvents were evaporated and the residue was partitioned between hexane and 0.1% aqueous TFA. The aqueous solution was lyophilized. This material was further purified by reverse phase HPLC (5-95% acetonitrile/0.1% TFA/water) to afford the title compound. ^{1}H NMR (CD_3OD) δ 8.65 (1H, d), 4.45 (1H, m), 4.3 (1H,

d), 3.7 (3H, s), 3.4 (1H, m), 3.15 (1H, d), 2.75-2.95 (m), 0.8-1.05 (18 H, m). FAB mass spectrum, m/z = 447 (M + 1).
Anal. Calcd for $C_{21}H_{42}N_4O_4S$ • 1.8 TFA:
C, 45.24; H, 6.75; N, 8.56.
Found: C, 45.26; H, 6.77; N. 8.50.

EXAMPLE 7

N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine (Compound 7-2)

Step A. Preparation of N-(2(R)-t-butoxycarbonylamino-3-triphenylmethylmercaptopropyl)-valyl-isoleucyl-leucine

The product of Example 6, Step A (60 mg, 0.076 mmol) was dissolved in 1 mL of methanol and 150 μL of 1N NaOH was added. After stirring overnight, the solution was acidified with 150 μL of 10% citric acid and the product was extracted with ether. The ether solution was washed with water and brine and dried (sodium sulfate). Evaporation provided the title compound as a solid.

Step B. Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine

Using the method of Example 6, Step B, the protecting groups were removed with TFA and triethylsilane to provide the title compound. FAB mass spectrum, m/z = 433 (M+1).
Anal. Calcd for $C_{20}H_{40}N_4O_4S$ • 2 TFA:
C, 43.63; H, 6.41; N, 8.48.
Found: C, 43.26; H, 6.60; N. 8.49.

EXAMPLE 8

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone (Compound 8-1) and 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-homoserine (Compound 8-2)

Step A: Preparation of N-(α-chloroacetyl)-L-isoleucinol

To a stirred solution of L-isoleucinol (20 g, 0.17 mol) and triethylamine (28.56 ml, 0.204 mol) in CH_2Cl_2 (500 ml) at -78°C was added chloroacetyl chloride (16.3 ml, 0.204 mol) over 5 minutes. The cooling bath was removed and the solution allowed to warm to -20°C. The mixture was diluted with EtOAc and washed sequentially with 1 M HCl, and brine and dried (Na_2SO_4). Evaporation in vacuo afforded the amide title compound (35 g, 100%).

Rf = 0.3 CH_2Cl_2: MeOH (95:5);

^1H NMR ($CDCl_3$) δ 6.80 (1H, brd, J = 5 Hz), 4.10 (2H, s), 3.84 (1H, m), 3.79 (2H, m), 2.65 (1H, brs), 1.72 (1H, m), 1.55 (1H, m), 1.17 (1H, m), 0.96 (3H, d, J = 6Hz) 0.90 (3H,t, J=6 Hz).

Step B: Preparation of 5(S)-[1(S)-methyl]propyl-2,3,5,6-tetra-hydro-4H-1,4-oxazin-3-one

To a stirred solution of N-(a-chloroacetyl)-L-isoleucinol (7.4 g, 0.038 mol) in THF (125 ml) under argon at 0°C was slowly added sodium hydride (2.2 g of a 60% dispersion in mineral oil, 0.055 mol) with concomitant gas evolution. After completing the addition, the mixture was warmed to room temperature (R.T.) and stirred for 16 hr. Water (2.8 ml) was added and the solvents evaporated in vacuo. The residue was dissolved in $CHCl_3$ (70 ml) and washed with water saturated NaCl solution. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed using silica gel eluting with CH_2Cl_2:MeOH (96:4) to afford the lactam title compound (4.35 g, 72%) as a white solid.

Rf = 0.35 CH_2Cl_2:MeOH (95:5);

^{1}H NMR δ ($CDCl_3$) 6.72 (1H, brs), 4.20 (1H, d, J = 14.5 Hz), 4.10 (1H, d, J = 14.5 Hz), 3.88 (1H, dd, J = 9 and 3.5 Hz), 3.58 (1H, dd, J = 9 and 6.5 Hz), 3.45 (1H, brqt, J = 3.5 Hz), 1.70-1.45 (2H, m), 1.34 - 1.15 (1H, m), 0.96 (3H, t, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz).

Step C: Preparation of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

5(S)-[1(S)-Methyl]propyl-2,3,5,6-tetrahydro 4H-1,4-oxazin-3-one (12.2 g, 0.0776 mol) and DMAP (18.9 g, 0.155 mol) were dissolved in methylene chloride (120 ml) under argon at R.T. Boc anhydride (33.9 g, 0.155 mol) was added to the stirred solution in one portion, with concomitant gas evolution and the mixture was stirred at R.T. for 16 hr. The solvent was evaporated in vacuo and the residue was taken up in ethyl acetate and washed sequentially with 10% citric acid, 50% $NaHCO_3$ and finally brine. The organic extract was dried (Na_2SO_4) and evaporated in vacuo. Chromatography of the residue over silica gel eluting with 20% EtOAc in hexanes afforded the title compound (14.1 g, 71%) as a white solid.

Rf = 0.75 EtOAc:hexanes (20:80); mp 59-60°C

Anal. Calc'd. for $C_{13}H_{23}O_4N$:

C, 60.68; H,9.01; N, 5.44.

Found: C, 60.75; H, 9.01; N, 5.58.

^{1}H NMR ($CDCl_3$) δ 4.25 (1H, d, J = 15 Hz), 4.15 (1H, d, J = 15 Hz), 4.15 - 4.00 (2H, m), 3.73 (1H, dd, J = 10 and 2 Hz), 1.88 (1H, qt, J = 6 Hz), 1.55 (9H, s), 1.50 - 1.36 (1H, m), 1.35 - 1.19 (1H, m) 1.00 (3H, d, J = 6 Hz) 0.95 (3H, d, J = 6.5 Hz).

Step D: Preparation of N-(tert-Butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

A solution of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.75 g, 22.34 mmol) in DME (100 ml) under argon was cooled to -60°C. The cold solution was transferred via canula to a second flask containing sodium

bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C under argon. After stirring for 10 minutes, benzyl bromide (2.25 ml, 18.99 mmol) was added over 5 minutes and the resulting mixture was stirred at -78°C for 3 hours. After this time, the reaction mixture was transferred via cannula to another flask containing sodium bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C, under argon. After stirring for a further 5 minutes, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (24.6 ml) and allowed to warm to room temperature. This mixture was diluted with brine (50 ml) and water (20 ml) and then extracted with ethyl acetate (2 x 100 ml). The organic extracts were washed with brine (50 ml) and evaporated in vacuo to afford an oil. Chromatography of the residue over silica gel (230-400 mesh, 300 g) eluting with 10-20% ethyl acetate in hexanes afforded the title compound (5.12 g, 67%) as a clear oil.
Rf = 0.25 EtOAc:Hexanes (20:80);
^{1}H NMR ($CDCl_3$) δ 7.35 - 7.15 (5H, m), 4.31 (1H, dd, J = 6 and 2 Hz), 4.03 (1H, d, J = 12 Hz), 3.88 (1H, dd, J = 6 and 1 Hz), 3.66 (1H, dd, J = 12 and 2 Hz), 3.29 (1H, dd, J = 12 and 3 Hz), 1.54 (9H, s), 3.12 (1H, dd, J = 12 and 7 Hz), 1.47 (1H, m), 1.25 (1H, m), 1.10 (1H, m), 0.83 (3H, d, J = 6 Hz), 0.80 (3H, t, J = 6 Hz).

Step E: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenyl-propionic acid

To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.1 g, 14.7 mmol) in THF (150 ml) and water (50 ml) at 0°C was added hydrogen peroxide (15 ml of a 30% aqueous solution, 132 mmol) and lithium hydroxide (3.0 g, 63.9 mmol). After stirring for 30 minutes, the reaction was quenched with a solution of sodium sulfite (28.25 g, 0.224 mol) in water (70 ml). The THF was evaporated in vacuo and the aqueous phase was acidified to pH 3-4 by addition of

10% citric acid solution and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), evaporated in vacuo and the residue purified by chromatography over silica gel eluting with 4% MeOH in CH_2Cl_2 to give the lactam 2(S)-benzyl-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (0.82 g 22%) and then with 20% MeOH in CH_2Cl_2 to afford the title compound (4.03 g, 75%) as a viscous oil.

Rf = 0.4 MeOH:CH_2Cl_2 (5:95) + 0.3% AcOH;

^1H NMR (d_6 DMSO) δ 7.35 - 7.10 (5H, m), 6.68 (1H, br, s), 3.75 (1H, dd, J = 7.5 and 2.5 Hz) 3.54 (1H, m), 3.5 - 3.2 (2H, m) 2.99 (1H, dd, J = 12.5 and 2.5 Hz), 2.75 (1H, dd, J = 12.5 and 7.5 Hz), 1.50 - 1.35 (11H, m), 0.98 (1H, sept, J = 6 Hz), 0.78 (3H, t, J = 6 Hz), 0.65 (3H, d, J = 6 Hz);

FAB MS 366 (MH^+) 266 (MH_2^+ - $CO_2{}^tBu$).

Step F: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenyl-propionyl-homoserine lactone

To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionic acid (0.53 g, 1.45 mmol) and 3-hydroxy-1,2,3,-benzotriazin-4(3H)-one (HOOBT) (0.26 g, 1.6 mmol) in DMF (15 ml) at room temperature was added EDC (0.307 g, 1.6 mmol) and L-homoserine lactone hydrochloride (0.219 g, 6.0 mmol). The pH was adjusted to pH= 6.5 by addition of NEt_3 (the pH was monitored by application of an aliquot of the reaction mixture to a moist strip of pH paper). After stirring at room temperature for 16 hr, the reaction was diluted with EtOAc and washed with saturated $NaHCO_3$ and then brine and dried ($NaSO_4$). Evaporation in vacuo (sufficient to remove DMF) and chromatography over silica gel eluting with 5% acetone in CH_2Cl_2 afforded the title compound (520 mg, 80%) as a white solid, mp 115-117°C.

Rf = 0.3 Acetone: CH_2Cl_2 (5:95).

^1H NMR ($CDCl_3$) δ 7.73 (1H, brd, J=5 Hz), 7.40-7.15 (5H, m), 4.68 (1H, dt, J=9 and 7.5 Hz), 4.65-4.35 (2H, m), 4.33-4.18 (1H, m), 4.20

(1H, dd, J=7 and 3 Hz), 3.78 (1H, m), 3.49 (1H, dd, J=7.5 and 4.0 Hz), 3.37 (1H, dd, J=7.5 and 6.5 Hz), 3.15 (1H, dd, J=11.5 and 2 Hz), 2.86 (1H, dd, J=11.5 and 7.5 Hz), 2.68 (1H, m) 2.11 (1H, q, J=9 Hz), 1.55-1.30 (11H, m), 1.07 (1H, m), 0.87 (3H, t, J=6.3 Hz), 0.79 (3H, d, J=6 Hz).

Step G: Preparation of 2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone hydrochloride

Anhydrous HCl gas was bubbled through a cold (0°C) solution of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl] pentyloxy-3-phenylpropionyl-homoserine lactone (3.0 g, 6.7 mmol) in ethyl acetate (120 ml) until a saturated solution was obtained. The resulting mixture was stirred at 0°C for 1 hr. The solution was purged with nitrogen and the mixture concentrated in vacuo to afford the title compound as a sticky foam which was used without further purification. ^{1}H NMR (d_6 DMSO) δ 8.60 (1H, d, J=7 Hz), 8.08 (3H, brs), 7.35-7.15 (5H, m), 4.60 (1H, qt, J=8 Hz), 4.36 (1H, t J=7.5 Hz), 4.22 (1H, q, J=7.5 Hz), 4.15-3.95 (2H, m), 3.64 (1H, dd, J=9 and 2.5 Hz), 3.15-3.00 (2H, m), 2.92 (1H, dd, J=12.5 and 5.0 Hz), 2.40-2.15 (2H, m), 1.65 (1H, m), 1.43 (1H, m), 1.07 (1H, m), 0.82 (3H, t, J=6 Hz), 0.72 (3H, d, J=6.0 Hz).

Step H: Preparation of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercap-to]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone

2(S)-[2(S)-Amino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-homoserine hydrochloride (6.7 mmol) and N-(tert-butoxy-carbonyl)-S-triphenylmethylcysteine aldehyde (0.74 g, 7.5 mmol) (prepared from N-(tert-butoxycarbonyl)-S-triphenylmethylcysteine by the procedure of Goel, O.P.; Krolls, U.; Stier, M.; Keston, S. Org. Syn. 1988, 67, 69.) and potassium acetate (3.66 g, 8.2 mmol) were dissolved in methanol (48 ml). Activated 4A molecular sieves (6g) and then $Na(CN)BH_3$ (0.70 g, 10.7 mmol) were added and the resulting slurry was stirred under argon at room temperature for 16 hr. The solids

were removed by filtration and the filtrate evaporated in vacuo. The residue was dissolved in EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and brine and then dried (Na_2SO_4). Evaporation in vacuo afforded an oil which was purified by chromatography over silica gel eluting with a gradient of 30-50% EtOAc in hexane to afford the title compound (2.34 g, 45%) contaminated with a small amount of the corresponding methyl ester.

^1H NMR (CD_3OD) δ 7.60-7.05(20H, m), 4.64 (1H, d, J=9.0Hz), 4.39 (1H, br t, J=9Hz), 4.25(1H, m), 3.93 (1H, m), 3.75-3.60(1H, m), 3.55 (1H, dd, J=9.0 and 2Hz), 3.20 (1H, dd, J=9.0 and 6.0 Hz), 3.04 (1H, dd, J=15.0 and 5.0 Hz), 2.85 (1H, dd, J=15.0 and 9.0 Hz), 2.60 (1H, dd, J=12.0 and 5.0 Hz), 2.50-2.15 (7H, m), 1.45 (9H, s), 1.40-1.20 (1H, m), 1.07 (1H, m), 0.87 (3H, t, J=6 Hz), 0.67 (3H, d, J=6.0 Hz).

Step I: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone

To a stirred solution of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone (2.72 g, 3.49 mmol) in CH_2Cl_2 (90 ml) was added $HSiEt_3$ (2.16 ml, 13.5 mmol) and TFA (43.2 ml, 0.56 mol) and the solution was stirred at R.T. under argon for 2 hrs. The solvent was evaporated in vacuo and the residue partitioned between 0.1% aqueous TFA (200 ml) and hexanes (100 ml). The aqueous layer was separated and washed with hexanes (20 ml) and then lyophilised. The resulting white lyophilate was chromatographed in 5 equal portions over a Waters Prepak cartridge (C-18, 15-20 mM 100 A) eluting with a gradient of 95:5 to 5:95 0.1% TFA in H_2O : 0.1% TFA in CH_3CN at 100 ml/min over 60 min. The desired compound eluted after 19 min. The CH_3CN was evaporated in vacuo and the aqueous solution lyophilised to afford the title compound (1.95 g, 77%) as the TFA salt.

The salt is hygroscopic and is prone to disulphide formation if left in solution and exposed to air.

^{1}H NMR δ (CD_3OD) 7.40-7.15 (5H,m), 4.55-5.40 (2H, m), 4.33 (1H, m), 4.18 (1H, m), 3.90-3.62 (3H, m), 3.53 (1H, dd, J=10.5 and 4.0 Hz), 3.37 (1H, dd, J=10.5 and 6.0 Hz), 3.23 (1H, m), 3.15-2.95 (2H, m), 2.88 (1H, dd, J=12.5 and 5.0 Hz), 2.55-2.25 (2H, m), 1.92 (1H, m), 1.49 (1H, m), 1.23 (1H, m), 0.94 (3H, t, J=6 Hz), 0.90 (3H, d, J=6Hz).
FAB MS 873 ($2M-H^+$) 438 (MH^+) 361 (MH±Ph)
Anal. calc'd for $C_{22}H_{36}O_4N_3S$ 2.6 TFA:
C, 43.58; H, 5.25; N, 5,82.
Found: C, 43.62; H, 5.07; N, 5.80.

Step J: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propyl-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone (0.00326 mmol) was dissolved in methanol (0.0506 ml) and 1N sodium hydroxide (0.0134 ml) was added followed by methanol (0.262 ml). The conversion of the lactone to the hydroxy-acid was confirmed by HPLC analysis and NMR.

EXAMPLE 9

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine

Step A: Preparation of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)-amino-3-triphenyl-methylmercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine

To a solution of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine methyl ester (120 mg, 0.143 mmol) in methanol (4 ml) was added sodium hydroxide (1N, 0.57 ml, 0.57 mmol) and the resulting mixture was stirred at room temperature for 3 hours. Another portion of sodium hydroxide (1N, 0.25 ml) was

added and stirring continued for 0.5 hours. The reaction mixture was concentrated and the residue was dissolved in a minimum amount of water and neutralized with hydrochloric acid (1N, 0.87 ml). The aqueous solution was extracted with ethyl acetate three times. The combined extracts were dried (Na_2SO_4) and concentrated to yield the title compound (110 mg, 0.133 mmol, 93%). NMR (CD_3OD) δ 0.70 (3H, d, J=6Hz), 0.80 (3H, t, J=6Hz), 1.05 (H, m), 1.34 (9H, s), 1.60 (H, m), 1.95 (3H, S), 2.7~2.9 (3H, m), 2.95~3.1 (2H, m), 3.95 (H, d of d, J=8, 4Hz), 4.27 (H, d of d, J=8.6Hz), 7.1~7.4 (20H, m).

Step B: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine

The title compound was prepared in the same manner as that described in Example 8, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine in place of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone. NMR (CD_3OD) δ 0.82 (3H, d, J=6Hz), 0.95 (3H, t, J=6Hz), 1.20 (H, m), 1.40 (H, m), 1.85 (H, m), 2.10 (3H, s), 2.4~2.6 (2H, m), 3.1~3.2 (2H, m), 3.35 (H, d of d, J=14, 6Hz), 3.55 (H, d of d, J=14, 5Hz), 4.20 (H, d of d, J=10, 5Hz), 4.63 (H, d of d, J=10.6Hz), 7.27 (5H, m).

Anal. Calcd for $C_{23}H_{39}N_3O_4S_2 \cdot 2CF_3CO_2H \cdot 2H_2O$:

C, 43.25; H, 6.05; N, 5.60.

Found: C, 43.09; H, 6.01; N, 5.46.

EXAMPLE 10

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester (Compound 10-1)

Step A: Preparation of Methionine sulfone methyl ester

Thionyl chloride (2.63 ml, 36 mmol) was added dropwise to a stirred solution of N-Boc-Met sulfone (5 g, 18 mmol) in methanol (40 ml) cooled at 0°C. After the completion of the addition, the resulting mixture was warmed to room temperature and stirred overnight. The reaction mixture was recooled to 0°C and slowly treated with solid sodium bicarbonate to adjust the pH to 7. The mixture was concentrated in vacuo to remove methanol and the residue was dissolved in a minimum amount of water (solution pH ca. 10) and extracted with ethyl acetate four times. The combined extracts were dried (Na_2SO_4) and concentrated to give the title compound (1.5 g). NMR (CD_3OD) δ 2.04 (H, m), 2.21 (H, m), 2.98 (3H, s), 3.23 (2H, t, J=7Hz), 3.63 (H, d of d, J=8.6Hz), 3.77 (3H, s).

Step B: Preparation of N-(tert-Butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenyl-propionyl-methionine sulfone methyl ester

The title compound was prepared in the same fashion as that described in Example 8, Step F, but using methionine sulfone methyl ester in place of homoserine lactone hydrochloride. NMR (CD_3OD) δ 0.80 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.12 (H, m), 1.47 (9H, s), 2.10 (H, m), 2.32 (H, m), 2.93 (3H, s), 3.5~3.7 (2H, m), 3.74 (3H, s), 4.01 (H, d of d, J=7.4Hz), 4.60 (H, d of d, J=9.5Hz), 6.60 (H, d, J=8Hz), 7.25 (5H, m).

Step C: Preparation of 2(S)-[2(S)-Amino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester hydrochloride

The title compound was prepared in the same fashion as that described in Example 8, Step G, but using N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester in place of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone. NMR (CD_3OD) δ 0.85 (3H, d, J=6Hz), 0.94 (3H, t, J=6Hz), 1.20 (H, m), 1.52 (H, m), 1.72 (H, m), 2.14 (H, m), 2.38 (H, m), 2.98 (3H, s), 3.57 (H, d of d, J=12, 6Hz), 3.73 (H, d of d, J=12, 9Hz), 3.78 (3H, s), 4.15 (H, d of d, J=8.6Hz), 4.63 (H, d of d, J=8.5Hz), 7.30 (5H, m).

Step D: Preparation of 2(S)-[2(S)-[2(R)-(tert-Butoxy-carbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 8, Step H, but using 2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine sulfone methyl ester hydrochloride in place of 2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone hydrochloride. NMR (CD_3OD) δ 0.70 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.10 (H, m), 1.47 (9H, s), 2.15 (H, m), 2.67 (H, m), 2.92 (3H, s), 3.67 (H, m), 4.68 (H, d of d, J=10, 6Hz), 7.15~7.45 (20H, m).

Step E: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 8, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethylmercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester in place of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)-amino-3-triphenyl-

methylmercapto]propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-homoserine lactone. NMR (CD_3OD) δ 0.83 (3H, d, J=6Hz), 0.93 (3H, t, J=6Hz), 1.20 (H, m), 1.51 (H, m), 1.80 (H, m), 2.22 (H, m), 2.43 (H, m), 3.00 (3H, s), 3.78 (3H, s), 4.20 (H, d of d, J=8.4Hz), 4.72 (H, d of d, J=10, 6Hz), 7.30 (5H, m).
FABMS m/z 532 (MH^+).

EXAMPLE 11

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone (Compound 11-1)

Step A: Preparation of 2(S)-[2(S)-[2(R)-(tert-Butoxy-carbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine sulfone

The title compound was prepared in a similar fashion as that described in Example 9, Step A, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester in place of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenyl-methylmercapto]propylamino-3(S)-methyl]pentyloxy-methionine methyl ester. NMR (CD_3OD) δ 0.79 (3H, d, J=6Hz), 0.90 (3H, t, J=6Hz), 1.47 (9H, s), 2.92 (3H, s), 4.08 (H, m), 4.32 (H, m), 7.15~7.35 (20H, m).

Step B: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone

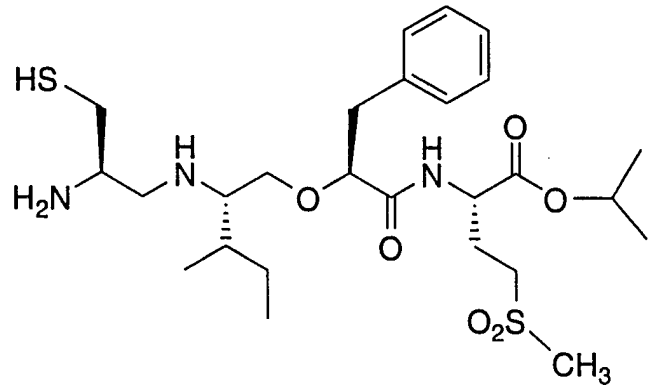
The title compound was prepared in a similar fashion as that described in Example 8, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-triphenylmethylmercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone in place of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethyl-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-

3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone. NMR (CD_3OD) δ 0.84 (3H, d, J=6Hz), 0.94 (3H, t, J=6Hz), 1.21 (H, m), 1.50 (H, m), 1.82 (H, m), 2.24 (H, m), 2.47 (H, m), 2.98 (3H, s), 3.6~3.75 (3H, m), 4.20 (H, d of d, J=9.5Hz), 4.64 (H, d of d, J=9.6Hz), 7.30 (5H, m).

Anal. Calcd for $C_{23}H_{39}N_3O_6S_2 \cdot 3CF_3CO_2H$:
C, 40.51; H, 4.92; N, 4.89.
Found: C, 40.47; H, 5.11; N, 4.56.

EXAMPLE 12

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester



The title compound was prepared using methods A-E from Example 10, except for Method A. Methionine sulfone isopropyl ester was prepared by coupling t-butyloxycarbonyl-methionine sulfone with isopropyl alcohol using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) followed by deprotection with HCl in EtOAc. NMR (CD_3OD) δ 0.83 (3H, d, J = 6 Hz), 0.94 (3H, t, J = 6 Hz), 1.11-1.56 (2H, m), 1.28 (6H, d, J = 6 Hz), 1.8-1.96 (1H, m), 2.12-2.27 (1H, m), 2.89-3.0 (2H, m), 3.01 (3H, s), 3.06-3.3 (4H, m), 3.42 (1H, dd, J = 6, 13 Hz), 3.65 (1H, dd, J = 6,13 Hz), 3.68-3.91 (3H, m), 4.2-4.27 (1H, m), 4.61-4.7 (1H, m), 4.96-5.12 (2H, m), 7.19-7.44 (5H, m).

Anal. Calc'd. for $C_{26}H_{45}N_3O_6S_2 \cdot 2\ CF_3CO_2H$:
C, 44.07; H, 5.67; N, 4.97;
Found C, 44.35; H, 5.68; N, 5.23

EXAMPLE 13

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

Step 1: 5-Chloro-5'-methyl-[1,2']bipyridinyl-2-one

5-Chloro-2-pyridinol (2.26g, 17.4 mmol), 2-bromo-5-methylpyridine (3.00g, 17.4 mmol), copper (0.022g, 0.35 mmol) and K_2CO_3 (2.66g, 19.2 mmol) were heated at 180°C for 16 hrs. The brown reaction mixture was cooled, diluted with EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, EtOAc: CH_2Cl_2 20:80 to 50:50 gradient elution) to afford the title compound as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.96(d, J=3.0Hz, 1H), 7.83 (d, J=8.4Hz, 1H), 7.65(dd, J=2.4 and 8.2Hz, 1H), 7.32(dd, J=2.9 and 9.7 Hz, 1H), 6.61(d, J=9.7Hz, 1H) and 2.39(s,3H)ppm.

Step 2: 5'-Bromomethyl-5-chloro-[1,2']bipyridinyl-2-one

A solution of the pyridine from Step 1(1.00g, 4.53 mmol), N-bromosuccinimide (0.81g, 4.53 mmol) and AIBN (0.030g, 0.18 mmol) in CCl_4 (40mL) was heated at reflux for 2 hrs. The solids were filtered and the filtrate collected. The solvent was evaporated in vacuo and the residue chromatographed (silica gel, EtOAc: CH_2Cl_2 25:75 to 50:50 gradient elution) to afford the title bromide.

^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04(d, J= 2.9 Hz, 1H), 8.01 (d, J=8.4Hz, 1H), 7.88 (dd, J=2.4 and 8.6Hz, 1H), 7.34(dd, J= 2.9 and 9.8Hz, 1H), 6.61(d, J=9.9Hz, 1H) and 4.51 (s,2H) ppm.

Step 3: 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile hydrochloride

The bromide from Step 2 (0.750g, 2.50 mmol) and the 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile (1.06g, 2.50 mmol) in CH_3CN (10 mL) were heated at 60°C. The reaction was cooled to room temperature and the solids collected by filtration and washed with EtOAc (10mL). The solid was suspended in methanol (50 mL) and heated at reflux for 1 hr, cooled and the solvent evaporated in vacuo. The sticky residue was stirred in EtOAc (40mL) for 4 hrs and the resulting solid hydrobromide salt collected by filtration and washed with EtOAc (40mL) and dried in vacuo. The hydrobromide salt was partitioned between sat. $NaHCO_3$ and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 4:96 to 5:95 gradient elution) to afford the free base which was converted to the hydrochloride salt to afford the title compound as a white solid.
^1H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.35 (s, 1H), 8.03(d, J=2.9Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.76 (dd, J=2.4 and 9.6Hz, 1H), 7.68-7.58 (m, 3H), 7.48 (s, 1H), 7.31(d, J=8.6Hz, 2H), 6.68 (d, J=9.3Hz, 1H), 5.53 (s, 2H) and 4.24 (s, 2H) ppm.

Analysis: Calc for $C_{22}H_{16}N_5OCl$: 1.75 HCl, 0.15 EtOAc
C 56.69, H 3.99, N 14.62
Found: C 56.72, H 4.05, N 14.54

BIOLOGICAL ASSAYS.

The ability of compounds of the present invention to inhibit cancer can be demonstrated using the following assays.

SPA Assay - αvβ3 Receptor Binding

The test procedures employed to measure αvβ3 binding activity of the antagonist compounds of the αvβ3 receptor of the present invention is described below.

N-(4-Iodo-phenylsulfonylamino)-L-asparagine (AR-2)

To a stirred solution of acid L-asparagine (4.39 g, 33.2 mmol), NaOH (1.49 g, 37.2 mmol), dioxane (30 ml) and H_2O (30 ml) at 0°C was added pipsyl chloride (10.34 g, 34.2 mmol). After ~5 minutes, NaOH (1.49, 37.2 mmol) dissolved in 15 ml H_2O, was added followed by the removal of the cooling bath. After 2.0 h, the reaction mixture was concentrated. The residue was dissolved in H_2O (300 ml) and then washed with EtOAc. The aqueous portion was cooled to 0°C and then acidified with concentrated HCl. The solid was collected and then washed with Et_2O to provide acid AR-2 as a white solid.
^1H NMR (300 MHz, D_2O) δ 7.86 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz) 3.70 (m, 1H), 2.39 (m, 2H).

2(S)-(4-Iodo-phenylsulfonylamino)-β-alanine (AR-3)

To a stirred solution of NaOH (7.14 g, 181.8 mmol) and H_2O (40 ml) at 0°C was added Br_2 (1.30 ml, 24.9 mmol) dropwise over a ten minute period. After ~5 minutes, acid AR-2 (9.9 g, 24.9 mmol), NaOH (2.00 g, 49.8 mmol) and H_2O (35 ml) were combined, cooled to 0°C and then added in a single portion to the reaction. After stirring for 20 minutes at 0°C, the reaction was heated to 90°C for 30 minutes and then recooled to 0°C. The pH was adjusted to ~7 by dropwise addition of concentrated HCl. The solid was collected, washed with EtOAc, and then dried *in vacuo* to provide acid AR-3 as a white solid.
^1H NMR (300 MHz, D_2O) δ 8.02 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.36 (m, 1H), 3.51 (dd, 1H, J=5Hz, 13Hz) 3.21 (m, 1H).

Ethyl 2(S)-(4-iodo-phenylsulfonylamino)-β-alanine-hydrochloride (AR-4)

HCl gas was rapidly bubbled through a suspension of acid AR-3 (4.0 g, 10.81 mmol) in EtOH (50 ml) at 0°C for 10 minutes. The cooling bath was removed and the reaction was heated to 60°C. After 18 h, the reaction was concentrated to provide ester AR-4 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.98 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.25 (q, 1H, J=5Hz), 3.92 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 1.01 (t, 3H, J=7Hz).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (AR-5)

A mixture of ester AR-5a (700 mg, 2.63 mmol), (for preparation, see: Scheme 29 of PCT International Application Publication No. WO 95/32710, published December 7, 1995) 10% Pd/C (350 mg) and EtOH were stirred under 1 atm H_2. After 20 h, the reaction was filtered through a celite pad and then concentrated to provide ester AR-5 as a brown oil.

TLC R_f = 0.23 (silica, 40% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 2H, J=8Hz), 7.26 (m, 3H), 6.43 (d, 1H, J=7Hz), 6.35 (d, 1H, J=8Hz), 4.37 (m, 4H), 3.05 (m, 2H), 2.91 (m, 2H), 1.39 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoic acid hydrochloride (AR-6)

A suspension of ester AR-5 (625 mg, 2.31 mmol) in 6N HCl (12 ml) was heated to 60°C. After ~20 h, the reaction was concentrated to give acid AR-6 as a tan solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.96 (d, 2H, J=8Hz), 7.80 (m, 1H), 7.33 (d, 2H, J=8Hz), 6.84 (d, 1H, J=9Hz), 6.69 (d, 1H, J=7Hz), 3.09 (m, 4H).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenylsulfonylamino)-β-alanine (AR-7)

A solution of acid AR-6 (400 mg, 1.43 mmol), amine AR-4 (686 mg, 1.57 mmol), EDC (358 mg, 1.86 mmol), HOBT (252 mg, 1.86 mmol), NMM (632 µl, 5.72 mmol) and DMF (10 ml) was stirred for ~20 h. The reaction was diluted with EtOAc and then washed with sat $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, EtOAC → 5% isopropanol/EtOAc) provided amide AR-7 as a white solid.

TLC R_f = 0.4 (silica, 10% isopropanol/EtOAc)

^{1}H NMR (300 MHz, CD_3OD) δ 7.79 (d, 2H, J=9Hz) 7.61 (d, 2H, J=8Hz), 7.52 (d, 2H, J=9Hz), 7.29 (m, 1H), 7.27 (d, 2H, J=8Hz), 4.20 (m, 1H), 3.95 (q, 2H, J=7Hz), 3.66 (dd, 1H, J=6Hz, 14Hz), 3.49 (dd, 1H, J=8Hz, 13Hz), 3.01 (m, 2H), 2.86 (m, 2H), 1.08 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenyl-sulfonylamino)-β-alanine (AR-8)

A solution of ester AR-7 (200 mg, 0.3213 mmol) and 6N HCl (30 ml) was heated to 60°C. After ~20 h, the reaction mixture was concentrated. Flash chromatography (silica, 20:20:1:1 EtOAc/EtOH/NH_4OH/H_2O) provided acid AR-8 as a white solid.

TLC R_f = 0.45 (silica, 20:20:1:1 EtOAc/EtOH/NH_4OH/H_2O)

^{1}H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.14 (Bs, 1H), 7.81 (d, 2H, J=8Hz), 7.62 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz), 7.27 (m, 3H), 6.34 (d, 1H, J=7Hz), 6.25 (d, 1H, J=8Hz), 5.85 (bs, 2H), 3.89 (bs, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H).

4-[2-(2-Aminopyridin-6-yl)ethyl)benzoyl-2(S)-(4-trimethylstannyl-phenylsulfonylamino-β-alanine (AR-9)

A solution of iodide AR-8 (70 mg, 0.1178 mmol), $(CH_3Sn)_2$ (49 µl, 0.2356 mmol), $Pd(PPh_3)_4$ (5 mg) and dioxane (7 ml) was heated to 90°C. After 2 h, the reaction was concentrated and then purified by prep HPLC (Delta-Pak C_{18} 15 µM 100A°, 40 x 100 mm; 95:5 → 5:95 H_2O/CH_3CN) provided the trifluoroacetate salt. The salt was suspended in H_2O (10 ml), treated with NH_4OH (5 drops) and then lyophilized to provide amide AR-9 as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.18 (d, 1H, J=8Hz), 7.67 (m, 5H), 7.56 (d, 2H, J=8Hz), 7.29 (d, 2H, J=8Hz), 6.95-7.52 (m, 2H), 6.45 (bs, 2H), 4.00 (m, 1H), 3.50 (m, 1H), 3.33 (m, 1H), 2.97 (m, 2H), 2.86 (m, 2H).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-4-^{125}iodo-phenylsulfonylamino-β-alanine (AR-10)

An iodobead (Pierce) was added to a shipping vial of 5 mCi of $Na^{125}I$ (Amersham, IMS30) and stirred for five minutes at room temperature. A solution of 0.1 mg of AR-9 in 0.05 mL of 10% H_2SO_4/MeOH was made and immediately added to the $Na^{125}I$/iodobead vial. After stirring for three minutes at room temperature, approximately 0.04-0.05 mL of NH_4OH was added so the reaction mixture was at pH 6-7. The entire reaction mixture was injected onto the HPLC for purification [Vydac peptide-protein C-18 column, 4.6 x 250 mm, linear gradient of 10% acetonitrile (0.1% (TFA):H_2O (0.1% TFA) to 90% acetonitrile (0.1% TFA):H_2O (0.1% TFA) over 30 minutes, 1 mL/min]. The retention time of AR-10 is 17 minutes under these conditions. Fractions containing the majority of the radioactivity were pooled, lyophilized and diluted with ethanol to give approximately 1 mCi of AR-10, which coeluted on HPLC analysis with an authentic sample of AR-8.

Instrumentation: Analytical and preparative HPLC was carried out using a Waters 600E Powerline Multi Solvent Delivery System with 0.1 mL heads with a Rheodyne 7125 injector and a Waters 990 Photodiode Array Detector with a Gilson FC203 Microfraction collector. For analytical and preparative HPLC a Vydac peptide-protein C-18 column, 4.6 x 250 mm was used with a C-18 Brownlee modular guard column. The acetonitrile used for the HPLC analyses was Fisher Optima grade. The HPLC radiodetector used was a Beckman 170 Radioisotope detector. A Vydac C-18 protein and peptide column, 3.9 x 250 mm was used for analytical and preparative HPLC. Solutions of radioactivity were concentrated using a Speedvac vacuum centrifuge. Calibration curves and chemical concentrations were determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer. Sample radioactivities were determined in a Packard A5530 gamma counter.

MATERIALS:

1. Wheatgerm agglutinin Scintillation Proximity Beads (SPA): Amersham
2. Octylglucopyranoside: Calbiochem
3. HEPES: Calbiochem
4. NaCl: Fisher
5. $CaCl_2$: Fisher
6. $MgCl_2$: SIGMA
7. Phenylmethylsulfonylfluoride (PMSF): SIGMA
8. Optiplate: PACKARD
9. AR-10 (specific activity 500-1000 Ci/mmole)
10. test compound
11. Purified integrin receptor: αvβ3 was purified from 293 cells overexpressing αvβ3(Duong *et al.*, *J. Bone Min. Res.*, *8*:S378, 1993) according to Pytela (*Methods in Enzymology*, *144*:475, 1987)
12. Binding buffer: 50 mM HEPES, pH 7.8, 100 mM NaCl, 1 mM Ca^{2+}/Mg^{2+}, 0.5 mM PMSF
13. 50 mM octylglucoside in binding buffer: 50-OG buffer

PROCEDURE:

1. Pretreatment of SPA beads:
   500 mg of lyophilized SPA beads were first washed four times with 200 ml of 50-OG buffer and once with 100 ml of binding buffer, and then resuspended in 12.5 ml of binding buffer.

2. Preparation of SPA beads and receptor mixture
   In each assay tube, 2.5 µl (40 mg/ml) of pretreated beads were suspended in 97.5 µl of binding buffer and 20 µl of 50-OG buffer. 5 µl (~30 ng/µl) of purified receptor was added to the beads in suspension with stirring at room temperature for 30 minutes. The mixture was then centrifuged at 2,500 rpm in a

Beckman GPR Benchtop centrifuge for 10 minutes at 4°C. The pellets were then resuspended in 50 µl of binding buffer and 25 µl of 50-OG buffer.

3. Reaction

The following were sequentially added into Optiplate in corresponding wells:

(i) Receptor/beads mixture (75 µl)

(ii) 25 µl of each of the following: compound to be tested, binding buffer for total binding or 8-8 for non-specific binding (final concentration 1 µM)

(iii) 8-10 in binding buffer (25 µl, final concentration 40 pM)

(iv) Binding buffer (125 µl)

(v) Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4°C

4. Plates were counted using PACKARD TOPCOUNT

5. % inhibition was calculated as follows:

A = total counts

B = nonspecific counts

C = sample counts

% inhibition = [{(A-B)-(C-B)}/(A-B)]/(A-B) x 100

αvβ5 ATTACHMENT ASSAY

Duong *et al.*, *J. Bone Miner. Res.*, *11*:S 290, which is incorporated by reference herein in its entirety describe a system for expressing the human avb5.

Materials:

1. Media and solutions used in this assay are purchased from BRL/Gibco, except BSA and the chemicals are from Sigma.
2. Attachment medium: HBSS with 1 mg/ml heat-inactivated fatty acid free BSA and 2 mM $CaCl_2$.

3. Glucosaminidase substrate solution: 3.75 mM p-nitrophenyl-N-acetyl-beta-D-glucosaminide, 0.1 M sodium citrate, 0.25% Triton, pH 5.0.
4. Glycine-EDTA developing solution: 50 mM glycine, 5 mM EDTA, pH 10.5.

Methods:

1. Plates (96 well, Nunc Maxi Sorp) are coated overnight at 4 °C with human vitronectin (3 ug/ml) in 50 mM carbonate buffer (pH 9/.6), using 100 µl/well. Plates are then washed 2X with DPBS and blocked with 2% BSA in DPBS for 2h at room temperature. After additional washes (2X) with DPBS, plates are used for cell attachment assay.
2. 293 (alpha v beta 5) cells are grown in MEM media in presence of 10% fetal calf serum to 90% confluence. Cells are then lifted from dishes with 1X Trypsin/EDTA and washed 3X with serum free MEM. Cells are resuspended in attachment medium (3 X 10^5 cells/ml).
3. Test compounds are prepared as a series of dilutions at 2X concentrations and added as 50 µl/well. Cell suspension is then added as 50 ml/well. Plates are incubated at 37 °C with 55 CO_2 for 1 hour to allow attachment.
4. Non-adherent cells are removed by gently washing the plates (3X) with DPBS and then incubated with glucosaminidase substrate solution (100 µl/well), overnight at room temperature in the dark. To quantitate cell numbers, a standard curve of glucosaminidase activity is determined for each experiment by adding samples of cell suspension directly to wells containing the enzyme substrate solution.
5. The next day, the reaction is developed by addition of 185 µl/well of gylcine/EDTA solution and reading absorbance at 405 nm using a Molecular Devices V-Max plate reader. Average test absorbance values (4 wells per test samples) are calculated. Then, the number of attached cells at each drug

concentration is quantitated versus the standard curve of cells using the Softmax program.

In vitro inhibition of farnesyl-protein transferase

Transferase Assays. Isoprenyl-protein transferase activity assays were carried out at 30 °C unless noted otherwise. A typical reaction contained (in a final volume of 50 μL): [^{3}H]farnesyl diphosphate or [^{3}H]geranylgeranyl diphosphate, Ras protein , 50 mM HEPES, pH 7.5, 5 mM $MgCl_2$, 5 mM dithiothreitol and isoprenyl-protein transferase. The FPTase employed in the assay was prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) *Biochemistry* **32**:5167-5176. The geranylgeranyl-protein transferase-type I employed in the assay was prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. After thermally pre-equilibrating the assay mixture in the absence of enzyme, reactions were initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions were allowed to stand for 15 m (to complete the precipitation process). After adding 2 mL of 100% ethanol, the reactions were vacuum-filtered through Whatman GF/C filters. Filters were washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801scintillation counter .

For inhibition studies, assays were run as described above, except inhibitors were prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. IC_{50} values were determined with both transferase substrates near K_M concentrations. Nonsaturating substrate conditions for inhibitor IC_{50} determinations were as follows: FTase, 650 nM Ras-CVLS, 100 nM farnesyl diphosphate; GGPTase-I, 500 nM Ras-CAIL, 100 nM geranylgeranyl diphosphate.

In vivo ras prenylation assay

The cell lines used in this assay consist of either Rat1 or NIH3T3 cells transformed by either viral Ha-*ras*; an N-*ras* chimeric gene in which the C-terminal hypervariable region of v-Ha-*ras* was substituted with the corresponding region from the N-*ras* gene; or ras-CVLL, a v-Ha-*ras* mutant in which the C-terminal exon encodes leucine instead of serine, making the encoded protein a substrate for geranylgeranylation by GGPTase I. The assay can also be performed using cell lines transformed with human Ha-*ras*, N-*ras* or Ki4B-*ras*. 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(s) (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, 400 μCi[^{35}S]methionine (1000 Ci/mmol) and test compound(s). Cells treated with lovastatin, a compound that blocks Ras processing in cells by inhibiting the rate-limiting step in the isoprenoid biosynthetic pathway (Hancock, J.F. et al. *Cell*, 57:1167 (1989); DeClue, J.E. et al. *Cancer Res.*, 51:712 (1991); Sinensky, M. et al. *J. Biol. Chem.*, 265:19937 (1990)), serve as a positive control in this assay. 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. Alternatively, four hours after the additon of the labelling media, the media is removed, the cells washed, and 3 ml of media containing the same or a different test compound added. Following an additional 16 hour incubation, the lysis is carried out as above. 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 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 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 prenylated and nonprenylated Ras proteins are compared to determine the percent inhibition of prenyl transfer to protein.

In vivo growth inhibition of Ras transformed cells 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. Cell lines transformed with human Ha-ras, N-ras or Ki4B-ras can also be utilized. 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 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 approximately 16 days after the cultures are seeded and comparisons are made.

In addition, the activity of the compounds of the present invention for treating cancer and/or inhibiting tumor growth is confirmed utilizing the nude mouse tumor xenograft assay described in Kohl et al., PNAS 91 (1994) 9141-45.

In vivo tumor growth inhibition assay (nude mouse)

Rodent fibroblasts transformed with oncogenically mutated human Ha-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Alternatively, the farnesyl-protein transferase inhibitor and/or the integrin antagonist may be administered by a continuous infusion pump. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 8-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

The following dosage groups are utilized to determine the efficacy of the combination of the farnesyl-protein transferase inhibitor (FTI) and integrin antagonist (antagonist):

Group	O	Vehicle controls
Group	A:	FTI at maximum no effect dose
Group	B:	FTI at minimal efficacy dose
Group	C:	antagonist at maximal no effect dose
Group	D:	antagonist at minimal efficacy dose
Group	E:	A + C
Group	F:	A + D
Group	G:	B + C
Group	H:	B + D

Additional doses of FTI and antagonist can be selected as needed.

WHAT IS CLAIMED IS:

1. A method for achieving a therapeutic effect in a mammal in need thereof which comprises administering to said mammal amounts of at least two therapeutic agents selected from a group consisting of:

a) a farnesyl-protein transferase inhibitor and

b) an integrin antagonist;

wherein the amount of a) alone or the amount of b) alone is insufficient to achieve said therapeutic effect.

2. The method according to Claim 1 wherein an amount of a farnesyl-protein transferase inhibitor and an amount of an integrin antagonist are administered simultaneously.

3. The method according to Claim 1 wherein the integrin antagonist is a selective antagonist of the $\alpha v\beta 3$ integrin.

4. The method according to Claim 1 wherein the integrin antagonist is a selective antagonist of the $\alpha v\beta 5$ integrin.

5. The method according to Claim 1 wherein the integrin antagonist is an antagonist of both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin.

6. A method for achieving a therapeutic effect in a mammal in need thereof which comprises administering to said mammal amounts of three therapeutic agents which are:

a) a farnesyl-protein transferase inhibitor;

b) a selective antagonist of the $\alpha v\beta 3$ integrin; and

c) a selective antagonist of the $\alpha v\beta 5$ integrin;

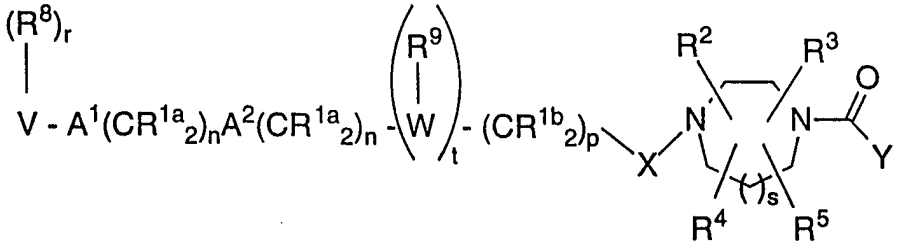
wherein the amount of a) alone, the amount of b) alone or the amount of c) alone is insufficient to achieve said therapeutic effect.

7. The method according to Claim 1 wherein the therapeutic effect is treatment of cancer.

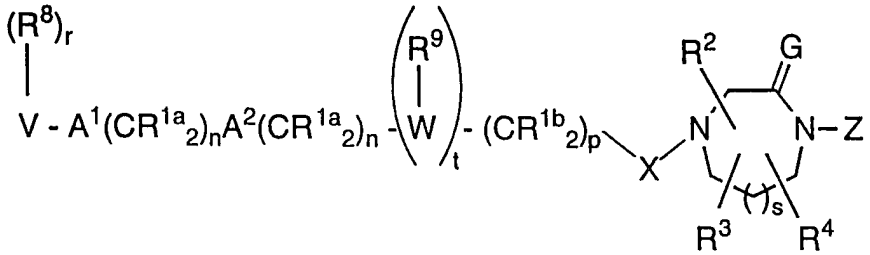
8. The method according to Claim 7 wherein the therapeutic effect is selected from inhibition of cancerous tumor growth and regression of cancerous tumors.

9. The method according to Claim 1 wherein the farnesyl-protein transferase inhibitor is selected from:

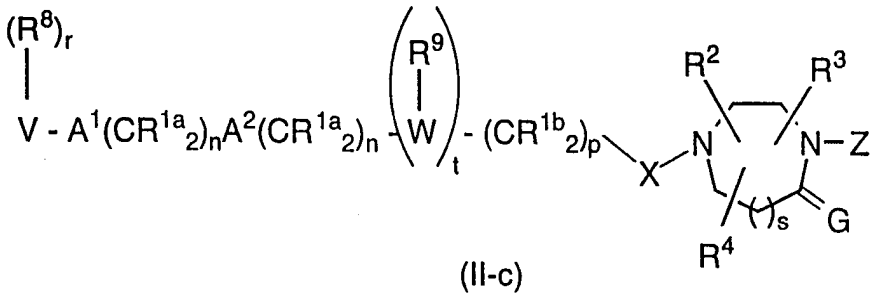
(a) a compound represented by formula (II-a) through (II-c):



(II-a)

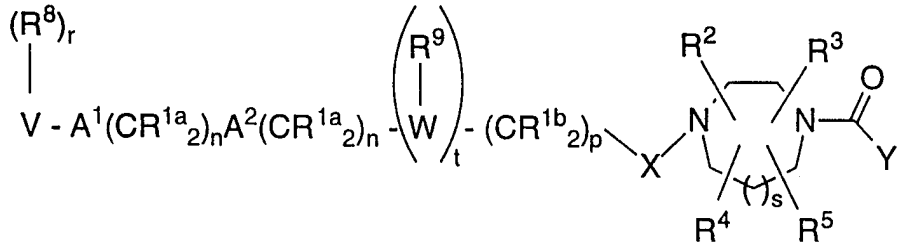


(II-b)



(II-c)

wherein with respect to formula (II-a):



(II-a)

or a pharmaceutically acceptable salt thereof,

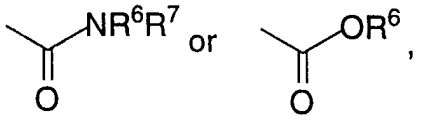
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



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

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,

c) $(CH_2)_pNR^6R^7$,

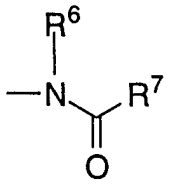
d) halogen,

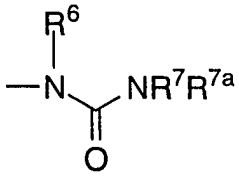
2) C_{3-6} cycloalkyl,

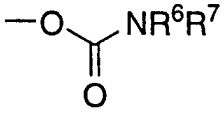
3) OR^6,

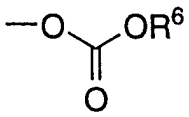
4) SR^6, $S(O)R^6$, SO_2R^6,

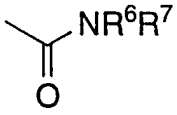
5) $-NR^6R^7$,

6)  ,

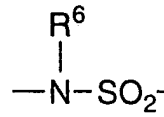
7)  ,

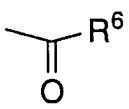
8)  ,

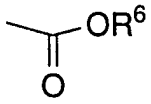
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  , or

14)  ; or

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

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

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

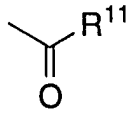
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f) $-SO_2R^{11}$, or

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

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

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

R^8 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, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

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

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

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

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, O, $-N(R^{10})$-, $-S(O)_2N(R^{10})$-, $-N(R^{10})S(O)_2$-, or $S(O)_m$;

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;

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

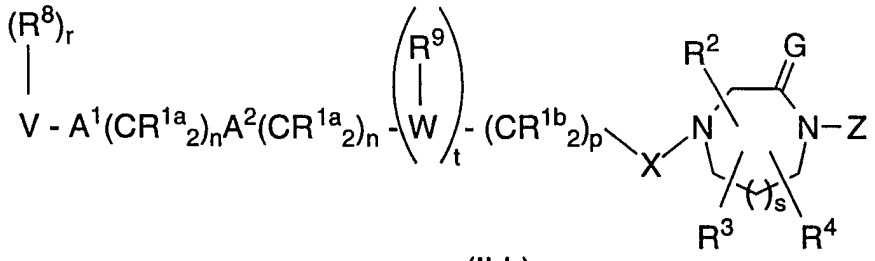
Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or

11) C_3-C_6 cycloalkyl;

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

with respect to formula (II-b):



(II-b)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, R^{7a}, u, R^8, A^1, A^2, V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

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

R^9 is selected from:

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

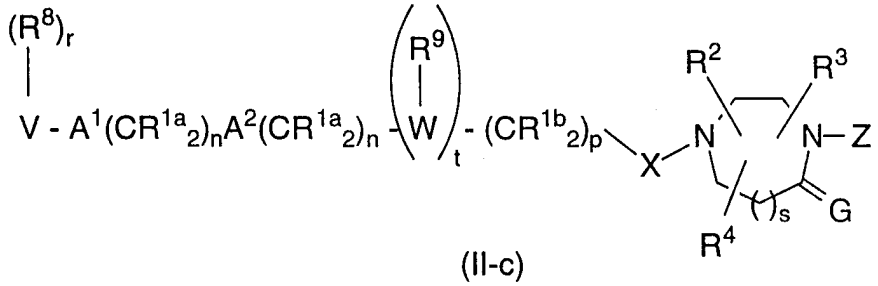
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

G is H_2 or O;

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

with respect to formula (II-c):



(II-c)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, u, R^{7a}, R^8, A^1, A^2, V, W, X, n, r and t are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

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

G is O;

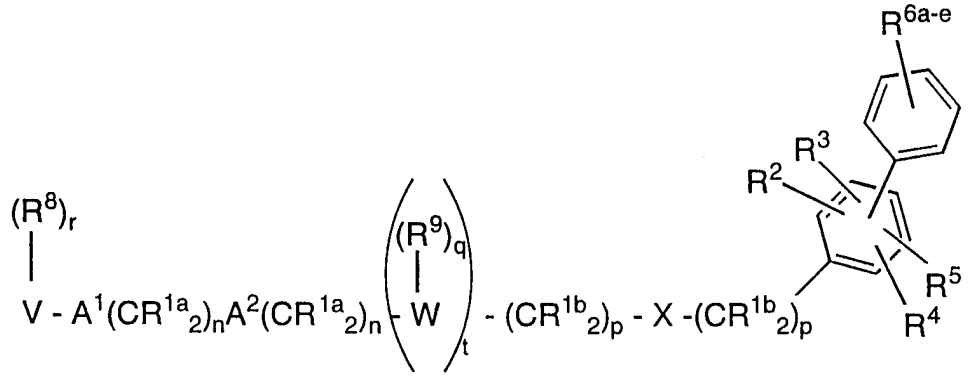
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,

6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl; and

s is 1;

(b) a compound represented by formula (II-d):



II-d

wherein:

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

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

$R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^2, R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

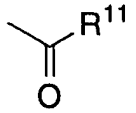
c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or

substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

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

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$,
g) $N(R^{10})_2$ or
h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl,

C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

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

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$- or $S(O)_m$;

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,

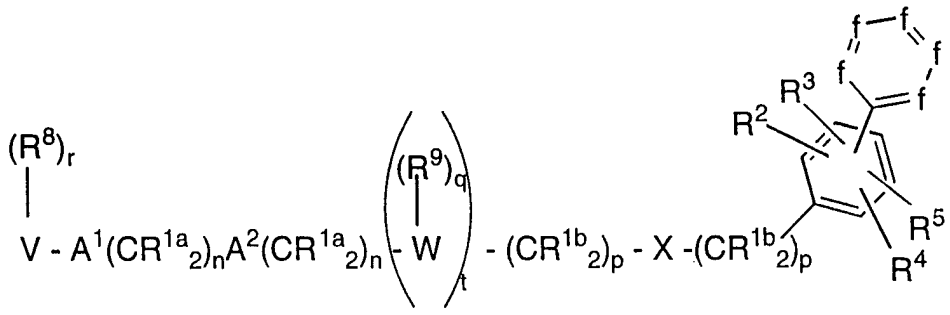
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, -C(O)O-, -OC(O)-, $-C(O)NR^7C(O)-$, $-NR^7-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ or $-S(=O)_m-$;

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

(c) a compound represented by formula (II-e):



II-e

wherein:

R^{1a}, R^{1b}, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-3 of f(s) are independently N, and the remaining f's are independently CR^6; and

each R^6 is independently selected from:

a) hydrogen,

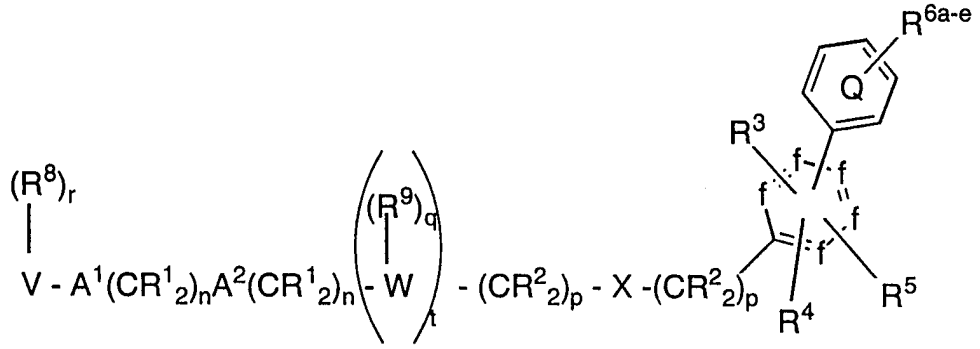
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

(d) a compound represented by formula (II-f):



II-f

wherein:

R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-2 of f(s) are independently N, and the remaining f's are independently CH; and

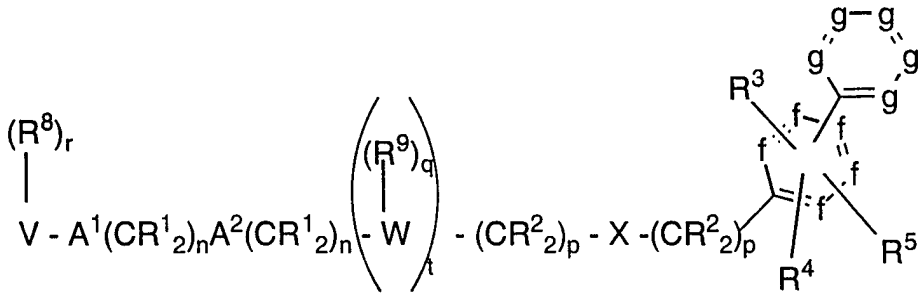
R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

(f) a compound represented by formula (II-g):



II-g

wherein:

R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-2 of f(s) are independently N, and the remaining f's are independently CH;

from 1-3 of g(s) are independently N, and the remaining g's are independently CR^6;

R^1 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, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; and

each R^6 is independently selected from:

a) hydrogen,

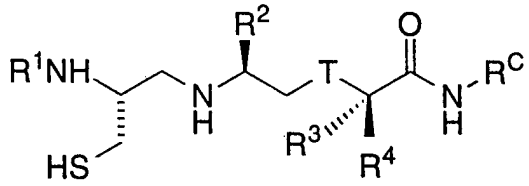
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, $-(CH_2)_4$- and $-(CH_2)_3$-;

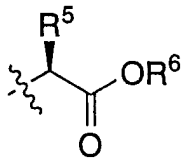
(g) a compound represented by formula (II-h):



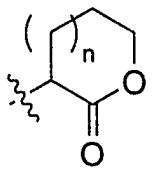
II-h

wherein

R^C is selected from:



and



;

R^1 is hydrogen, an alkyl group, an aralkyl group, an acyl group, an aracyl group, an aroyl group, an alkylsulfonyl group, aralkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

R^2 and R^3 are
the side chains of naturally occurring amino acids, including their oxidized forms which may be methionine sulfoxide or methionine sulfone, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substitutents may be substituted with an aromatic or heteroaromatic ring;

R^4 is hydrogen or an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

R^5 is selected from:

a) a side chain of naturally occurring amino acids,

b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,

c) substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl, or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituent is optionally substituted with an aromatic or heteroaromatic ring, and

d) $-CH_2CH_2OH$ or $-CH_2CH_2CH_2OH$;

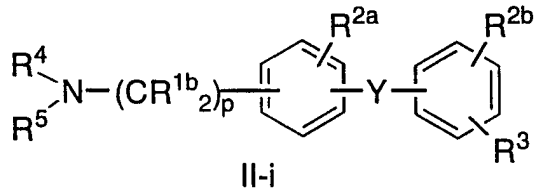
R^6 is a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;

T is O or $S(O)_m$;

m is 0, 1 or 2;

n is 0, 1 or 2;

(h) a compound represented by formula (II-i):



II-i

wherein:

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

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_6 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 unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_6 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^{2a}, R^{2b} and R^3 are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

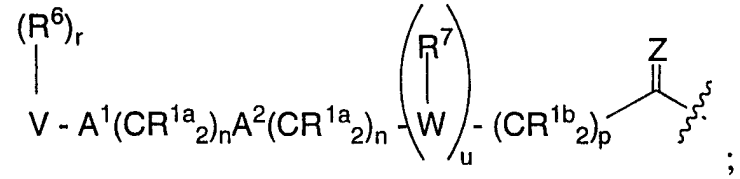
c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, halogen or $R^9OC(O)NR^8$-, and

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

R^4 and R^5 are independently selected from:

a) hydrogen, and

b)



;

R6 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C3-C6 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 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) C1-C6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C3-C6 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 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 $R^8OC(O)NH$-;

R7 is selected from:

a) hydrogen,

b) C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 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) C1-C6 alkyl unsubstituted or substituted by C1-C6 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 $R^9OC(O)NR^8$-;

R8 is independently selected from hydrogen, C1-C6 alkyl, substituted or unsubstituted C1-C6 aralkyl and substituted or unsubstituted aryl;

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

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 aralkyl 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-, -NR^8C(O)-, O, -N(R^8)-, -$S(O)_2N(R^8)$-, -N(R^8)$S(O)_2$-, or $S(O)_m$;

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;

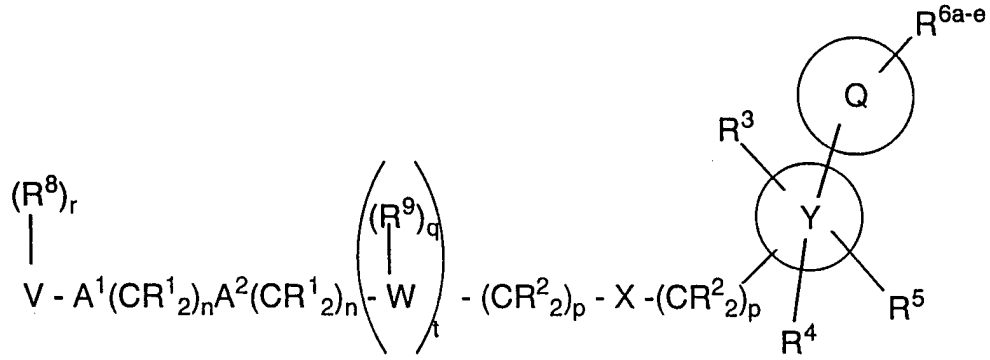
Y is selected from: a bond, -C(R^{10})=C(R^{10})-, -C≡C-, -C(O)-, -C(R^{10})$_2$-, -C(OR^{10})R^{10}-, -CN(R^{10})$_2R^{10}$-, -OC(R^{10})$_2$-, -NR^{10}C(R^{10})$_2$-, -C(R^{10})$_2$O-, -C(R^{10})$_2$$NR^{10}$-, -C(O)$NR^{10}$-, -$NR^{10}$C(O)-, O, -NC(O)$R^{10}$-, -NC(O)$OR^{10}$-, -$S(O)_2N(R^{10})$-, -N($R^{10}$)$S(O)_2$-, or $S(O)_m$;

Z is H_2 or O;

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
u is 0 or 1;

(e) a compound represented by formula (II-m):



II-m

wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR13)- or sulfonyl moiety adjacent to the nitrogen atom attached to Y;

Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R1 and R2 are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl,

C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-,

$R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

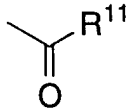
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, $-CH=CH-CH_2$-, $-(CH_2)_4$- and $-(CH_2)_3$-;

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

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle,

C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

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

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

R^{13} is selected from hydrogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkylsulfonyl and C_1-C_6 acyl;

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

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 heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

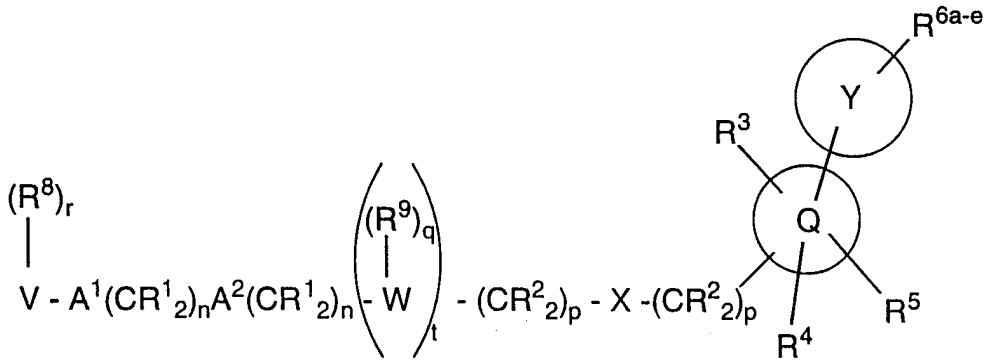
provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^7C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^7C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

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

(f) a compound represented by formula (II-n):

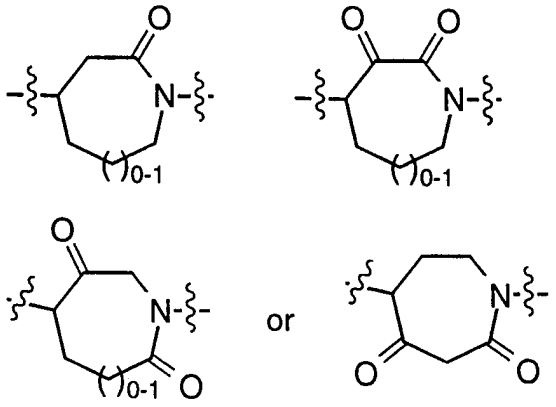


II-n

wherein:

R^1, R^2, R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-m);

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

or a pharmaceutically acceptable salt or disulfide thereof.

10. The method according to Claim 7 wherein the protein substrate competitive inhibitor is selected from:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[*N*-ethyl-2-acetamido]-2-piperazinone

(±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one

4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)piperazin-2-one

5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one

4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)-piperazin-2-one

4-[5-(4-Cyanobenzyl)-1-imidazolylethyl]-1-(3-chlorophenyl)piperazin-2-one;

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methy1-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto)propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]pentyloxypentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5-pentyloxy-4-methylpentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-methylpentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercaptolpropylamino-3(S)-methyllpentyloxy-3-methylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester (Compound 5),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound 6),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyt-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyI-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyllpentyloxy-3-methybutanoyl-methionine methyl ester.

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methybutanoyl-methionine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyI-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester

1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-methylimidazole

1-(4-Biphenylmethyl)-5-(4-cyanophenyloxy)-imidazole

5-(4-Cyanophenyloxy)-1-(2'-methyl-4-biphenylmethyl)-imidazole

5-(4-Biphenyloxy)-1-(4-cyanobenzyl)-imidazole

5-(2'-Methyl-4-biphenoxy)-1-(4-cyanobenzyl)-imidazole

5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl) methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl) methylimidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-methoxy-1-(4-cyanophenyl)-methylimidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)-imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl-imidazole

5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

1-(4-Biphenylmethyl)-5-(4-bromophenyloxy)-imidazole

1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl}-5-(pyrid-2-yl)-2-amino-pyrimidine

N,N-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene

N-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-[1-(4-Cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

(±)-4-[(4-imidazolylmethyl)amino]pentyl-1-(phenoxy)benzene

1-[(N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(n-butyl)amino)methyl]-4-(phenoxy)benzene

4-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(n-butyl)amino]-1-(phenylthio)benzene

(±)-4-[N-(1-(4-cyanobenzyl)-4-imidazolylmethyl)-N-(n-butyl)amino]-1-(phenylsulfinyl)benzene

3-[N-(4-imidazolylmethyl)-N-(n-butyl)amino]-N-(phenyl)benzenesulfonamide and

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

4-{3-[4-(-2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-3-Methyl-2-oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-(-2-Oxo-piperidin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

(4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

11. The method according to Claim 1 wherein the integrin antagonist is selected from:

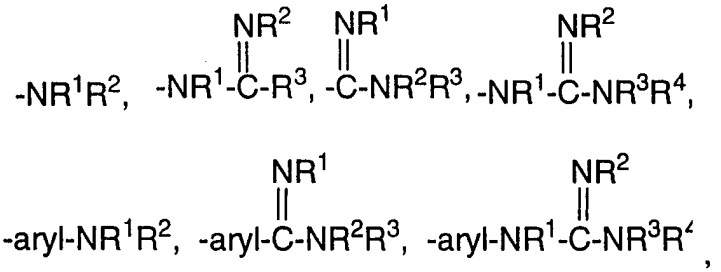
(a) a compound of the formula I-a:

X-Y-Z-Aryl-A-B

wherein:

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms and either unsubstituted or substituted with R^8 and R^9;

X is selected from



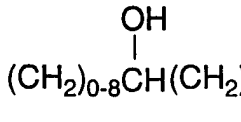
a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1, R^2, R^3 and R^4, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1, R^2, R^3 and R^4 ;

Y is selected from

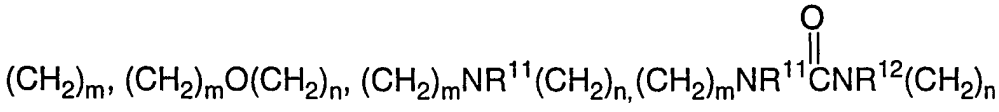
C_{0-8} alkylene,

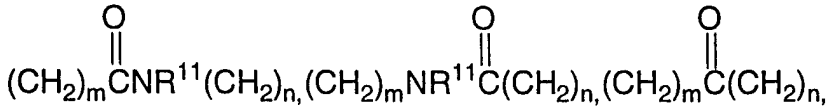
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^{10}-CO-C_{0-8} alkylene,
C_{0-8} alkylene-$CONR^{10}$-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^{10}-C_{0-8} alkylene,
C_{0-8} alkylene-$S(O)_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^{10}-C_{0-8} alkylene,
C_{0-8} alkylene-NR^{10}-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NR^{10}-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl$NR^{10}CO(CH_2)_{0-6}$, or

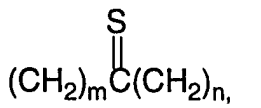


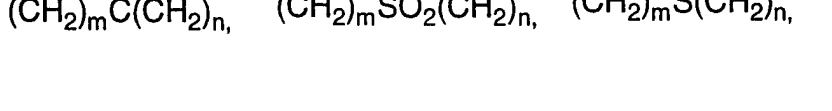
;

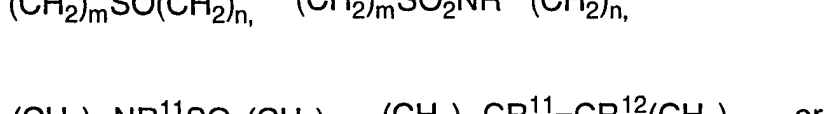
Z and A are each independently selected from





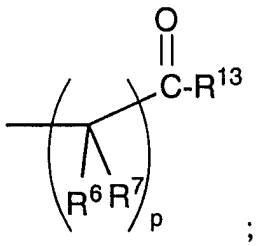






where m and n are each independently an integer from 0 to 6;

B is



;

where p is an integer from 1 to 3;

R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11} and R^{12} are each independently selected from

hydrogen,
halogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
hydroxycarbonyl C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
hydroxycarbonyl C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl or
hydroxy C_{0-6} alkyl;

R^6 is selected from

hydrogen,
fluorine,

C_{1-8} alkyl,
hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylcarbonyl,
aryl C_{0-6} alkylcarbonyl,
C_{1-6} alkylcarbonyloxy,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-6} alkylaminocarbonyloxy,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, or
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl;
wherein the alkyl or N atoms may be unsubstituted or substituted with R^5;

R^7 is selected from

hydrogen,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
aryl C_{0-6} alkyloxycarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl and
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylsulfonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylcarbonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl;
C_{7-20} polycyclyl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl or
C_{7-20} polycyclyl C_{0-8} alkyloxycarbonylamino C_{0-6} alkyl;

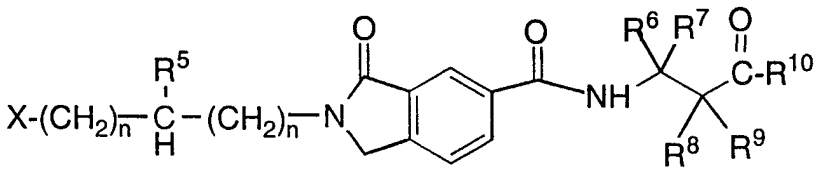
wherein the polycyclyl may be unsubstituted or substituted with R^{14}, R^{15}, R^{16} and R^{17}; and wherein any of the alkyl groups may be unsubstituted or subsituted with R^{14} and R^{15};

R^{13} is selected from
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
C_{1-6} dialkylaminocarbonylmethyloxy,
aryl C_{1-6} dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{14}, R^{15}, R^{16} and R^{17} are each independently selected from
hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, oxo, aryl,
aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl,
C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl,

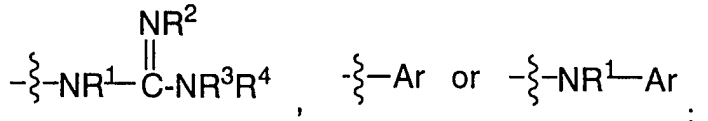
hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy, C_{1-8} alkyl-$S(O)_q$, C_{1-8} alkylaminocarbonyl, C_{1-8} dialkylaminocarbonyl, C_{1-8} alkyloxycarbonylamino, C_{1-8} alkylaminocarbonyloxy or C_{1-8}alkylsulfonylamino;

(b) a compound of the formula I-b:



I-b

wherein X is selected from



;

Ar is a 4- to 10-membered mono- or polycyclic aromatic or non-aromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S and wherein the mono- or polycyclic aromatic or non-aromatic ring system is either unsubstituted or substituted with R^1, R^2, R^3 and R^4;

R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, hydroxyl, C_{1-8} alkyl, halogen, aryl C_{0-8} alkyl, oxo, thio, amino-C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl, C_{1-6} alkylamino C_{0-8} alkyl, C_{1-6} dialkylamino C_{0-8} alkyl, aryl C_{0-6} alkylamino C_{0-6} alkyl, C_{1-4} alkoxyamino C_{0-8} alkyl, hydroxy C_{1-6} alkylamino C_{0-8} alkyl, C_{1-4} alkoxy C_{0-8} alkyl, carboxy C_{0-8} alkyl, C_{1-4} alkoxycarbonyl-C_{0-8} alkyl, carboxy C_{0-8} alkoxy, hydroxy C_{0-8} alkyl or C_{3-8} cycloalkyl C_{0-6} alkyl;

R^5 is selected from hydrogen, C_{1-6} alkyl, C_{0-6} alkylaryl, aryl or C_{3-8} cycloalkyl C_{0-6} alkyl;

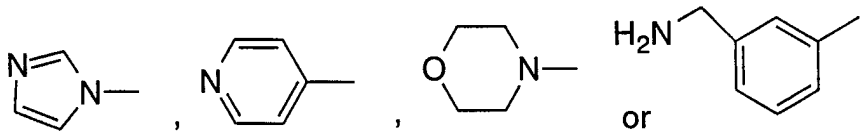
R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, fluorine, C_{1-8} alkyl, hydroxyl, hydroxy C_{1-6} alkyl, carboxy-C_{0-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylamino-carbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, C_{1-8} alkylsulfonylamino-C_{0-6} alkyl, aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl, C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, aryl C_{0-8} alkoxycarbonylamino C_{0-8} alkyl, aryl-C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkylcarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino-C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, C_{0-8} alkylamino-sulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino-C_{0-6} alkyl, C_{1-6} alkylsulfonyl C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl-C_{0-6} alkyl, C_{1-6} alkylcarbonyl C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl-C_{0-6} alkyl, C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkyl-thiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino C_{0-6} akyl, C_{3-8} cycloalkyl-C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonyloxy or C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

R^{10} is selected from hydroxyl, C_{1-8} alkoxy, aryl C_{0-6} alkoxy, C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy, aryl C_{1-8} alkylcarbonyloxy-C_{1-4} alkoxy, C_{1-6} dialkylaminocarbonylmethoxy, aryl C_{1-6} dialkylaminocarbonylmethoxy or an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of the amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

each n is independently an integer from 0 to three;

provided that when R^5 is hydrogen and X is Ar and Ar is a 6-membered monocyclic non-aromatic ring system containing one nitrogen atom and R^6 and R^7 are each hydrogen, and R^8 is selected from hydrogen or C_{1-6} alkyl, and R^{10} is selected from hydroxyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy or an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of the amino acid is as the free acid or is esterified with C_{1-6} alkyl, then R^9 is selected from fluorine, hydroxyl, hydroxy C_{1-6} alkyl, carboxy-C_{0-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylamino-carbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, aryl C_{0-8} alkoxycarbonyl-amino C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkyl-carbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylamino-carbonylamino C_{0-6} alkyl, C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl, C_{1-6} alkylsulfonyl-C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl, C_{1-6} alkylcarbonyl-C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl, C_{1-6} alkylthiocarbonyl-amino C_{0-6} alkyl, aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino-C_{0-6} akyl, C_{3-8} cycloalkyl C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl-C_{0-6} alkylaminocarbonyloxy or C_{3-8} cycloalkyl C_{0-6} alkylamino-carbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

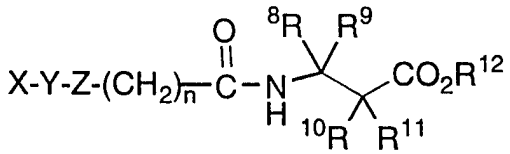
and provided further that when R^5 is hydrogen and X is Ar and Ar is



and R^6, R^7 and R^8 are each hydrogen, and R^{10} is selected from hydroxyl and C_{1-8} alkoxy, then R^9 is selected from fluorine,

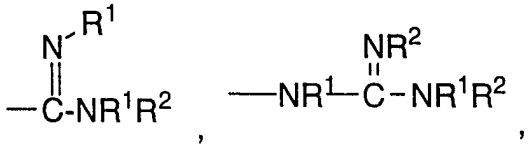
C_{1-8} alkyl, hydroxyl, hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, aryl C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, aryl C_{0-6} alkylcarbonyloxy, C_{1-6} alkylaminocarbonyloxy, C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{0-6} alkylamino-C_{0-6} alkyl, C_{0-6} dialkylamino C_{0-6} alkyl, C_{1-8} alkylsulfonylamino-C_{0-6} alkyl, C_{0-8} alkyl-SO_2NR^3-C_{0-8} alkyl, aryl C_{0-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkoxycarbonylamino C_{0-8} alkyl, C_{1-8} alkylcarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonylamino-C_{0-6} alkyl, C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl, aryl C_{0-8} alkylaminosulfonylamino-C_{0-6} alkyl, C_{1-6} alkylsulfonyl C_{0-6} alkyl, aryl C_{0-6} alkylsulfonyl-C_{0-6} alkyl, C_{1-6} alkylcarbonyl C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyl-C_{0-6} alkyl, C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkylsulfonylamino C_{0-6} akyl, C_{3-8} cycloalkyl-C_{0-6} alkylcarbonyl, C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonyloxy or C_{3-8} cycloalkyl C_{0-6} alkylaminocarbonylamino; wherein any of the alkyl groups may be unsubstituted or substituted with R^1 and R^2;

(c) a compound of the formula I-c:



I-c

wherein X is selected from

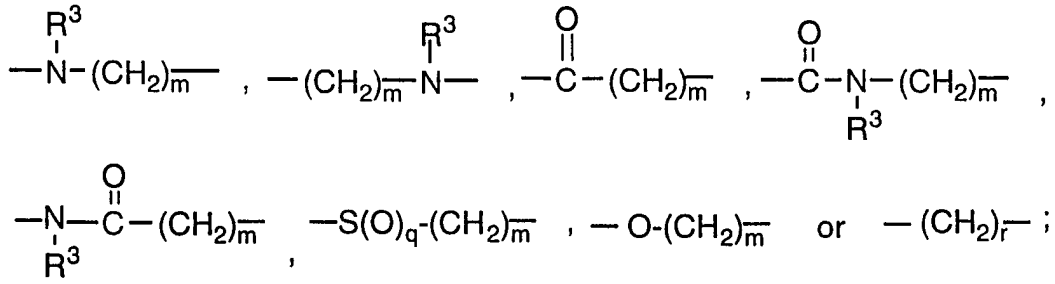


a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O

or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 and R^2;

Y is selected from



Z is a 5-11 membered aromatic or nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^4, R^5, R^6 and R^7; provided that Z is not a 6-membered monocyclic aromatic ring system; preferably, Z is a 5-11 membered nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^4, R^5, R^6 and R^7;

R^1, R^2, R^4, R^5, R^{13} and R^{14} are each independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino,

C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy, C_{1-8} alkyl-$S(O)_q$, C_{1-8} aminocarbonyl, C_{1-8} dialkylaminocarbonyl, C_{1-8} alkyloxycarbonylamino, C_{1-8} alkylaminocarbonyloxy or C_{1-8} alkylsulfonylamino;

R^3 is selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
hydroxyl,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{3-8} cycloalkyl,
amino C_{1-6} alkyl,
arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino C_{1-6} alkyl,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-8} alkylsulfonyl,
C_{1-8} alkoxycarbonyl,
aryloxycarbonyl,
aryl C_{1-8} alkoxycarbonyl,
C_{1-8} alkylcarbonyl,
arylcarbonyl,

aryl C_{1-6} alkylcarbonyl,
C_{1-8} alkylaminocarbonyl,
aminosulfonyl,
C_{1-8} alkylaminosulfonyl,
arylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonyl,
C_{1-6} alkylsulfonyl,
arylsulfonyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylcarbonyl,
C_{1-6} alkylthiocarbonyl,
arylthiocarbonyl, or
aryl C_{1-6} alkylthiocarbonyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{13} and R^{14};

R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
halogen,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
oxo,
amino,
C_{1-6} alkylamino,
amino C_{1-6} alkyl,
arylaminocarbonyl,

aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylaminocarbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or hydroxycarbonyl C_{1-5} alkyl,
$-(CH_2)_S$ C≡CH,
$-(CH_2)_S$ C≡C-C_{1-6} alkyl,
$-(CH_2)_S$ C≡C-C_{3-7} cycloalkyl,
$-(CH_2)_S$ C≡C-aryl,
$-(CH_2)_S$ C≡C-C_{1-6} alkylaryl,
$-(CH_2)_S$ CH=CH_2,
$-(CH_2)_S$ CH=CH C_{1-6} alkyl,
$-(CH_2)_S$ CH=CH-C_{3-7} cycloalkyl,
$-(CH_2)_S$ CH=CH aryl,
$-(CH_2)_S$ CH=CH C_{1-6} alkylaryl,
$-(CH_2)_S$ SO_2C_{1-6} alkyl,
$-(CH_2)_S$ SO_2C_{1-6} alkylaryl,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,
arylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino,
aryl C_{1-6} alkylamino C_{1-6} alkyl,

arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,
aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
C_{1-6} alkylsulfonyl,
C_{1-6} alkylsulfonyl C_{1-6} alkyl,

arylsulfonyl C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl, or
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{13} and R^{14}; and provided that the carbon atom to which R^8 and R^9 are attached is itself attached to no more than one heteroatom; and provided further that the carbon atom to which R^{10} and R^{11} are attached is itself attached to no more than one heteroatom;

R^{12} is selected from
hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-8} alkyl,
hydroxy,
C_{1-8} alkoxy,
aryloxy,
aryl C_{1-6} alkoxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkoxy,

C_{1-8} alkylaminocarbonylmethyleneoxy, or
C_{1-8} dialkylaminocarbonylmethyleneoxy;

m is an integer from 0 to 3;
n is an integer from 1 to 3;
p is an integer from 1 to 4;
q is an integer from 0 to 2;
r is an integer from 0 to 6; and
s is an integer from 0 to 3;

(d) a compound of the formula I-d:

X-Y-Z-Ring-A-B
I-d

wherein:

Ring is a 4 to 10-membered mono-or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, and either unsubstituted or substituted with R^{27} and R^{28};

X is selected from

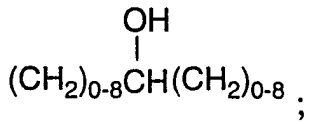
$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^3$, $-\overset{\overset{NR^2}{\|}}{C}-NHR^4$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$,

$-aryl-NR^1R^2$, $-aryl-\overset{\overset{NR^1}{\|}}{C}-NR^2R^3$, $-aryl-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$,

or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^{13}, R^{14}, R^{15} or R^{16};

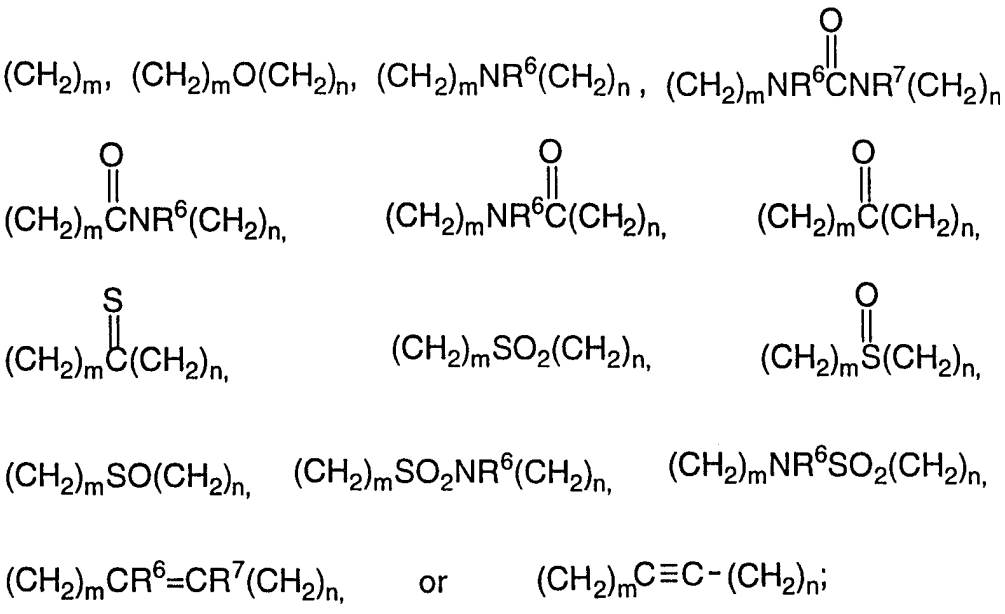
Y is selected from

C_{0-8} alkylene,
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-CONR^5-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-S(O)$_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NR^5-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-NR^5-CO-$(CH_2)_{0-6}$, or



;

Z is selected from

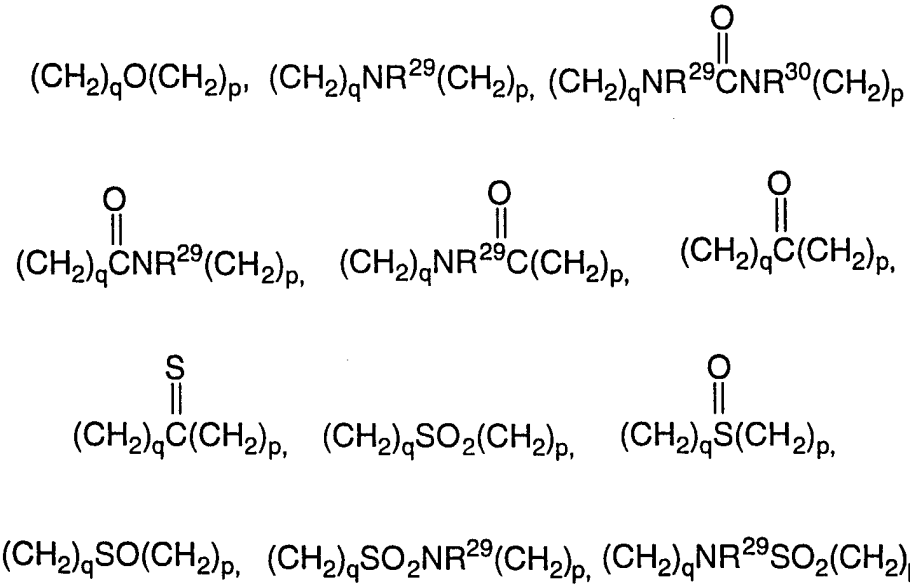


or

;

where m and n are each independently an integer from 0 to 6;

A is selected from



$(CH_2)_qO(CH_2)_p$, $(CH_2)_qNR^{29}(CH_2)_p$, $(CH_2)_qNR^{29}\overset{O}{\overset{\|}{C}}NR^{30}(CH_2)_p$

$(CH_2)_q\overset{O}{\overset{\|}{C}}NR^{29}(CH_2)_p$, $(CH_2)_qNR^{29}\overset{O}{\overset{\|}{C}}(CH_2)_p$, $(CH_2)_q\overset{O}{\overset{\|}{C}}(CH_2)_p$,

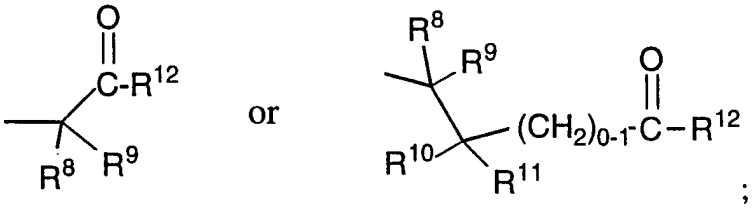
$(CH_2)_q\overset{S}{\overset{\|}{C}}(CH_2)_p$, $(CH_2)_qSO_2(CH_2)_p$, $(CH_2)_q\overset{O}{\overset{\|}{S}}(CH_2)_p$,

$(CH_2)_qSO(CH_2)_p$, $(CH_2)_qSO_2NR^{29}(CH_2)_p$, $(CH_2)_qNR^{29}SO_2(CH_2)_p$,

$(CH_2)_qCR^{29}=CR^{30}(CH_2)_p$ or $(CH_2)_qC\equiv C-(CH_2)_p$;

where p and q are each independently an integer from 0 to 6;

B is selected from



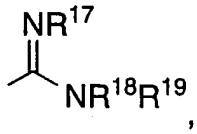
or

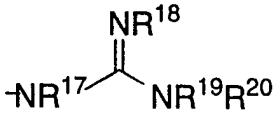
;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29} and R^{30} are each independently selected from

hydrogen,
halogen,
$C_{1\text{-}10}$ alkyl,
aryl $C_{0\text{-}8}$ alkyl,

amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,


, or


;

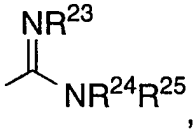
R^8, R^9, R^{10}, and R^{11} are each independently selected from
hydrogen,
fluorine,
C_{1-8} alkyl,
hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylcarbonyl,
aryl C_{0-6} alkylcarbonyl,
C_{1-6} alkylcarbonyloxy,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-6} alkylaminocarbonyloxy,

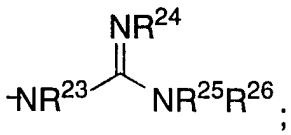
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, or
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl
wherein the alkyl or N atoms may be unsubstituted or substituted with one or more substituents selected from R^{21} and R^{22} (e.g., any amino group such as -NH- can be substituted with R^{21} to be -NR^{21}-);

R^{12} is selected from
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{0-8} alkylcarbonyloxy C_{1-4} alkyloxy,
C_{1-6} dialkylaminocarbonylmethyloxy,
aryl C_{1-6} dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and

wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

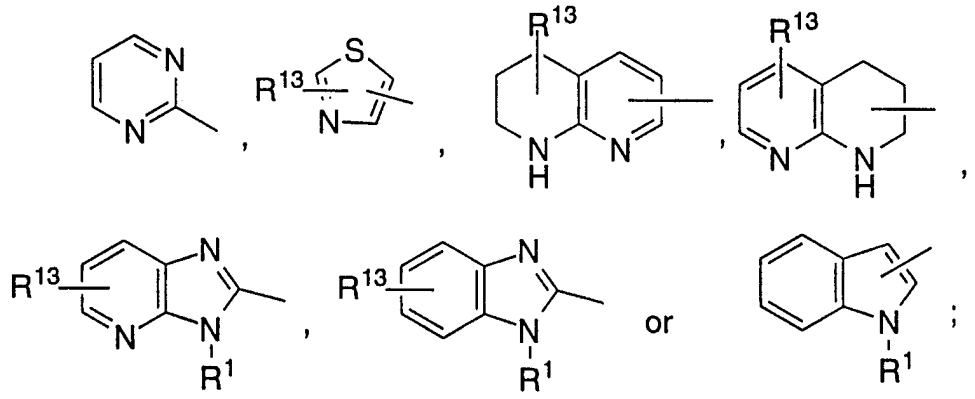
R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from
hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,


, or

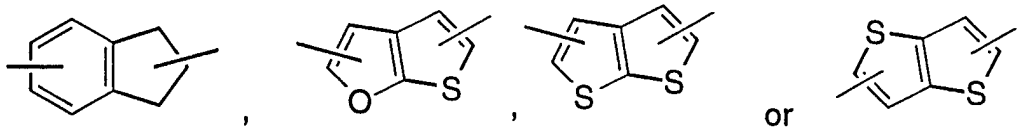

;

provided that Ring is not a 6-membered monocyclic aromatic ring;

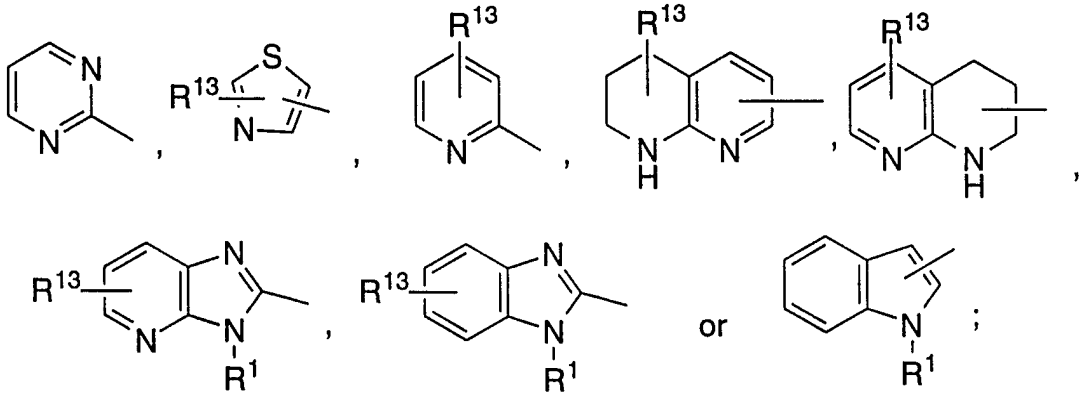
provided further that when Ring is thiophene, then X is selected from



provided further that when Ring is selected from isoxazole, isoxazoline, imidazole, imidazoline, benzofuran, benzothiophene, benzimidazole, indole, benzothiazole, benzoxazole,



then X is selected from



and the pharmaceutically acceptable salts thereof.

In one embodiment of the invention is the compound wherein Y is selected from

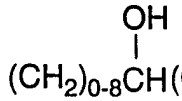
C_{0-8} alkylene,

C_{3-10} cycloalkyl,

C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,

C_{0-8} alkylene-$CONR^5$-C_{0-8} alkylene,

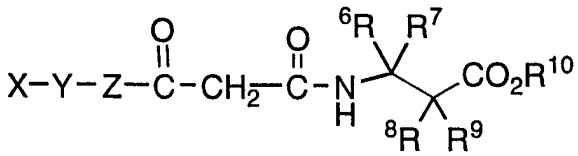
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-S(O)$_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NH-$(CH_2)_{0-6}$, or



;

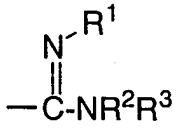
Z is $(CH_2)_m$ where m is an integer from 0 to 3; preferably, m is zero; and all other variables are as defined above;

(e) a compound of the formula I-e:

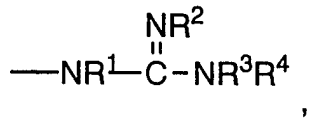


I-e

wherein X is selected from



,

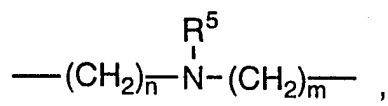


,

a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2, or

a 9- to 10-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted on a carbon atom with R^1 and R^2;

Y is selected from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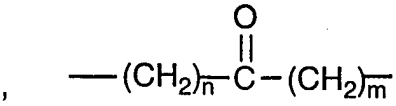
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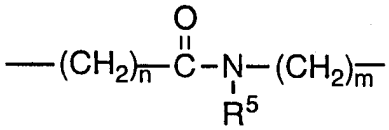
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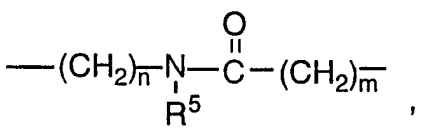
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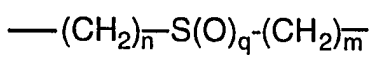

,

,

or

;

Z is absent or is a 4-11 membered aromatic or nonaromatic mono- or polycyclic ring system containing 0 to 6 double bonds, and containing 0 to 6 heteroatoms chosen from N, O and S, and wherein the ring system is either unsubstituted or substituted on a carbon or nitrogen atom with one or more groups independently selected from R^{14}, R^{15}, R^{16} and R^{17}; preferably, Z is not a 6-membered monocyclic aromatic ring system;

R^1, R^2, R^3, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{16} and R^{17} are each independently selected from

hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl,

hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy or hydroxy C_{1-6} alkyl;

R^6, R^7, R^8, R^9, R^{14} and R^{15} are each independently selected from
hydrogen,
aryl,
$-(CH_2)_p$-aryl,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
oxo,
amino,
C_{1-6} alkylamino,
amino C_{1-6} alkyl,
arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylamino-carbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylamino-carbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or

hydroxycarbonyl C_{1-5} alkyl,
$-(CH_2)_r$ C≡CH,
$-(CH_2)_r$ C≡C-C_{1-6} alkyl,
$-(CH_2)_r$ C≡C-C_{3-7} cycloalkyl,
$-(CH_2)_r$ C≡C-aryl,
$-(CH_2)_r$ C≡C-C_{1-6} alkylaryl,
$-(CH_2)_r$ CH=CH_2,
$-(CH_2)_r$ CH=CH C_{1-6} alkyl,
$-(CH_2)_r$ CH=CH-C_{3-7} cycloalkyl,
$-(CH_2)_r$ CH=CH aryl,
$-(CH_2)_r$ CH=CH C_{1-6} alkylaryl,
$-(CH_2)_r$ SO_2C_{1-6} alkyl,
$-(CH_2)_r$ SO_2C_{1-6} alkylaryl,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,
arylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino,
aryl C_{1-6} alkylamino C_{1-6} alkyl,
arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,

aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
C_{1-6} alkylsulfonyl,
C_{1-6} alkylsulfonyl C_{1-6} alkyl,
arylsulfonyl C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,

C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl, or
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,

wherein any of the alkyl groups may be unsubstituted or substituted with R^{11} and R^{12}; and provided that the carbon atom to which R^6 and R^7 are attached is itself attached to no more than one heteroatom; and provided further that the carbon atom to which R^8 and R^9 are attached is itself attached to no more than one heteroatom;

R^{10} is selected from
hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-8} alkyl,
aryl C_{1-6} alkoxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyl,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyl,
C_{1-8} alkylaminocarbonylmethylene, or
C_{1-8} dialkylaminocarbonylmethylene;

m, n and r are each independently an integer from 0 to 3;
p is an integer from 1 to 4; and
q is an integer from 0 to 2;

or a pharmaceutically acceptable salt thereof.

12. The method according to Claim 11 wherein the integrin antagonist is selected from:
4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-benzyloxycarbonylamino-β-alanine,

4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-phenylsulfonylamino-β-alanine,

2(S)-Phenylsulfonylamino-3-[4-(4-guanidobutyloxy)phenyl]-propionic acid,

2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-propionic acid,

4-(3-Guanidinopropyloxy)benzoyl-2-(S)-phenylsulfonylamino-β-alanine,

4-(3-Formamidinopropyloxy)benzoyl-2-(S)-phenylsulfonylamino-β-alanine,

3-Methoxy-4-(3-guanidinopropyloxy)benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

3-Methoxy-4-(3-aminopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

3-(3-Guanidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine,

2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid,

4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxybenzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,

4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonyl-amino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate,

2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy)phenyl]-propionic acid,

2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-butyloxy)phenyl]propionic acid,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino-β-alanine t-butyl ester,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino-β-alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenylsulfonylamino-β-alanine,

4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino-β-alanine t-butyl ester,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine t-butyl ester,

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine methyl ester,

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(1H-Imidazo[4,5-6]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine t-butyl ester,

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,

4-[2-(1,8-Naphthyidin-7-yl)ethenyl)benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butylester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β-alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β-alanine,

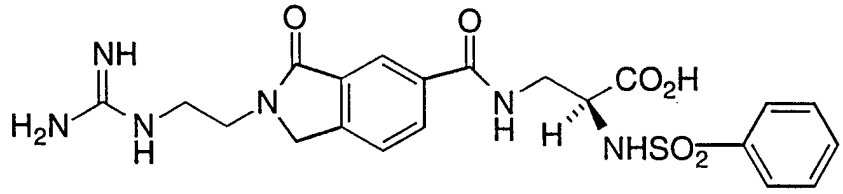
4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-β-alanine ethyl ester,

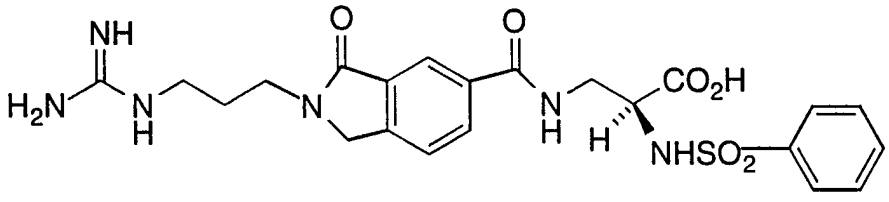
4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate,

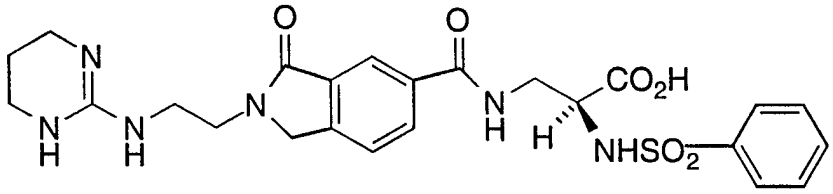
4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate,

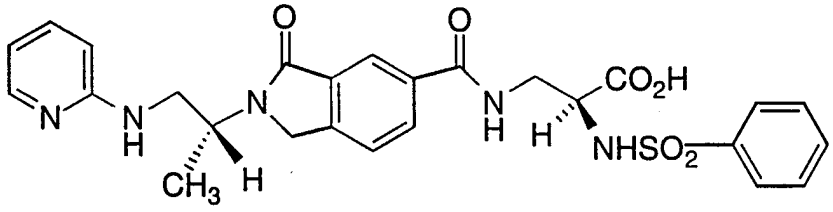
4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester, and

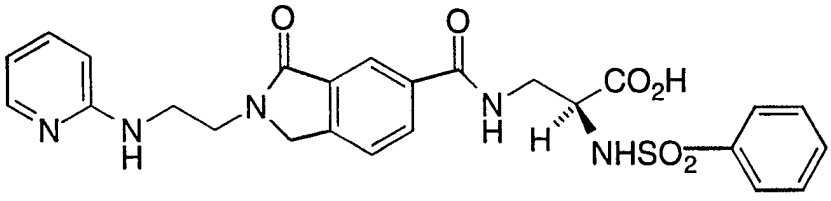
4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine.

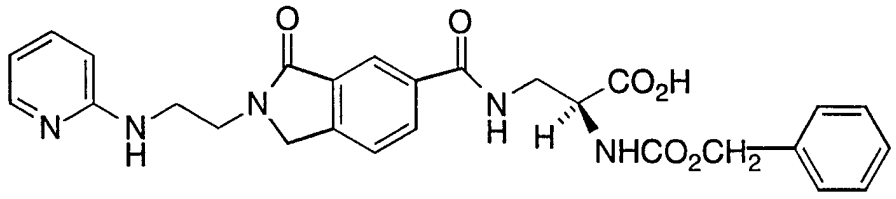


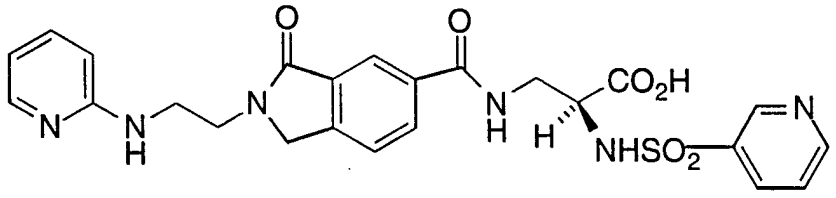












;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]piperidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]piperin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine trifluoroacetate;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine ethyl ester;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]-pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3(S)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine ethyl ester;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-alkynyl-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]-pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl)acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]-tetrahydropyrimidin-l-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl}ethyl]-tetrahydropyrimidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]imidazolidin-l-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

2-Oxo-3-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl}ethyl]-imidazolidin-1-yl-acetyl-3(S)-pyridin-3-yl-β-alanine;

Ethyl 2-oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]pyrrolidin-l-yl)acetyl-3(R)-(2-ethylindol-3-yl)-β-alanine;

2-Oxo-3(R)-[2-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)ethyl]pyrrolidin-l-yl)acetyl-3(R)-(2-ethylindol-3-yl)-β-alanine;

Ethyl 3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-pyridin-3-yl-propionic acid;

3-(S)-(2-{2-Oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]pyrrolidin-1-yl}-acetylamino)-3-(S)-pyridin-3-yl-propionic acid;

3-(S)-(2-{2-oxo-3-[(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-amino]-pyrrolidin-1-yl}-acetylamino)-3-(S)-quinolin-3-yl-propionic acid;

3-{2-[6-Oxo-1-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-hexahydro-(3aS, 6aS)pyrrolo[3,4-b]pyrrol-5-yl]-acetylamino}-3-(S)-pyridin-3-yl-propionic acid;

3-{2-[6-Oxo-1-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-ylmethyl)-hexahydro-(3aR, 6aR)pyrrolo[3,4-b]pyrrol-5-yl]-acetylamino}-3-(S)-pyridin-3-yl-propionic acid;

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine ethyl ester;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine;

6-[(1,4,5,6-Tetrahydropyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;
Ethyl 3(S)-pyridin-3-yl-3-{2-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)propylcarbamoyl]acetylamino}propionate;

3(S)-pyridin-3-yl-3-{2-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)propylcarbamoyl]acetylamino}propionic acid;

3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-ylmethyl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine ethyl ester; or

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidinyl-malonyl-3(S)-pyridin-3-yl-β-alanine;

or the pharmaceutically acceptable salts and optical isomers thereof.

13. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises amounts of at least two therapeutic agents selected from a group consisting of:

a) a farnesyl-protein transferase inhibitor and

b) an integrin antagonist;

wherein the amount of a) alone or the amount of b) alone is insufficient to achieve said therapeutic effect.

14. The pharmaceutical composition according to Claim 13 comprising amounts of two therapeutic agents which are a farnesyl-protein transferase inhibitor and a compound that is an integrin antagonist.

15. The pharmaceutical composition according to Claim 14 wherein the integrin antagonist is a selective antagonist of the $\alpha v\beta 3$ integrin.

16. The pharmaceutical composition according to Claim 14 wherein the integrin antagonist is a selective antagonist of the $\alpha v\beta 5$ integrin.

17. The pharmaceutical composition according to Claim 14 wherein the integrin antagonist is an antagonist of both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin.

18. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises amounts of three therapeutic agents which are:

a) a farnesyl-protein transferase inhibitor;

b) a selective antagonist of the $\alpha v\beta 3$ integrin; and

c) a selective antagonist of the $\alpha v\beta 5$ integrin;

wherein the amount of a) alone, the amount of b) alone or the amount of c) alone is insufficient to achieve said therapeutic effect.

19. The pharmaceutical composition according to Claim 13 wherein the therapeutic effect is treatment of cancer.

20. The pharmaceutical composition according to Claim 13 wherein the therapeutic effect is selected from inhibition of cancerous tumor growth and the regression of cancerous tumors.

21. A method of preparing a pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises mixing amounts of at least two therapeutic agents selected from a group consisting of:

a) a farnesyl-protein transferase inhibitor and

b) an integrin antagonist;

wherein the amount of a) alone or the amount of b) alone is insufficient to achieve said therapeutic effect.

22. The method of preparing a pharmaceutical composition according to Claim 21 comprising mixing an amount of a farnesyl-protein transferase inhibitor and an amount of an integrin antagonist.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06823

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/42, 43/60; A61K 31/445, 31/495

US CL :514/247,252,253,255,300,307,308,309,310,311,312,313,314

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. : 514/247,252,253,255,300,307,308,309,310,311,312,313,314

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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	Database WPIDS, London: Derwent Publications Ltd., AN 91-334169 [46], SQUIBB & SONS INC., "Assaying Farnesyl-Protein Transferase", abstract, EP 456180, 13 November 1991, see entire abstract.	1-22
A	Database WPIDS, London: Derwent Publications Ltd., AN 96-371576 [37], GEN HOSPITAL CORP., "In Vitro Identification of Integrin Function Antagonists", abstract, WO 9624063, 08 August 1996, see entire abstract.	1-22

☐ 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
"B"	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)	"&"	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	Date of mailing of the international search report
10 JUNE 1998	30 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FREDERICK KRASS Telephone No. (703) 308-2351

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