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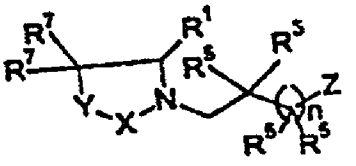
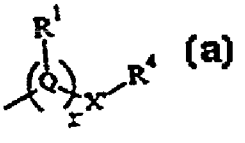
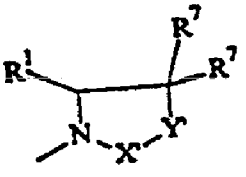
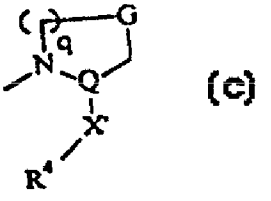
(54) **INHIBITEURS DE L'ASPARTYLE PROTEASE**
(54) **ASPARTYL PROTEASE INHIBITORS**









(57) L'invention concerne une nouvelle classe de composés de la formule (I) qui sont des inhibiteurs de l'aspartyle protéase. Dans une forme d'exécution, cette invention concerne une nouvelle classe d'inhibiteurs de l'aspartyle protéase, caractérisée par des propriétés physicochimiques et des structures qui sont spécifiques.

(57) This invention relates to a novel class of compounds of formula (I) that are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising

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Cette invention concerne également des compositions pharmaceutiques comprenant ces composés. Les composés et les compositions pharmaceutiques de cette invention sont particulièrement efficaces pour inhiber l'activité protéasique de VIH-1 et VIH-2 et, par conséquent, ils peuvent être utilisés d'une manière avantageuse comme agents anti-viraux contre les virus VIH-1 et VIH-2. Cette invention concerne également des procédés pour inhiber l'activité de l'aspartyle protéase et des méthodes pour traiter des infections virales dans lesquelles on utilise les compositions de cette invention. Dans la formule (I), Z a la formule (a), (b) ou (c), un Z quelconque pouvant être fusionné avec R^6, chaque X et X' est choisi d'une manière indépendante dans le groupe constitué par C-C(O)-, -C(O)C(O)-, -S(O)- et $S(O)_2$, et chaque Y et Y' est choisi, d'une manière indépendante, dans le groupe constitué par $-(C(R^2)_2)_p-$, NR^2, $-(C(CR^2)_2)_p$-M-, $C=C(R^2)_2$ et $-N(R^2)-CH_2-$.

these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting aspartyl protease activity and methods for treating viral infections using the compounds and compositions of this invention. A compound according to formula (I) wherein each Z is (a) or (b) or (c) wherein any Z may be optionally fused with R^6; each X and X' is independently selected from the group consisting of C-C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$; each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(CR^2)_2)_p$-M-, $C=C(R^2)_2$, and $-N(R^2)-CH_2-$.

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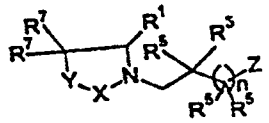
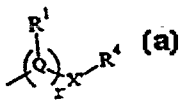
(57) Abstract

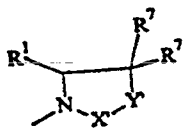
This invention relates to a novel class of compounds of formula (I) that are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting aspartyl protease activity and methods for treating viral infections using the compounds and compositions of this invention. A compound according to formula (I) wherein each Z is (a) or (b) or (c) wherein any Z may be optionally fused with R^6; each X and X' is independently selected from the group consisting of C-C(O)-, -C(O)C(O)-, -S(O)- and -S(O)$_2$; each Y and Y' is independently selected from the group consisting of -(C(R^2)$_2$)$_p$-, -NR^2-, -(C(CR^2)$_2$)$_p$-M-, C=C(R^2)$_2$, and -N(R^2)-CH$_2$-.



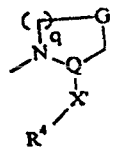
(I)



(a)



(b)



(c)

ASPARTYL PROTEASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel class of compounds which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting aspartyl protease activity, methods for treating viral infections using the compounds and compositions of this invention, and methods for making intermediates and compounds of this invention.

BACKGROUND OF THE INVENTION

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS") -- a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections -- and its precursor AIDS-related complex ("ARC") -- a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss.

As in the case of several other retroviruses, HIV encodes the production of a protease which carries out post-translational cleavage of precursor polypeptides in a process necessary for the formation of infectious virions (S. Crawford et al., "A Deletion Mutation in the 5' Part of the pol Gene of Moloney Murine Leukemia Virus Blocks Proteolytic Processing of the gag and pol Polyproteins", J. Virol., 53, p. 899 (1985)). These gene products include pol, which encodes the virion RNA-dependent DNA polymerase (reverse transcriptase), an endonuclease, HIV protease, and gag, which encodes the core-proteins of the virion (H. Toh et al., "Close Structural Resemblance Between Putative Polymerase of a Drosophila Transposable Genetic Element 17.6 and pol gene product of Moloney Murine Leukemia Virus", EMBO J., 4, p. 1267 (1985); L.H. Pearl et al., "A Structural Model for the Retroviral Proteases", Nature, pp. 329-351 (1987); M.D. Power et al., "Nucleotide Sequence of SRV-1, a Type D Simian Acquired Immune Deficiency Syndrome Retrovirus", Science, 231, p. 1567 (1986)).

A number of synthetic anti-viral agents have been designed to target various stages in the

replication cycle of HIV. These agents include compounds which block viral binding to $CD4^+$ T-lymphocytes (for example, soluble CD4), and compounds which interfere with viral replication by inhibiting viral reverse transcriptase (for example, didanosine and zidovudine (AZT)) and inhibit integration of viral DNA into cellular DNA (M.S. Hirsh and R.T. D'Aqulia, "Therapy for Human Immunodeficiency Virus Infection", N.Eng.J.Med., 328, p. 1686 (1993)). However, such agents, which are directed primarily to early stages of viral replication, do not prevent the production of infectious virions in chronically infected cells. Furthermore, administration of some of these agents in effective amounts has led to cell-toxicity and unwanted side effects, such as anemia and bone marrow suppression.

More recently, drug design efforts have been directed toward creating compounds which inhibit the formation of infectious virions by interfering with the processing of viral polyprotein precursors. Processing of these precursor proteins requires the action of virus-encoded proteases which are essential for replication (Kohl, N.E. et al. "Active HIV Protease is Required for Viral Infectivity" Proc. Natl. Acad. Sci. USA, 85, p. 4686 (1988)). The anti-viral potential of HIV protease inhibition has been demonstrated using peptidal inhibitors. Such peptidal compounds, however, are typically large and complex molecules that tend to exhibit poor bioavailability and are not generally consistent with oral administration. Accordingly, the need still exists for compounds that can effectively inhibit the action of viral proteases, for use as agents for preventing and treating chronic and acute viral infections. Such agents would be expected to act

as effective therapeutic agents in their own right. In addition, since they act at a separate stage in the virus life cycle from previously described antiretroviral agents, the administration of a combination of agents would be expected to result in increased therapeutic efficacy.

International Publication WO 94/19329 discloses cyclic carbonyls and derivatives thereof as protease inhibitors. International Publication WO 95/24385 discloses sulfonamide protease inhibitors.

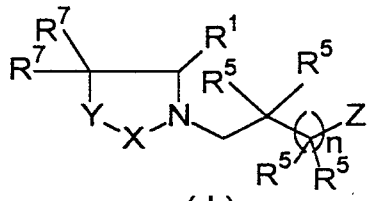
SUMMARY OF THE INVENTION

The present invention provides a novel class of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of aspartyl proteases, and in particular, HIV aspartyl protease. The compounds of this invention can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

According to a preferred embodiment, the compounds of this invention are capable of inhibiting HIV viral replication in human CD_4^+ cells including T-cells, monocytic lines including macrophages and dendrocytes and other permissive cells. These compounds are useful as therapeutic and prophylactic agents to treat or prevent infection by HIV-1 and related viruses which may result in asymptomatic infection, AIDS-related complex ("ARC"), acquired immunodeficiency syndrome ("AIDS"), or similar disease of the immune system.

It is a principal object of this invention to provide a novel class of compounds that are aspartyl

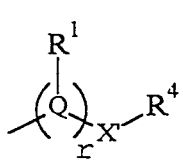
protease inhibitors, and particularly, HIV aspartyl protease inhibitors. This novel class of compounds is represented by formula I:



(I)

wherein

each Z is



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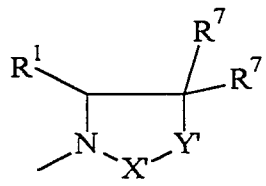
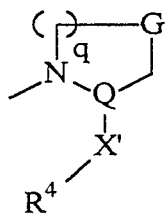


or



wherein any Z may be optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where R^1's are attached to adjacent atoms, the R^1's together with their attached adjacent atoms form a carbocyclic or heterocyclic ring system which may be optionally fused with R^6; where any member of R^1 may be optionally substituted by one or more R^2;

each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom may form a spirocarbocyclic or spiroheterocyclic ring system; where any member of R^2 may be optionally substituted by one or more R^3;

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)$-X-R^9, $N(R^9)$-X-OR^9, $N(R^9)$-X-$N(R^9)_2$, SR^9, X-R^9, O-X-$N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; X-R^9; $C(O)N(R^9)_2$; R^6; C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^4 may be optionally substituted by one or more groups independently selected from the group consisting of R^9 and R^3;

each R^5 is independently selected from the group consisting of H, OH, O and R^1;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)$-X-R^9, SR^9, -X-R^9, -O-X-$N(R^9)_2$, $-R^9$-OR^9, -CN, $-CO_2R^9$, -X-$N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, and heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl and heterocyclylalkyl wherein any aryl, carbocyclyl or heterocyclyl may be optionally fused with R^8 and wherein any member of R^8 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^8$, $-N(R^8)_2$, -CN, $-NO_2$, $-X-R^8$, $-X-N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)-XNR^8$, and halogen;

each Q is independently selected from CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, -O-, -S-, -S(O)- and $-S(O)_2-$;

each n is 1 or 2;

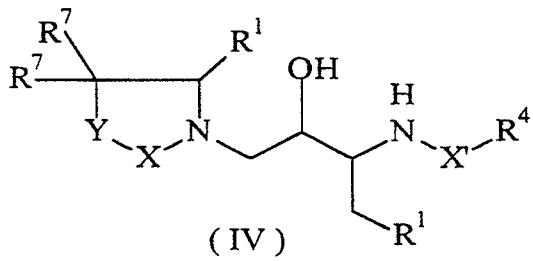
each r is 0,1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

each G is independently selected from the group consisting of -NH-, $-NR^2-$, -O-, -S-, -S(O)-, $S(O)_2$, $-C(O)-$, and $-C(R^2)_2-$.

An alternate object of this invention is a novel class of compounds represented by formula IV:



(IV)

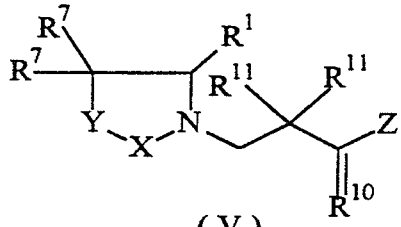
wherein:

X and X' are independently $-C(O)-$ or $-S(O)_2-$;

Y is $-(C(R^2)_2)-M-$, $-(C(R^2)_2)_p-$, $-N(R^2)-$ or $-N(R^2)-CH_2-$; and

each R^1, R^2, R^7, R^4, p and M is independently as defined for formula I.

Another object of this invention is a novel class of compounds represented by formula V:



(V)

wherein:

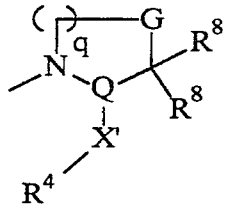
X is $-C(O)-$ or $-S(O)_2-$;

Y is $-(C(R^2)_2)-M-$, $-(C(R^2)_2)_p-$, $-N(R^2)-$ or $-N(R^2)-CH_2-$;

R^{10} is O or H_2;

each R^{11} is independently H, OH or O, wherein both R^{11} are not simultaneously hydrogen;

Z is a structure of formula VI:



(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 substituents independently selected from R^2; and

each R^1, R^2, R^7, R^4, R^8, p, q, G, M, Q and X' is independently as defined for formula I.

It is also an object of this invention to provide pharmaceutical compositions comprising the compounds of formulas I, IV and V and methods for their use as inhibitors of aspartyl protease, and particularly, HIV aspartyl protease.

It is a further object of this invention to provide methods for treating viral diseases, and in particular HIV-related diseases, using the compounds and compositions of this invention.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation	Reagent or Fragment
Ac	acetyl
Me	methyl
Et	ethyl
Bn	benzyl
Trityl	triphenylmethyl
Asn	D- or L-asparagine
Ile	D- or L-isoleucine
Phe	D- or L-phenylalanine
Val	D- or L-valine
Boc	tert-butoxycarbonyl
Cbz	benzyloxycarbonyl (carbobenzyloxy)
Fmoc	9-fluorenylmethoxycarbonyl
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
HOSu	1-hydroxysuccinimide
TFA	trifluoroacetic acid
DIEA	diisopropylethylamine
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
EtOAc	ethyl acetate
t-Bu	tert-butyl
iBu	iso-butyl
DMF	dimethylformamide
THP	tertrahydropyran
THF	tetrahydrofuran
DMSO	dimethylsulfoxide

The following terms are employed herein:

Unless expressly stated to the contrary, the terms "$-SO_2-$" and "$-S(O)_2-$" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branch-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1-10 and more preferably from 1-5 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl", alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-6 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E- and Z,Z-hexadienyl and the like.

The term "anti-viral agent" or "anti-retroviral agent" refers to a compound or drug which

possesses viral inhibitory activity. Such agents include reverse transcriptase inhibitors (including nucleoside and non-nucleoside analogs) and protease inhibitors. Preferably the protease inhibitor is an HIV protease inhibitor. Examples of nucleoside analog reverse transcriptase inhibitors include, but are not limited to, zidovudine (AZT), dideoxycytidine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89 and 524W91. Examples of non-nucleoside analog reverse transcriptase inhibitor include, but are not limited to TIBO, delavirdine (U90) and nevirapine. Examples of HIV protease inhibitors include, but are not limited to VX-478 (Vertex, also known as 141W94 (Glaxo-Wellcome) and KVX-478 (Kissei)), saquinavir (Ro 31-8959, Roche), indinavir (L-735,524, Merck)), ritonavir (ABT 538, Abbott), nelfinavir (AG 1343, Agouron), palinavir (Bila 2011 BS), U-103017 (Upjohn), XM 412 (DuPont Merck), XM 450 (DuPont Merck), BMS 186318 (Bristol-Meyers Squibb), CPG 53,437 (Ciba Geigy), CPG 61,755 (Ciba Geigy), CPG 70,726 (Ciba Geigy), ABT 378 (Abbott), GS 3333 (Gilead Sciences), GS 3403 (Gilead Sciences), GS 4023 (Gilead Sciences), GS 4035 (Gilead Sciences), GS 4145 (Gilead Sciences), GS 4234 (Gilead Sciences), and GS 4263 (Gilead Sciences).

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "carbocycle" and "carbocyclyl" radical, refers to a non-aromatic stable 3- to 8-

membered carbon ring which may be saturated, mono-unsaturated or poly-unsaturated. The carbocycle may be attached at any endocyclic carbon atom which results in a stable structure. Preferred carbocycles have 5-6 carbons.

The term "heterocycle" and "heterocyclyl" radical, unless otherwise defined herein, refers to a stable 3-7 membered monocyclic heterocyclic ring or 8-11 membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. In addition, any ring nitrogen may be optionally substituted with a substituent R^2, as defined herein for compounds of formula I. A heterocyclyl radical may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 memebered bicyclic heterocycles. Preferred heterocycles defined above include, for example, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, ß-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl,

oxoazepinyl, azepinyl, isoxazolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl and sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and tetrahydropyranofuranyl.

The term "halogen" refers to a radical of fluorine, chlorine, bromine or iodine.

The terms "HIV protease" and "HIV aspartyl protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency virus type 1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

The term "inert solvent" refers to a solvent reaction medium which allows the reagents to react together at a substantially increased rate relative to any reagent reacting with the designated solvent.

The term "leaving group" or "LG" refers to groups readily displaceable by a nucleophile, such as an amine, alcohol, phosphorous or thiol nucleophile or their respective anions. Such leaving groups are well known and include carboxylates, N-hydroxysuccinimide, N-hydroxybenzotriazole, halogen (halides), triflates, tosylates, mesylates, alkoxy, thioalkoxy, phosphinates, phosphonates and the like. Other potential nucleophiles include organometallic reagents known to those skilled in the art.

The term "protecting group" refers to a suitable chemical group which may be attached to a functional group and removed at a later stage to reveal the intact functional group. Examples of suitable protecting groups for various functional groups are

described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

The term "fused" whether preceded by the term "optionally" or not, refers to a structure wherein two distinct ring systems are joined together such that both rings share at least two common atoms. This can be envisioned as the replacement of a carbon-hydrogen or nitrogen-hydrogen bond on a ring atom with a carbon-carbon (from a second ring) or nitrogen-carbon (from a second ring) bond. For example, a cyclohexyl ring fused to a second cyclohexyl ring results in a decahydronaphthalene, a cyclohexyl ring fused to a piperidine ring results in a decahydroquinoline or decahydroisoquinoline, or a phenyl ring fused to a thiazole ring results in a benzothiazole.

The term "substituted", whether preceded by the term "optionally" or not, and substitutions contained in formulas of this invention, refer to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in a given structure may be substituted with more than one substituent selected from a specified group, the substituents may be either the same or different at every position (for example, the moiety $-N(R^2)(R^2)$). Typically, when a structure may be optionally substituted, 0-3 substitutions are preferred, and 0-1 substitutions is more preferred. Most preferred substituents are those which enhance protease inhibitory activity or intracellular antiviral activity in permissive mammalian cells or immortalized mammalian cell lines, or which enhance deliverability

by enhancing solubility characteristics or enhancing pharmacokinetic or pharmacodynamic profiles as compared to the unsubstituted compound. Other more preferred substituents include those used in the compounds shown in Tables 1-5.

The term "pharmaceutically effective amount" refers to an amount effective in treating HIV infection in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. Specifically, with respect to HIV, effective treatment using the compounds and compositions of this invention would result in an improvement in an HIV associated ascertainable measurement. The term "prophylactically effective amount" refers to an amount effective in preventing HIV infection in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiretroviral agent.

As used herein, the compounds of this invention, including the compounds of formula I are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this

invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-$(C_{1-4}$ alkyl$)_4^+$ salts.

The term "thiocarbamates" refers to compounds containing the functional group N-SO_2-O.

The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as

racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

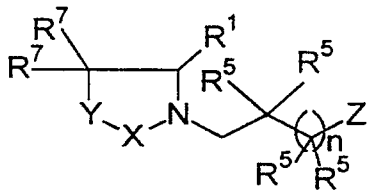
Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

The compounds of the present invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,

methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

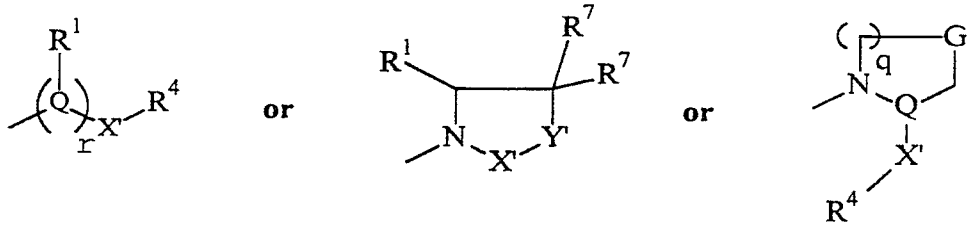
The compounds of this invention are those of formula I:



(I)

wherein

each Z is



wherein any Z may be optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where R^1's are attached to adjacent atoms, the R^1's together with their attached adjacent atoms form a carbocyclic or heterocyclic ring system which may be optionally fused with R^6; where any member of R^1 may be optionally substituted by one or more R^2;

each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom may form a spirocarbocyclic or spiroheterocyclic ring system; where any member of R^2 may be optionally substituted by one or more R^3;

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)$-X-R^9, $N(R^9)$-X-OR^9, $N(R^9)$-X-$N(R^9)_2$, SR^9, X-R^9, O-X-$N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; X-R^9; $C(O)N(R^9)_2$; R^6; C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^4 may be optionally substituted by one or more groups independently selected from the group consisting of R^9 and R^3;

each R^5 is independently selected from the group consisting of H, OH, O and R^1;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)$-X-R^9, SR^9, -X-R^9, -O-X-$N(R^9)_2$, $-R^9$-OR^9, -CN, $-CO_2R^9$, -X-$N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, and heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl and heterocyclylalkyl wherein any aryl, carbocyclyl or heterocyclyl may be optionally fused with R^8 and wherein any member of R^8 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^8$, $-N(R^8)_2$, -CN, $-NO_2$, -X-R^8, -X-$N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)$-XNR^8, and halogen;

each Q is independently selected from CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, -O-, -S-, -S(O)- and $-S(O)_2-$;

each n is 1 or 2;

each r is 0,1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

each G is independently selected from the group consisting of -NH-, $-NR^2-$, -O-, -S-, -S(O)-, $S(O)_2$, -C(O)-, and $-C(R^2)_2-$.

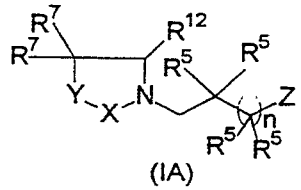
Except where expressly noted to the contrary, the term "[variable] as defined for formula I" refers to the definitions shown directly above. In addition, where no reference is made to a particular definition for a given variable, the definition is to be taken as that defined for formula I shown directly above.

Preferred compounds of formula I are those wherein

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, and $-N(R^2)-CH_2-$; and

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, SR^9, $X-R^9$, $O-X-N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6.

Alternate preferred compounds of formula I are those having the structure of formula IA:



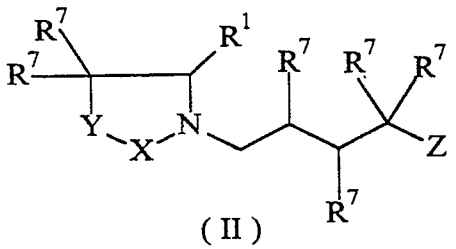
(IA)

wherein

each R^{12} is independently selected from the group consisting of R^6; C_1-C_6 alkyl optionally substituted

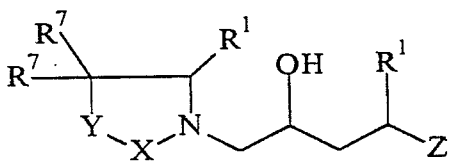
with R^6; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^{12} may be optionally substituted by one or more R^2.

Preferred compounds of formula I are those wherein n is equal to 1; those having the structure of formula II:



(II)

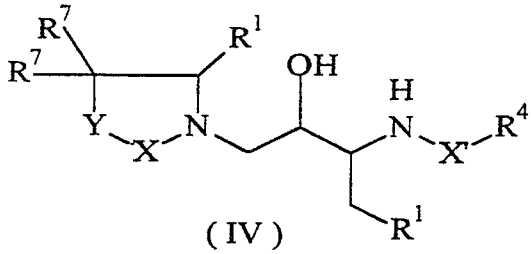
and those having the structure of formula III:



(III)

Also preferred are compounds according to formula I wherein X is $-C(O)-$ or $-S(O)_2-$ and Y is $-(C(R^2)_2)_p-M-$; those wherein X is $-C(O)-$ or $-S(O)_2-$ and Y is $(-C(R^2)_2-)_p$; those wherein X is $-C(O)-$, $-C(O)C(O)-$ or $-S(O)_2-$; and Y is $-N(R^2)-$ or $-N(R^2)-CH_2-$.

An alternate object of this invention is a novel class of compounds represented by formula IV:



(IV)

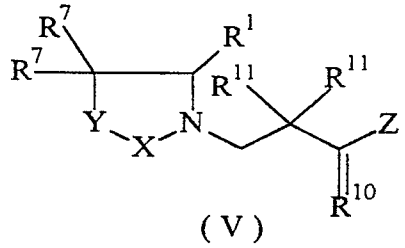
wherein:

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-; and

each R^1, R^2, R^7, R^4, p and M is independently as defined for formula I.

Another object of this invention is a novel class of compounds represented by formula V:



(V)

wherein:

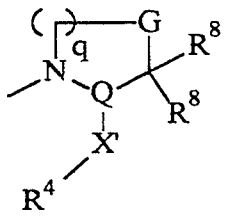
X is -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-;

R^{10} is O or H$_2$;

each R^{11} is independently H, OH or O, wherein both R^{11} are not simultaneously hydrogen;

Z is a structure of formula VI:



(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 substituents independently selected from R^2 (where in formula V, if R^{10} is H_2, a methylene is implied); and each R^1, R^2, R^7, R^4, R^8, p, q, G, M, Q and X' is independently as defined for formula I.

Also preferred are those compounds having the structure of formula V, wherein

R^{10} and R^{11} are O;

compounds having the structure of formula V, wherein

R^{10} and R^{11} are O;

q is 1;

G is S; and

X' is -C(O)-;

compounds having the structure of formula V, wherein

R^{10} and R^{11} are O;

q is 1;

G is S;

X' is -C(O)-; and

R^4 is t-butylamino;

compounds having the structure of formula V, wherein

R^{10} and R^{11} are O;

X is -C(O)-;

Y is $-(C(R^2)_2)_p-$; and

R^7 is H;

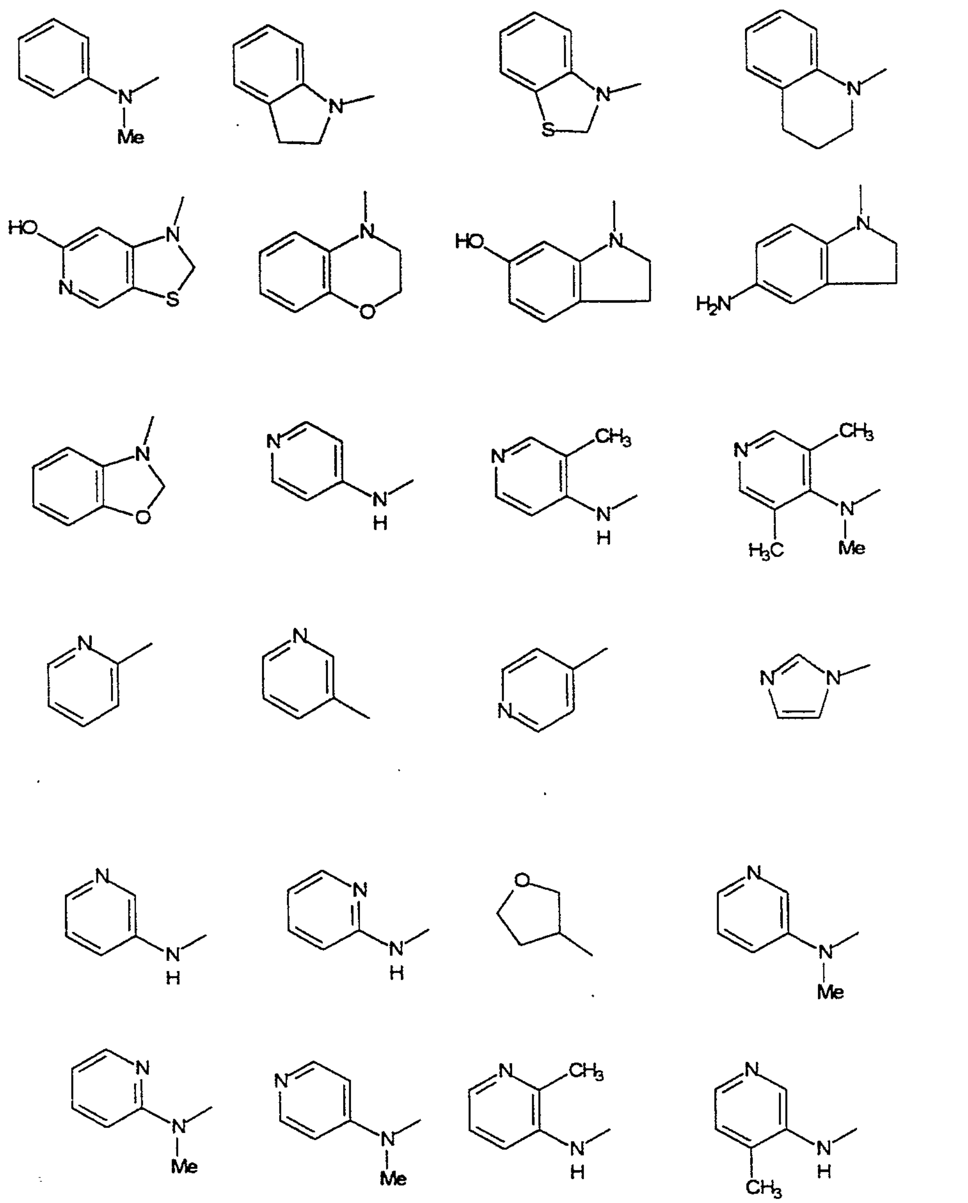
compounds having the structure of formula V wherein

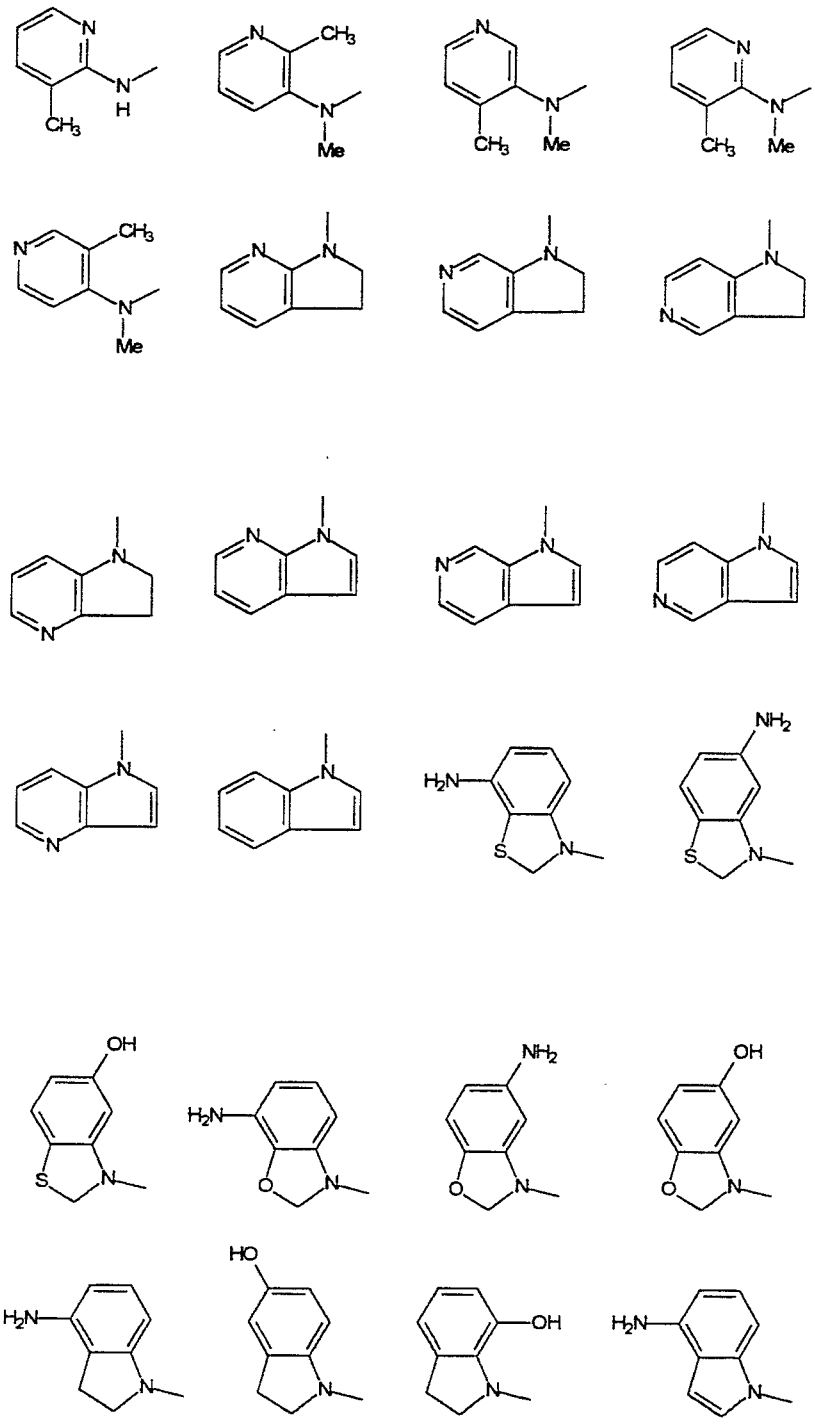
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH;

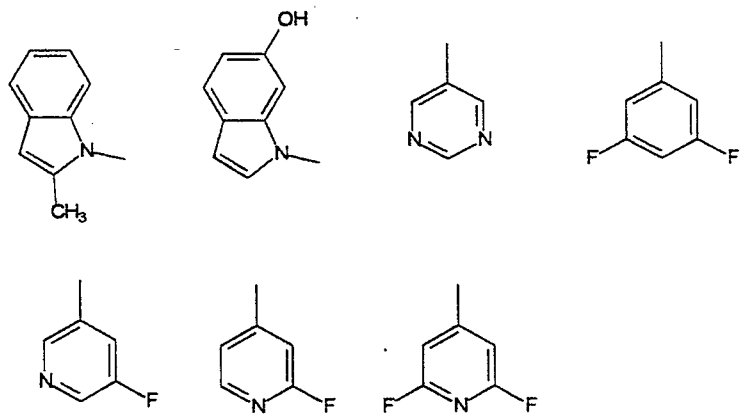
Also preferred are those compounds of formula V wherein
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2;
one R^{11} is H and one R^{11} is OH; and
R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3;
those compounds of formula V wherein
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2;
one R^{11} is H and one R^{11} is OH; and
R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;
those compounds of formula V wherein
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2;

one R^{11} is H and one R^{11} is OH; and

R^2 within the definition of Y is selected from the group consisting of:







those compounds according to formula V wherein:

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2;

one R^{11} is H and one R^{11} is OH; and

at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula V wherein:

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2;

one R^{11} is H and one R^{11} is OH; and

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula V wherein:

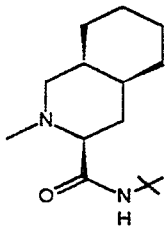
X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;
R^{10} is H_2;
one R^{11} is H and one R^{11} is OH;
at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3; and
at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

those compounds according to formula V wherein:
X and X' is $-C(O)-$;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2;
one R^{11} is H and one R^{11} is OH;
at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3; and
R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

Also preferred are those compounds according to any of the aforementioned preferred compounds of formula V wherein:
R^1 is benzyl; and Z is



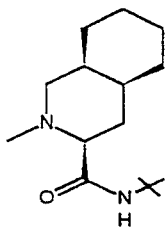
those compounds according to any of the aforementioned preferred compounds of formula V wherein:

R^1 is benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula V wherein:

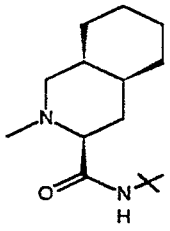
R^1 is benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$; and

Z is

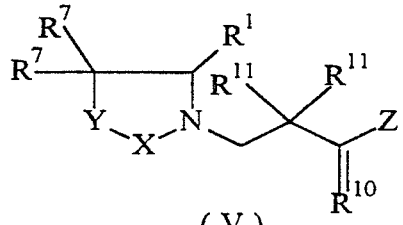


those compounds according to any of the aforementioned preferred compounds of formula V wherein R^1 is benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2;

those compounds according to any of the aforementioned preferred compounds of formula V wherein R^1 is benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2 and wherein Z is



An alternate embodiment of this invention is compounds according to formula V, wherein:



(V)

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and

each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined for formula I; and

those compounds according to formula V, wherein:

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy;

R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3; and

each X, X', Y, Y', Z, R^1, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined for formula I.

those compounds of formula V wherein

X and X' is $-C(O)-$;

Y is $-N(R^2)-$;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH; and

those compounds of formula V wherein

X and X' is $-C(O)-$;

Y is $-(C(R^2)_2)-M-$;

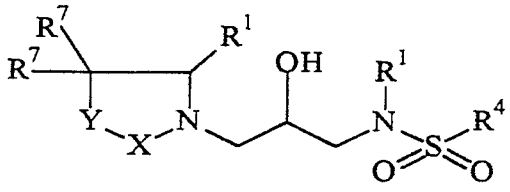
M is O;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH.

Also preferred is the compound of formula I having the structure of formula IX:



(IX)

wherein

X is -C(O)- or -S(O)$_2$-; and the compounds of formula IX wherein

X is -C(O)-;

Y is -(C(R^2)$_2$)-M-; and

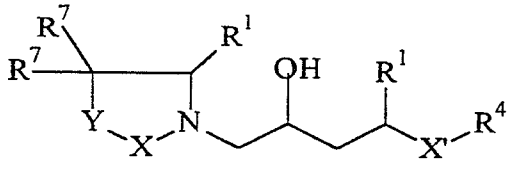
R^7 is H; and those compounds of formula IX wherein

X is -C(O)-;

Y is -N(R^2)-; and

R^7 is H; and those compounds of formula IX wherein X is -C(O)-; Y is -(C(R^2)$_2$)-; and R^7 is H.

Also preferred are those compounds of formula I having the structure of formula XII:



(XII)

wherein

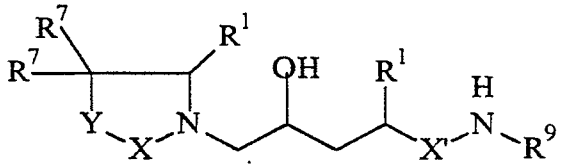
X and X' are independently -C(O)- or -S(O)$_2$-; those compounds of formula I having the structure of formula XII, wherein

X and X' are independently -C(O)- or -S(O)$_2$-; and

R^4 is 1-amino-2-hydroxyindanyl; and

compounds of formula I having the structure of formula XII, wherein R^4 is 1(S)-amino-2(R)-hydroxyindanyl.

Also preferred are the compounds according to formula I, having the structure of formula XIII:



(XIII)

wherein

X and X' are independently -C(O)- or $-S(O)_2-$;

compounds according formula I having the structure of formula XIII, wherein

X is -C(O)- or $-S(O)_2-$;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$ or $-N(R^2)-$; and

R^7 is H;

compounds of formula I having the structure of formula XIII, wherein

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$; and

R^7 is H;

those compounds of formula XIII wherein

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^2 within the definition of Y is selected from hydrogen, R^3, or C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with 1-3 groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula XIII wherein:

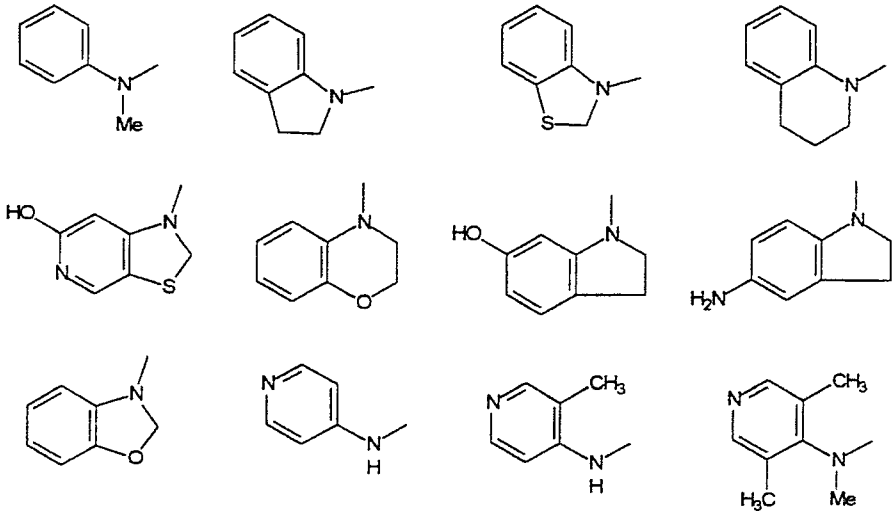
X is -C(O)-;

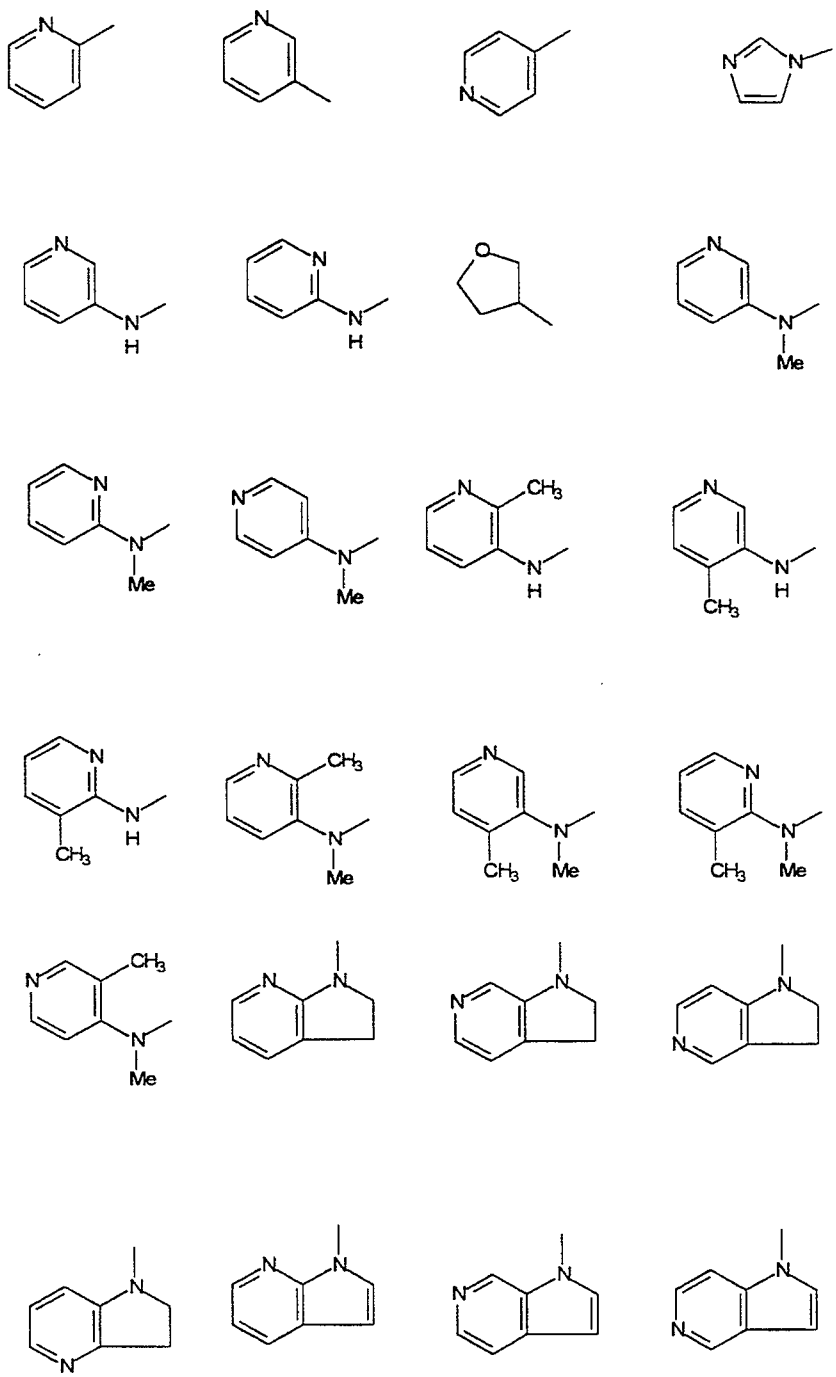
X' is -C(O)-;

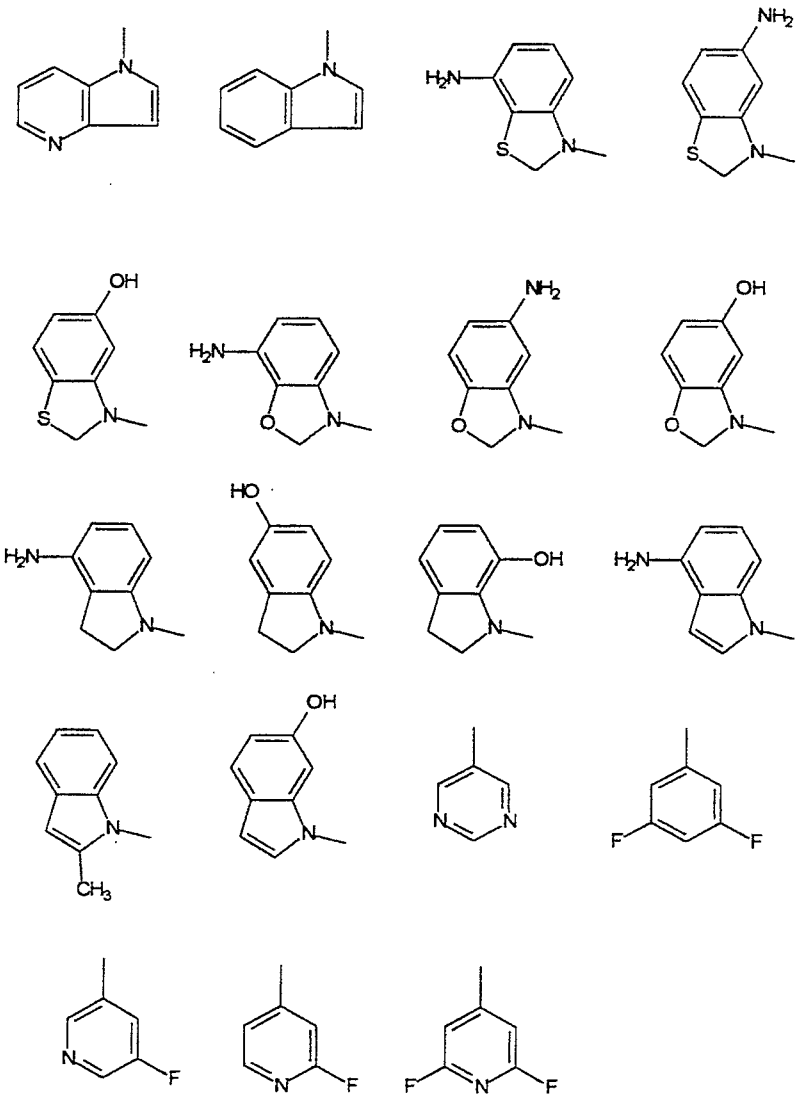
Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is selected from the group consisting of:







those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula XIII wherein:

X is $-C(O)-$;

X' is $-C(O)-$;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula XIII wherein:

X is $-C(O)-$;

X' is $-C(O)-$;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$;

those compounds according to formula XIII wherein:

X is $-C(O)-$;

X' is $-C(O)-$;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$,

$-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is benzyl; and

each R^9 not within the definition of Y is 2-hydroxyindanyl.

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$; and

each R^9 not within the definition of Y is 2-hydroxyindanyl;

those compounds according to any of the aforementioned preferred compounds wherein:

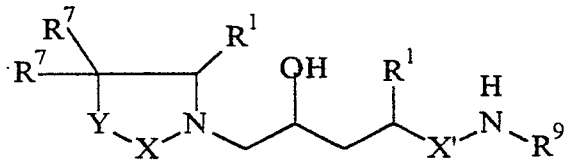
each R1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2; and

those compounds according to any of the aforementioned preferred compounds wherein:

each R1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2;

each R^9 not within the definition of Y is 2-hydroxyindanyl.

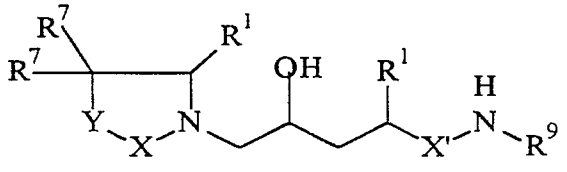
Another embodiment is compounds according to formula XIII, wherein:



(XIII)

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and
each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined for formula XIII.

Another embodiment is compounds according to formula XIII, wherein:



(XIII)

wherein R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and

each X, X', Y, Y', Z, R^1, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined for formula XIII.

Another embodiment is compounds of formula I having the structure of formula XIII, wherein

X is $-C(O)-$;

X' is $-C(O)-$;

Y is $-N(R^2)-$; and

R^7 is H;

compounds of formula I having the structure of formula XIII, wherein

X is $-SO_2-$;

X' is $-C(O)-$;

Y is $-(C(R^2)_2)-$; and

R^7 is H; and

compounds of formula I having the structure of formula XIII, wherein

X is $-SO_2-$;

X' is $-C(O)-$;

Y is $-N(R^2)-$; and

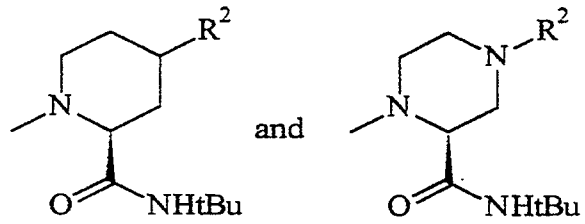
R^7 is H.

In an alternate embodiment, preferred compounds are those of formula V wherein

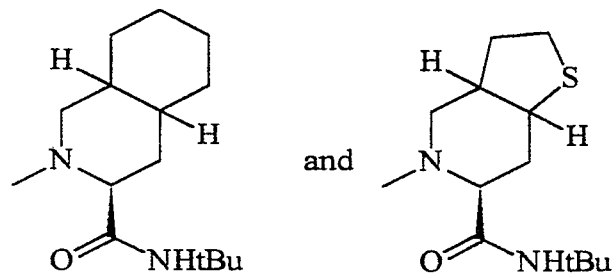
R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH; and

Z is selected from the group consisting of:



and R^2 is as defined in formula I; and those of formula V wherein Z is selected from the group consisting of



R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH.

Also preferred are those compounds of formula V wherein X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH; and

those compounds of formula V wherein

X and X' is -C(O)-;

Y is $-N(R^2)-$;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH, and those compounds of formula V, wherein

X and X' is -C(O)-;

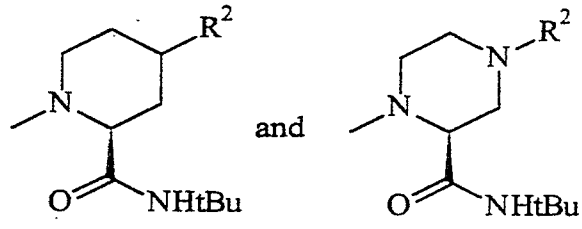
Y is $-(C(R^2)_2)-M-$;

M is O;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH, and the aforementioned compounds of formula V wherein Z is selected from the group consisting of:



and R^2 is as defined in claim 1.

Also preferred are those compounds of formula V wherein X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH; and those compounds of formula V wherein

X and X' is -C(O)-;

Y is $-N(R^2)-$;

R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH, and those compounds of formula V, wherein

X and X' is -C(O)-;

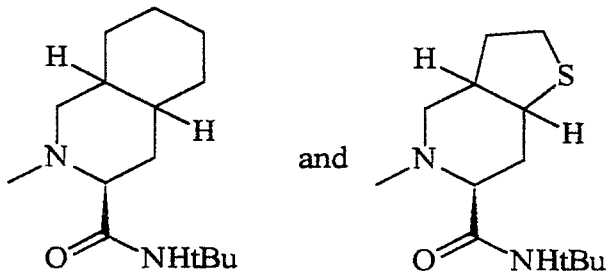
Y is $-(C(R^2)_2)-M-$;

M is O;

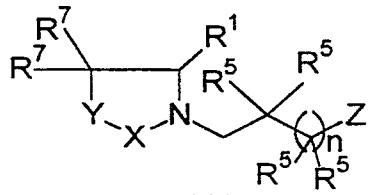
R^7 is H;

R^{10} is H_2; and

one R^{11} is H and one R^{11} is OH, and the aforementioned compounds of formula V wherein Z is selected from the group consisting of:

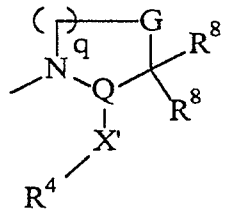


Also preferred are compounds of formula I wherein:



(I)

Z is selected from the group consisting of $-X'R^4$, $-N(R^1)-X'-R^4$, $-N(R^1)-N(R^1)-X'-R^4$, and formula VI;

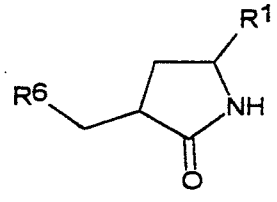


(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 members independently selected from R^2; and

each X, X', Y, Y' R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined in for formula I.

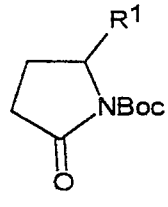
Another embodiment of this invention relates to the process for preparing a compound of formula XIV:



XIV

wherein R^1 and R^6 are defined as in formula I, comprising the steps of:

(1) reacting a compound of formula XV:

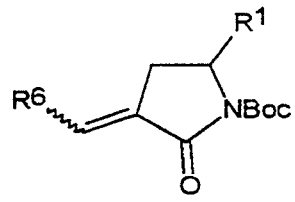


XV

wherein R^1 is defined as in formula I,
in an inert solvent, preferably an ethereal solvent such as diethyl ether or THF, with a base, preferably an alkali metal amide such as lithiumdiisopropylamide at a temperature between about -78 °C to about 25 °C;

(2) reacting the product of step (1) with an aldehyde R^6CHO followed by an optional treatment with a dehyrating agent, preferably Martin's sulfurane

dehydrating agent, wherein R^6 is defined as in formula I to give a compound of formula XVI:

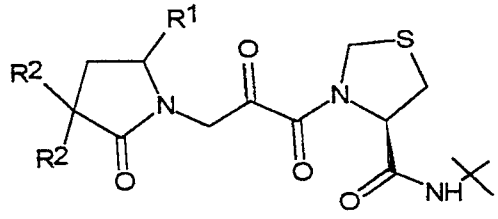


XVI

wherein R^1 and R^6 are defined as in formula I;

(3) reacting the product of step (2) in an inert solvent, preferably methanol, with hydrogen gas in the presence of an hydrogenation catalyst, preferably 10% palladium on carbon, followed by treatment with an anhydrous acid, preferably trifluoroacetic acid or 4N HCl in dioxane to give a product of formula XIV.

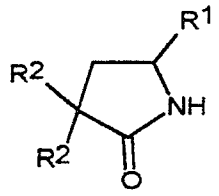
Another embodiment of this invention relates to the process for preparing a compound of formula XVII:



XVII

wherein R^1 and R^2 are defined as in formula I, comprising the steps of:

(1) reacting a compound of formula XVIII:



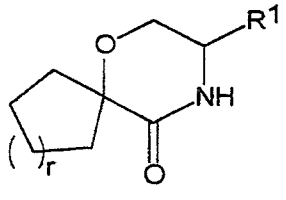
XVIII

wherein R^1 and R^2 are as defined in formula I, in an inert solvent, preferably DMF or THF, with a base preferably sodium hydride, then bromomethylacrylic acid at a temperature between about -78 °C to about 25 °C;

(2) reacting the product of step (1) with an oxidizing agent, preferably ozone and if necessary a reductive work-up with a reducing agent such as dimethylsulfide;

(3) reacting the product of step (2) in an inert solvent, such as DMF, with thioproline t-butylamide and suitable amide-bond coupling reagents, preferably EDC, HOBT and N-methylmorpholine, to give a product of formula XVII.

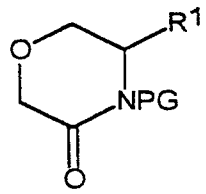
Another embodiment of this invention relates to the process for preparing a compound of formula XIX:



XIX

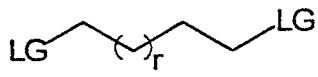
wherein R^1 and r are defined as in formula I, comprising the steps of:

(1) reacting a compound of formula XX



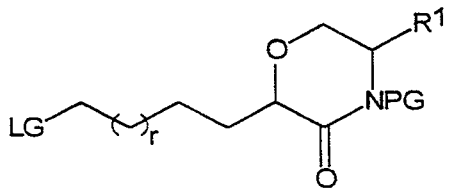
XX

wherein R^1 is defined as in formula I and PG is a N-protecting group, such as those described in Greene and Wuts (infra), preferably p-methoxybenzyl, an inert solvent, preferably THF, with a base, preferably lithiumdiisopropylamide at between about -78 °C to about 25 °C, then a bis-leaving group alkane of formula XXI:



XXI

wherein LG is selected from halo, preferably chloro or iodo, arylsulfonate esters, preferably tosyl, and alkylsulfonate esters, preferably mesyl, and r is defined as in formula I, to give a product of formula XXII:

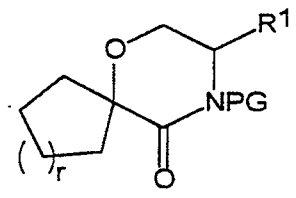


XXII

wherein R^1 and PG are defined as in formula XX and LG and r are defined as in formula XXI;

(2) reacting the product of step (1) in an inert solvent, preferably THF, with a base, preferably

lithiumdiisopropylamide, at between about -78 °C to about 25 °C to give a product of formula XXIII:

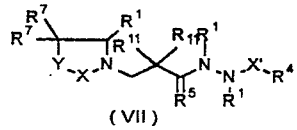


XXIII

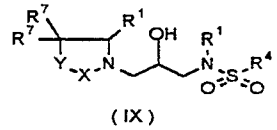
wherein R^1 is defined as in formula I and PG is a N-protecting group;

(3) reacting the product of step (2) in an inert solvent with a reagent suitable for removal of the N-protecting group PG, such as those described in Greene and Wuts (infra), to give a compound of formula XIX.

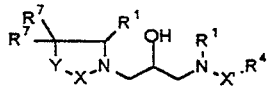
In another embodiment, compounds of formula I with structures VII, VIII, IX, and X are preferred:



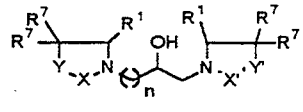
(VII)



(IX)



(VIII)



(X)

where all definitions of variables for formula I apply.

Preferred R^2 groups for formula I include: C_1-C_6 alkyl and alkenyl optionally substituted with R^6; where two R^2 taken together form a spriocyclic ring and C_3-C_6 cycloalkyl or cycloalkenyl optionally fused with R^6.

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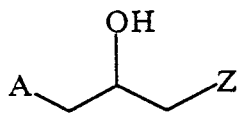
SIEBERTSTR. 4
31675 MÜNCHEN
19. Feb. 1998

Preferred compounds of this invention of formula I include the specific compounds contained in Tables 1-5.

TABLE 1



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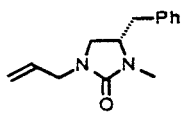
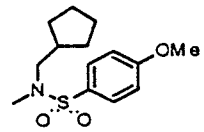
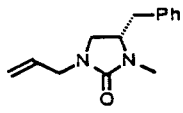
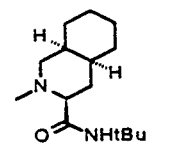
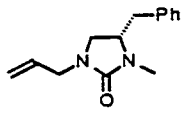
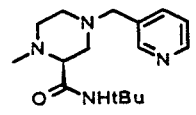
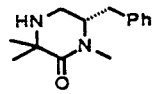
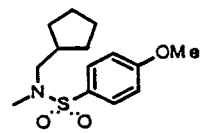
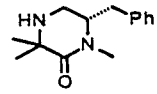
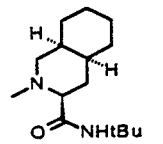
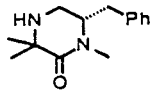
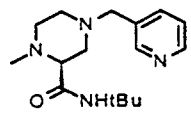
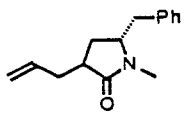
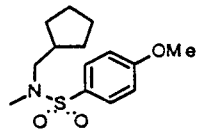
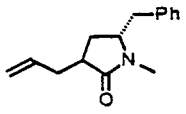
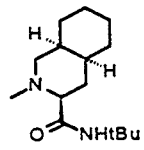
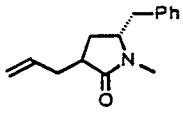
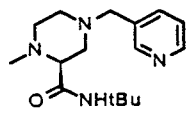
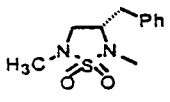
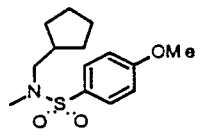
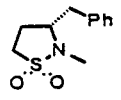
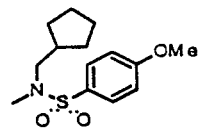
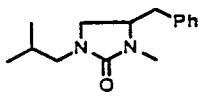
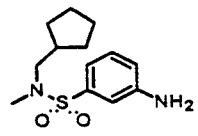
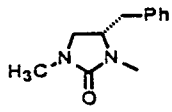
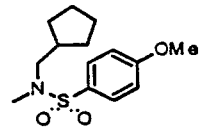
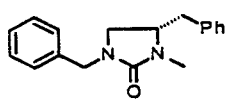
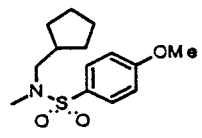
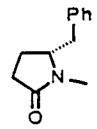
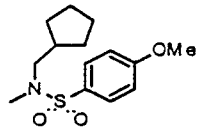
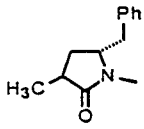
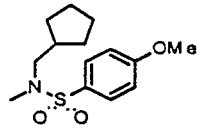
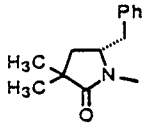
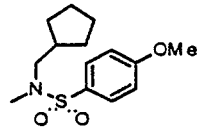
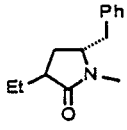
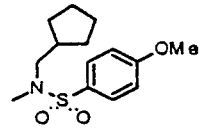
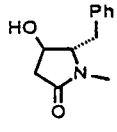
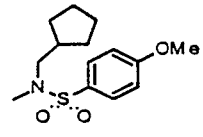
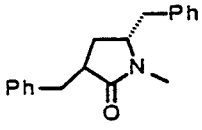
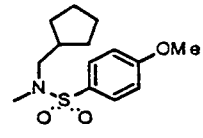
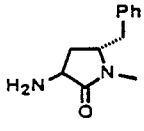
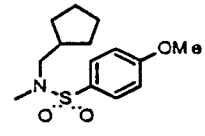
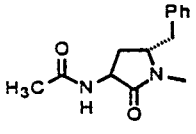
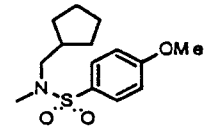
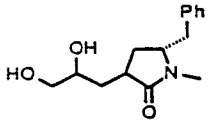
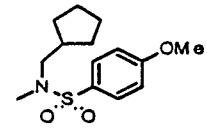
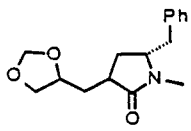
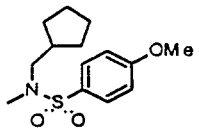
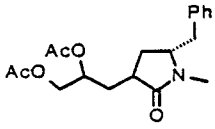
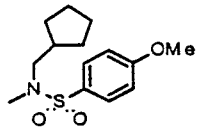
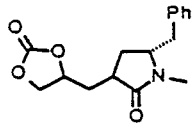
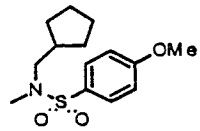
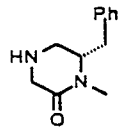
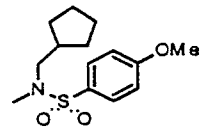
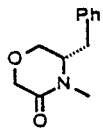
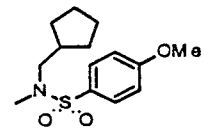
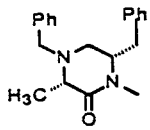
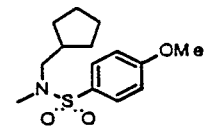
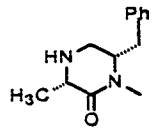
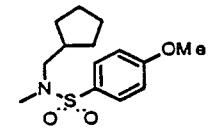
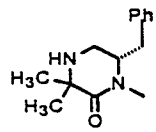
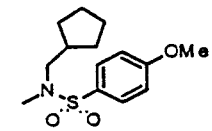
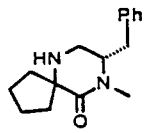
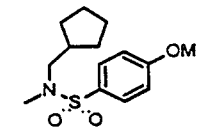
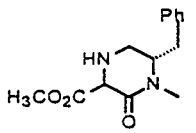
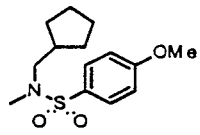
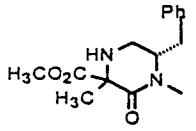
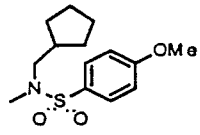
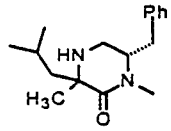
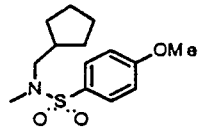
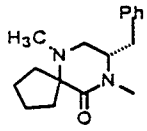
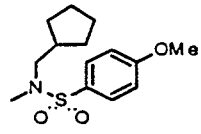
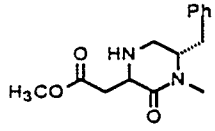
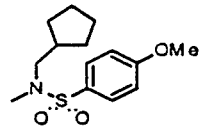
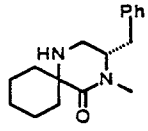
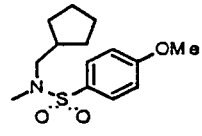
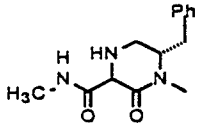
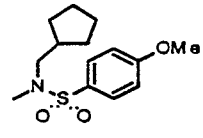
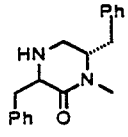
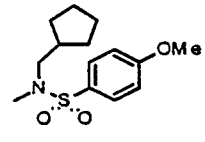
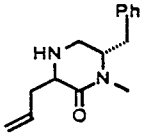
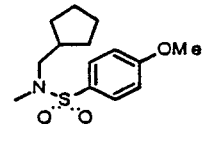
1		
2		
3		
4		
5		

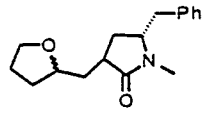
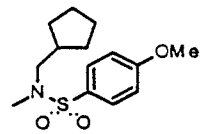
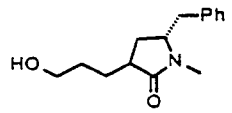
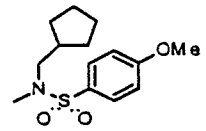
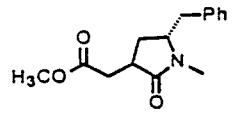
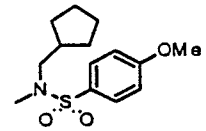
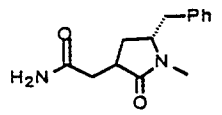
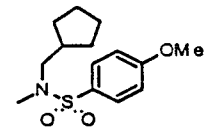
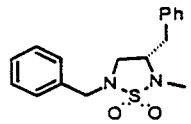
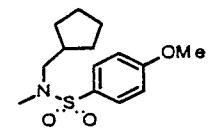
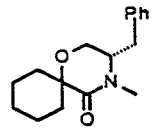
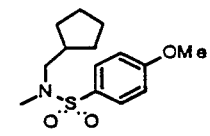
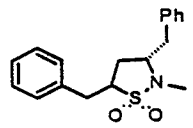
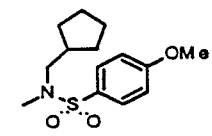
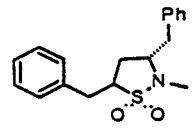
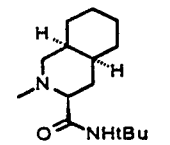
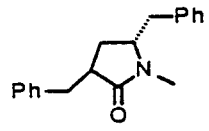
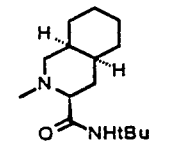
6		
7		
8		
9		
10		
11		
12		
13		
14		

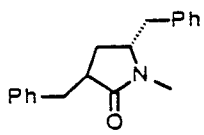
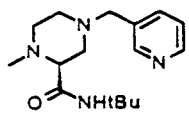
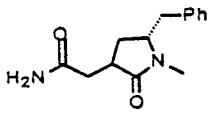
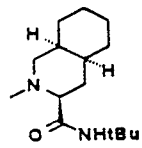
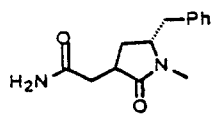
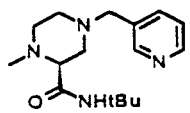
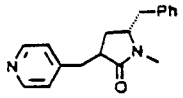
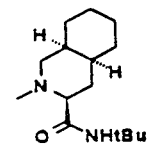
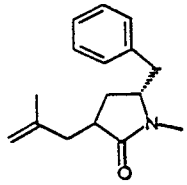
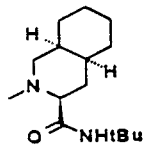
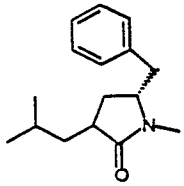
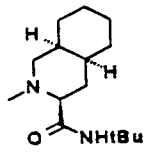
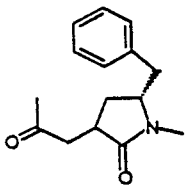
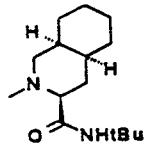
15		
16		
17		
18		
19		
20		
21		
22		
23		

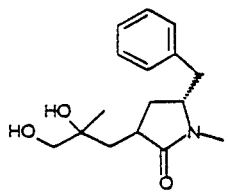
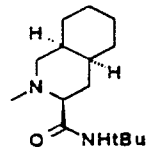
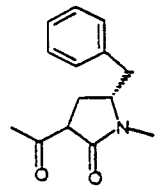
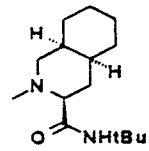
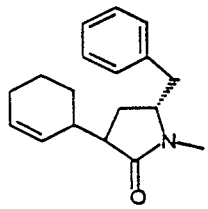
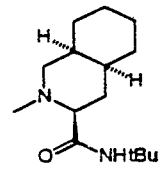
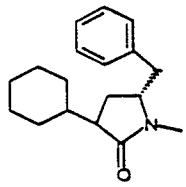
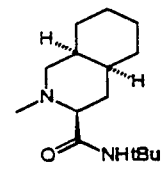
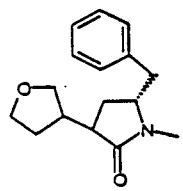
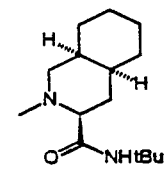
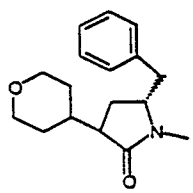
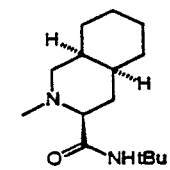
24		
25		
26		
27		
28		
29		
30		
31		
32		

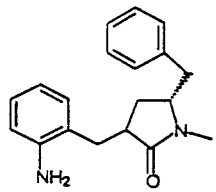
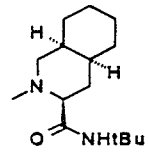
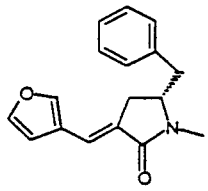
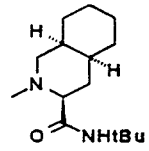
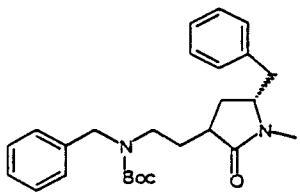
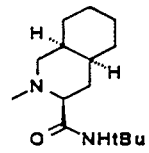
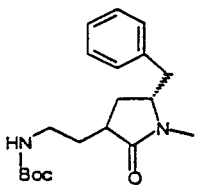
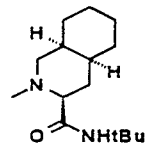
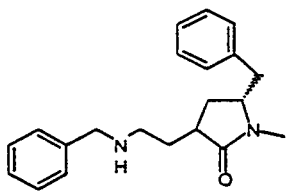
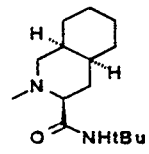
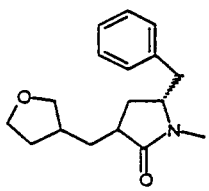
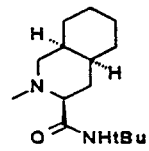
AMENDED SHEET

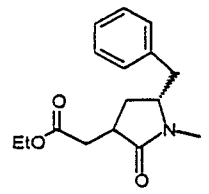
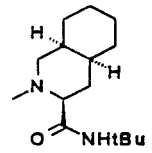
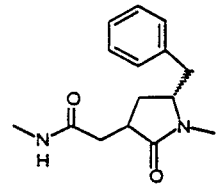
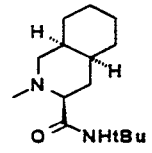
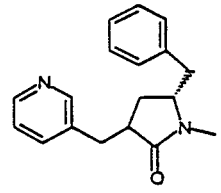
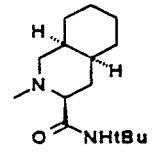
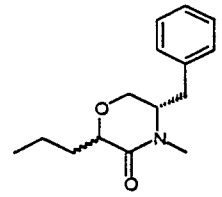
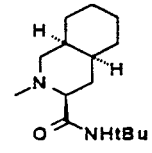
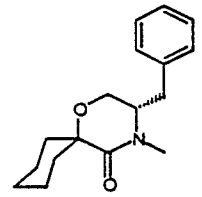
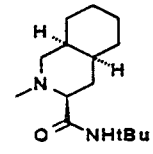
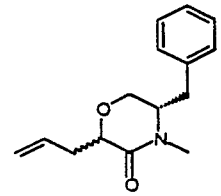
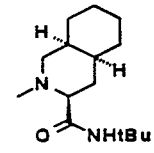
33		
34		
35		
36		
37		
38		
39		
40		
41		

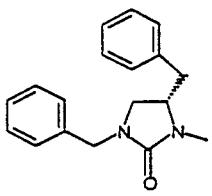
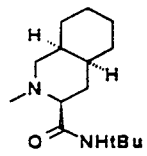
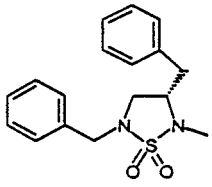
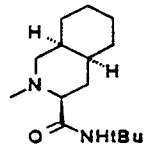
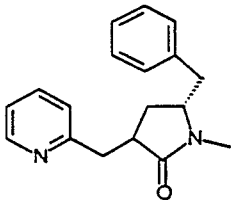
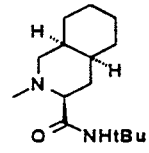
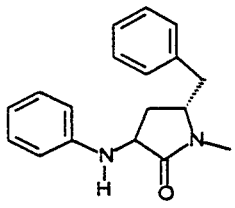
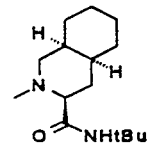
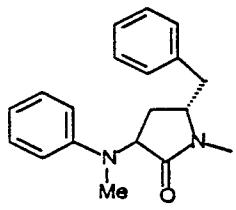
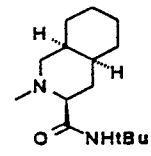
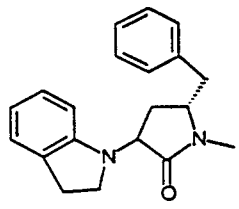
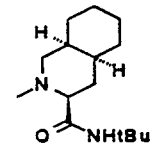
42		
43		
44		
45		
46		
47		
48		
49		
50		

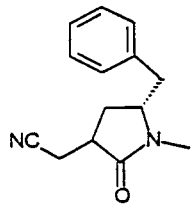
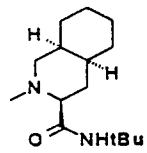
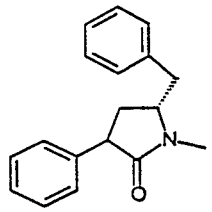
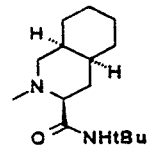
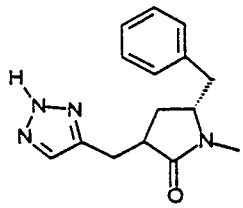
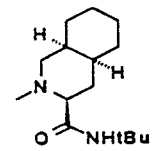
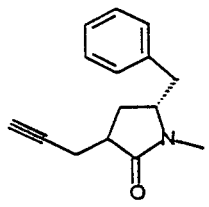
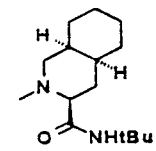
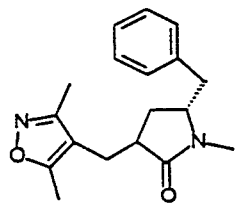
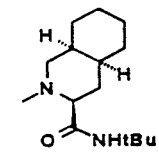
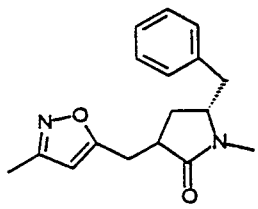
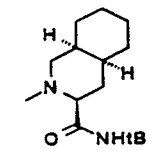
51		
52		
53		
54		
55		
56		
57		

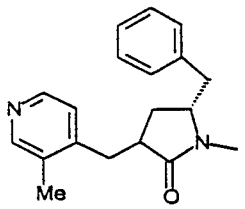
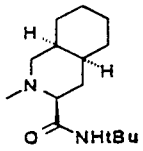
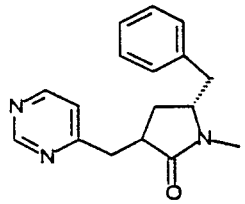
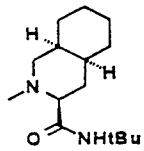
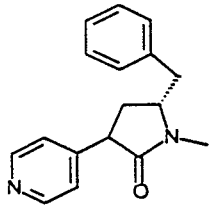
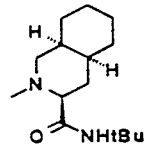
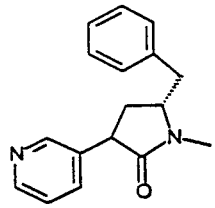
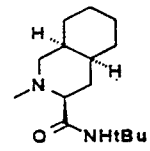
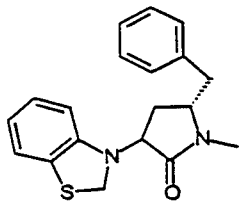
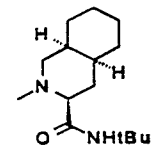
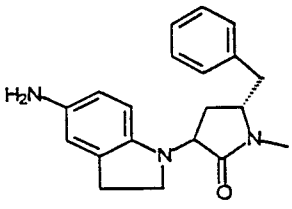
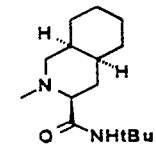
58		
59		
60		
61		
62		
63		

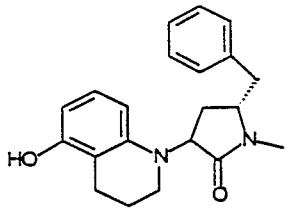
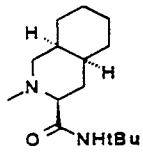
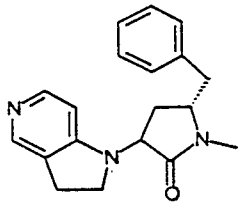
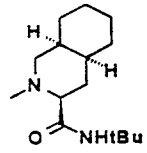
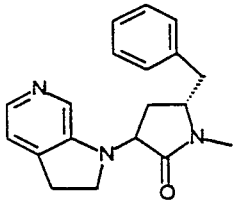
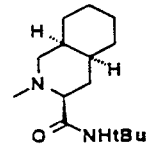
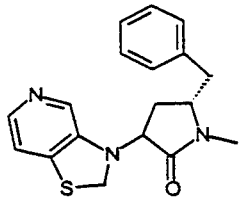
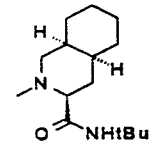
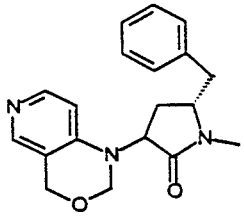
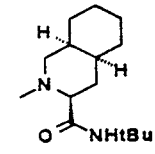
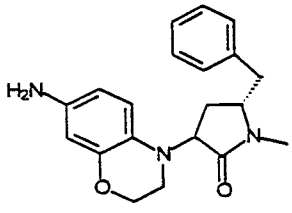
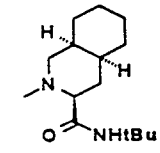
64		
65		
66		
67		
68		
69		

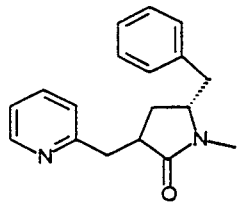
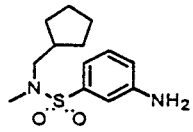
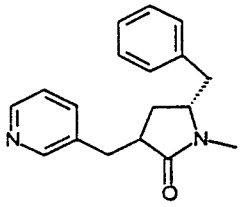
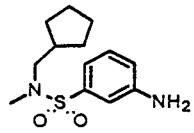
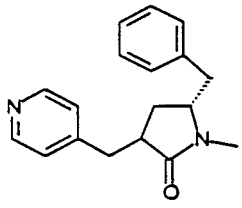
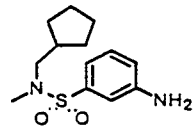
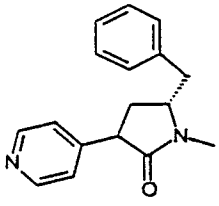
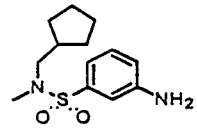
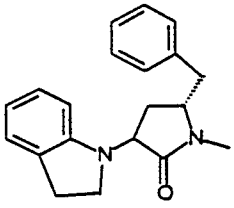
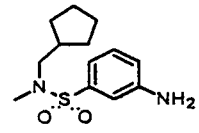
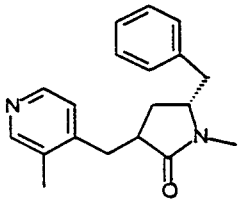
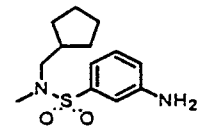
70		
71		
72		
73		
74		
75		

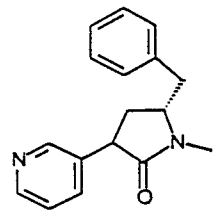
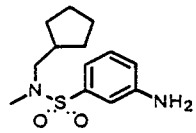
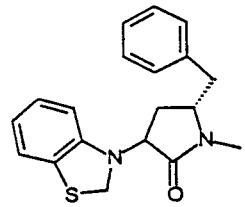
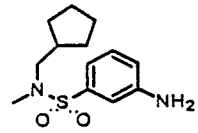
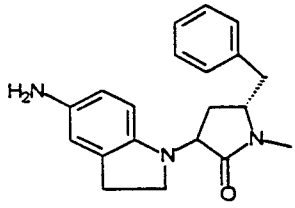
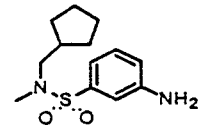
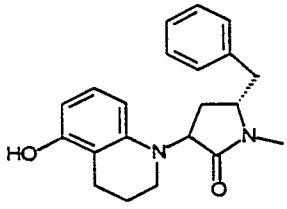
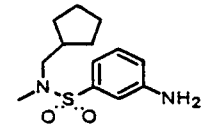
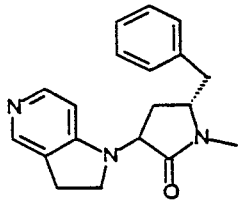
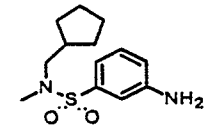
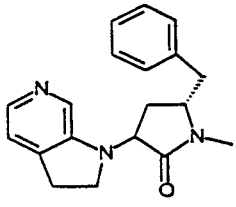
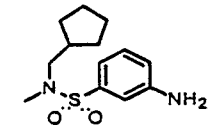
76		
77		
123		
124		
125		
126		

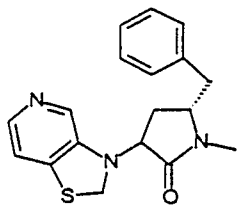
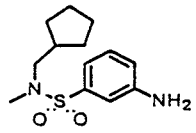
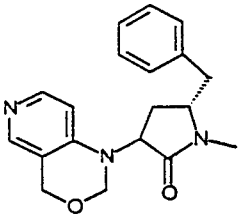
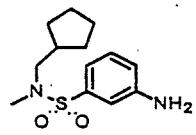
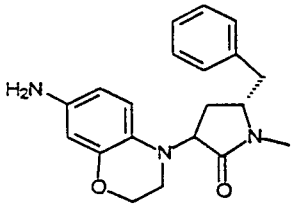
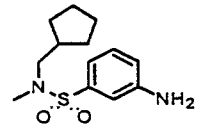
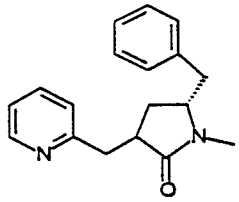
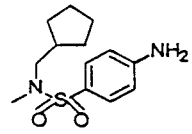
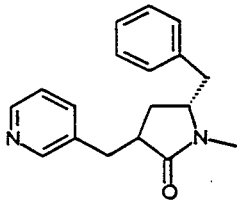
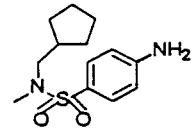
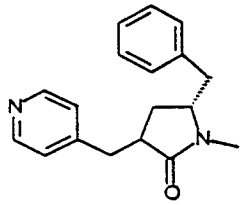
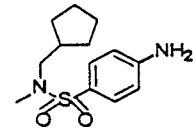
127		
128		
129		
130		
131		
132		

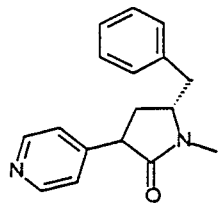
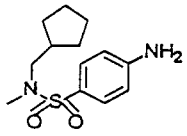
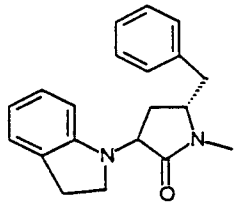
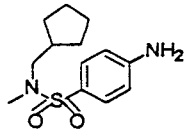
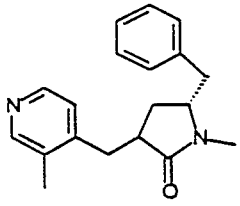
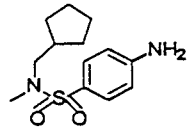
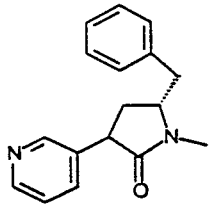
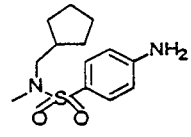
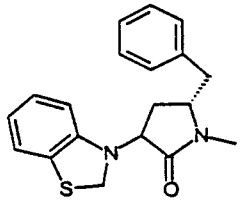
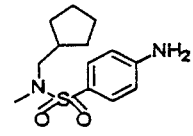
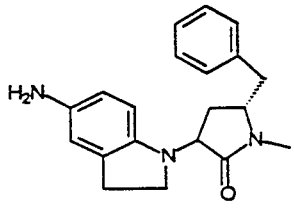
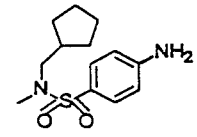
133		
134		
135		
136		
137		
138		

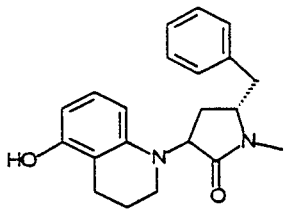
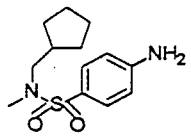
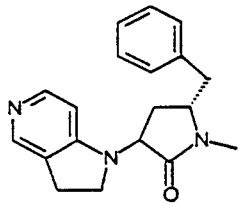
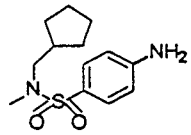
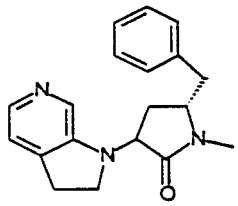
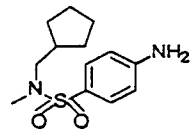
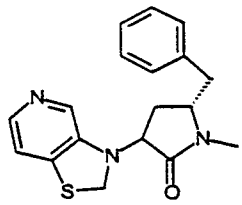
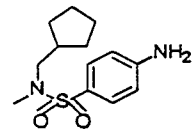
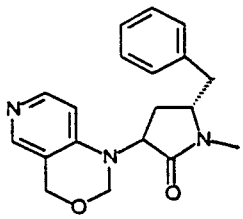
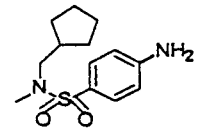
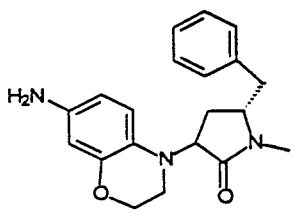
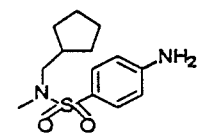
139		
140		
141		
142		
143		
144		

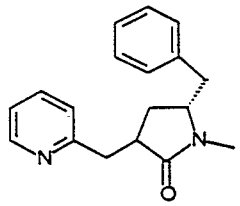
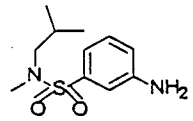
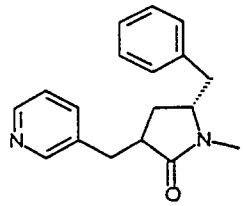
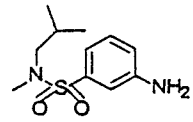
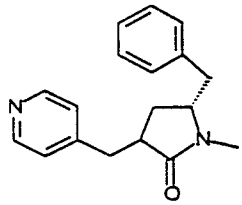
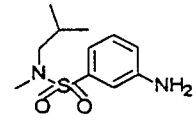
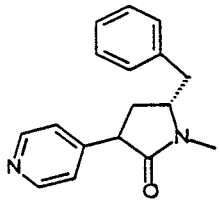
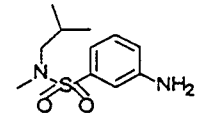
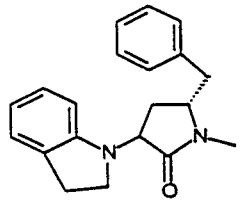
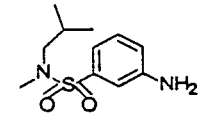
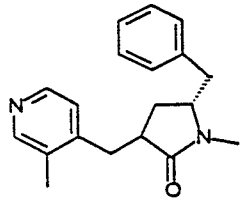
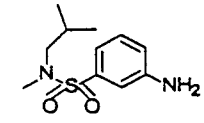
145		
146		
147		
148		
149		
150		

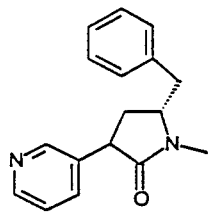
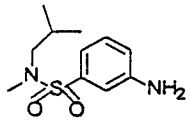
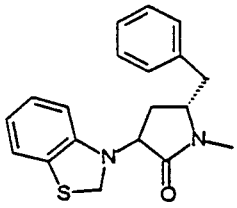
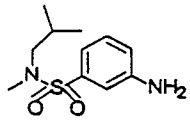
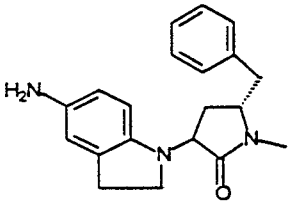
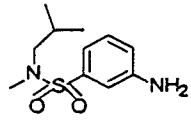
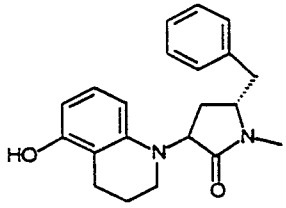
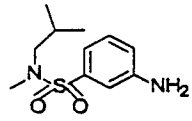
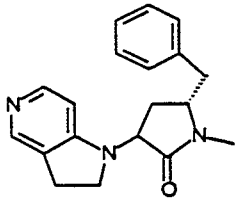
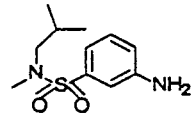
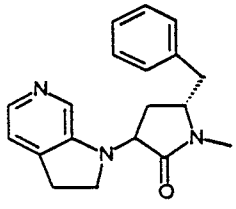
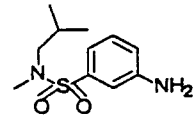
151		
152		
153		
154		
155		
156		

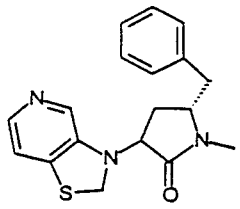
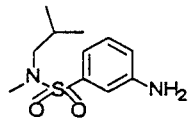
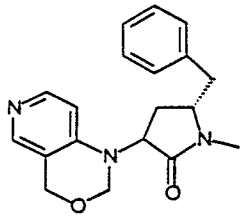
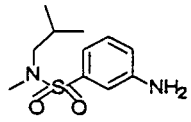
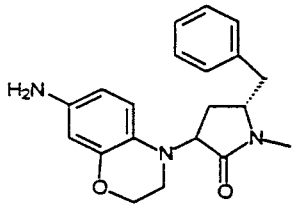
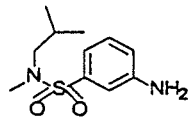
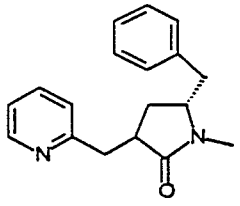
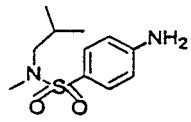
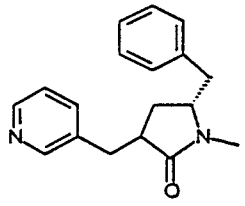
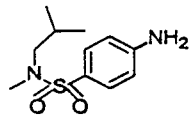
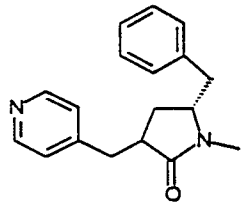
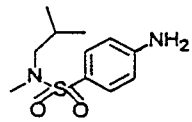
157		
158		
159		
160		
161		
162		

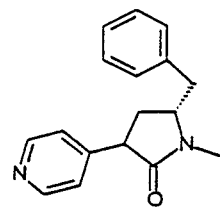
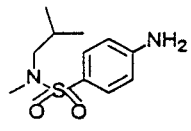
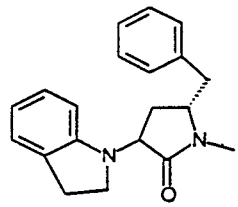
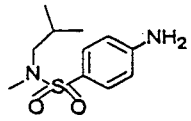
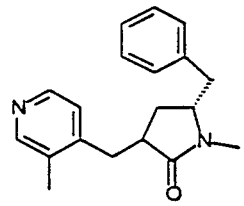
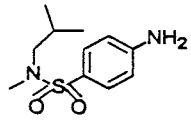
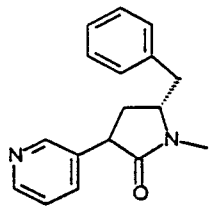
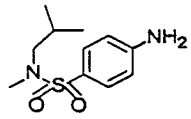
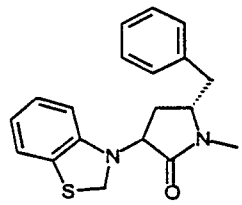
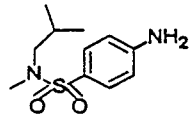
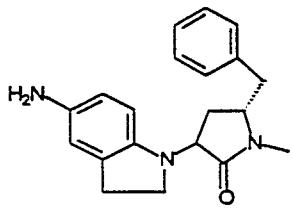
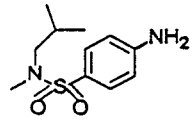
163		
164		
165		
166		
167		
168		

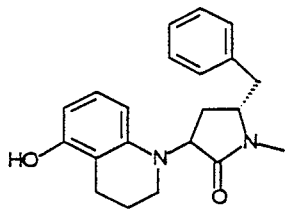
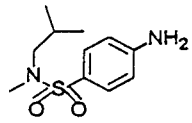
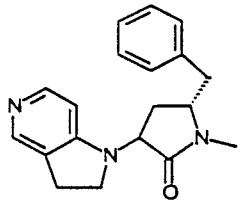
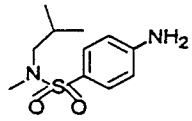
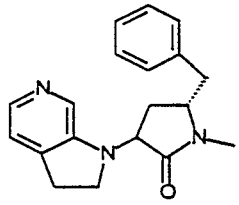
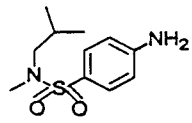
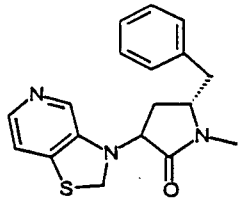
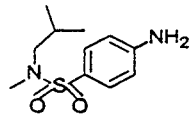
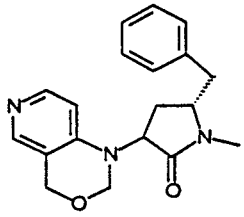
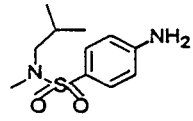
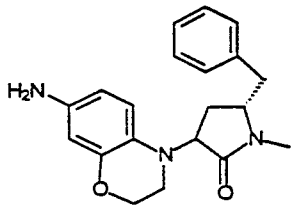
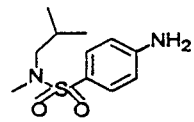
169		
170		
171		
172		
173		
174		

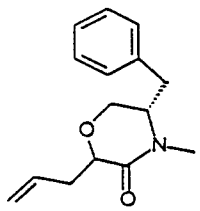
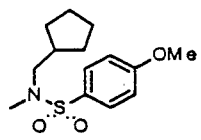
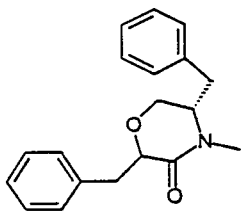
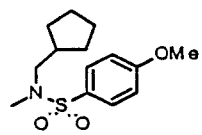
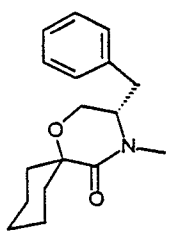
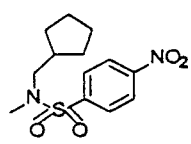
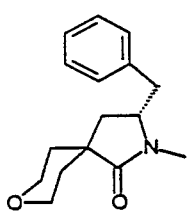
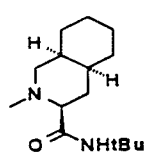
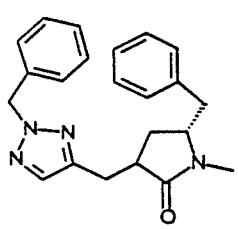
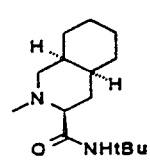
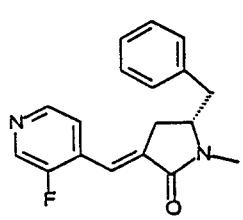
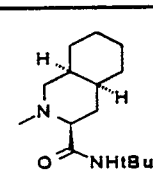
175		
176		
177		
178		
179		
180		

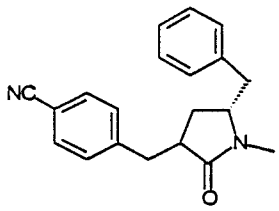
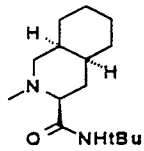
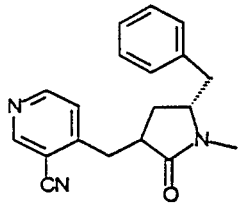
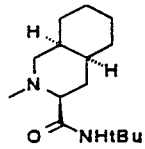
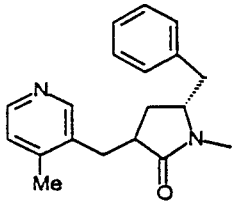
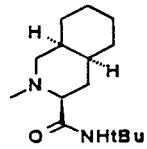
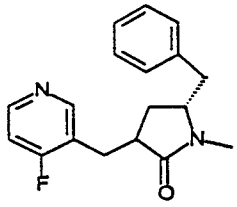
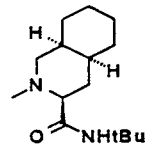
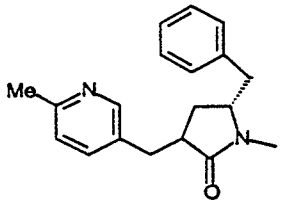
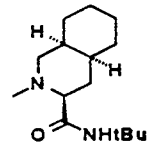
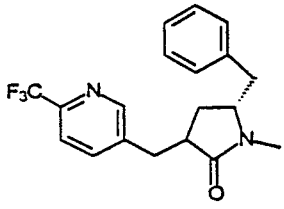
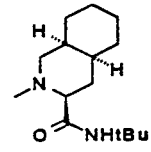
181		
182		
183		
184		
185		
186		

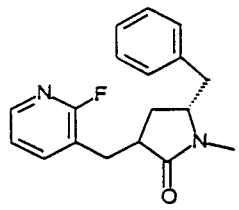
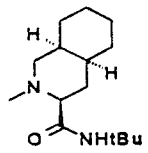
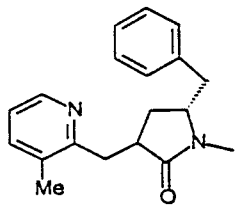
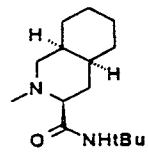
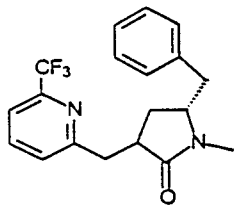
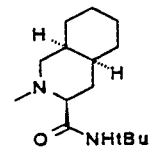
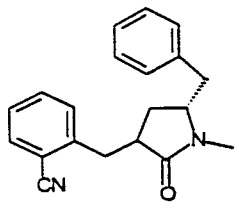
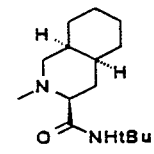
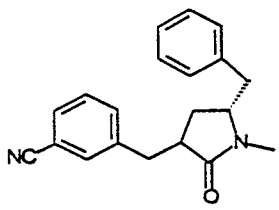
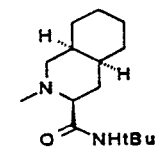
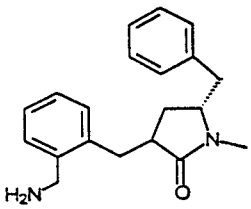
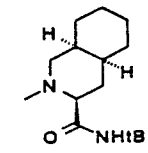
187		
188		
189		
190		
191		
192		

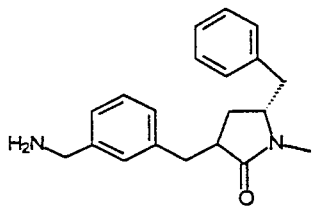
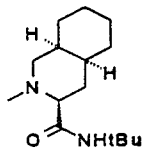
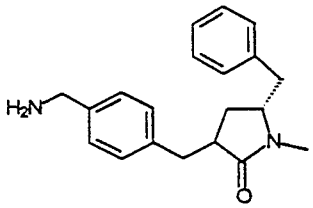
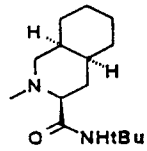
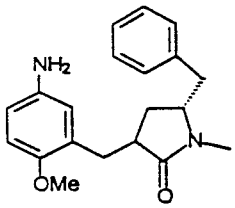
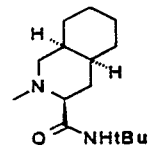
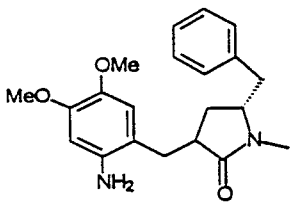
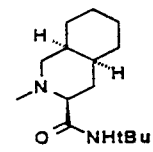
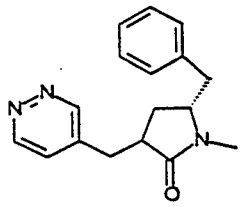
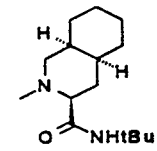
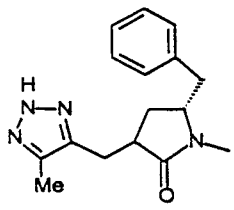
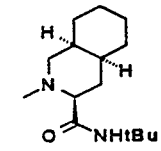
193		
194		
195		
196		
197		
198		

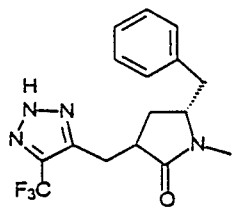
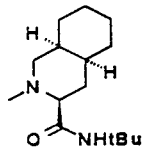
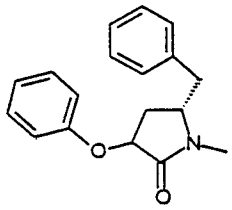
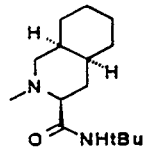
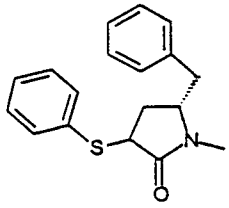
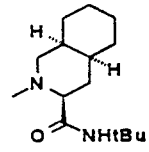
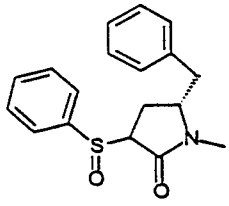
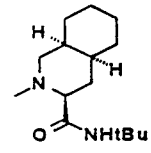
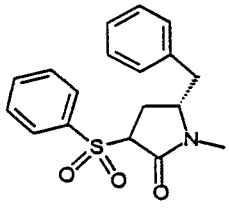
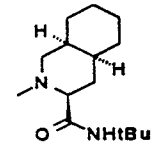
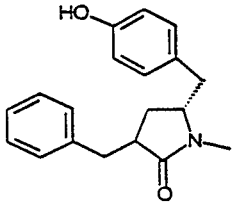
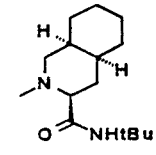
199		
200		
201		
202		
203		
204		

205		
206		
207		
259		
260		
299		

300		
301		
302		
303		
304		
305		

306		
307		
308		
309		
310		
311		

312		
313		
314		
315		
316		
317		

318		
319		
320		
321		
322		
323		

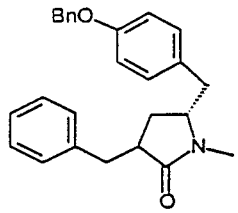
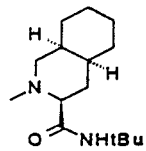
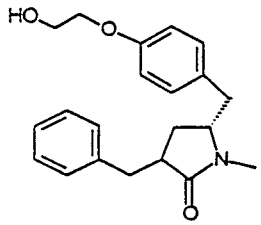
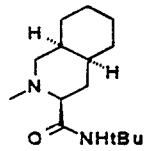
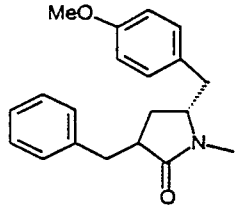
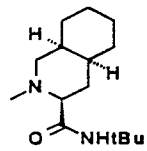
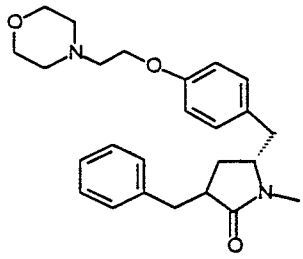
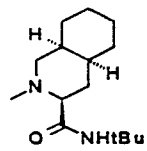
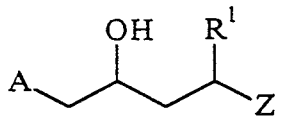
324		
325		
326		
327		

TABLE 2



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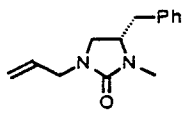
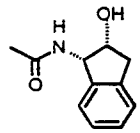
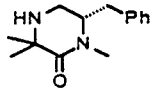
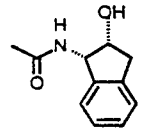
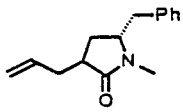
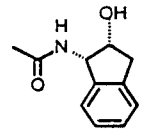
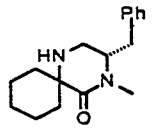
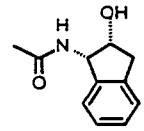
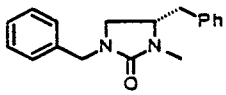
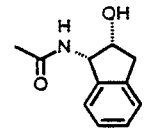
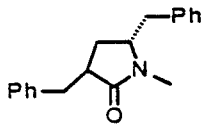
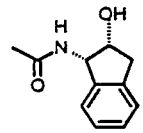
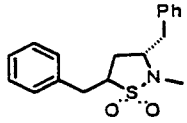
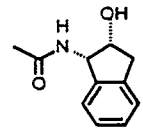
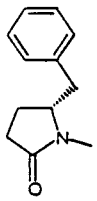
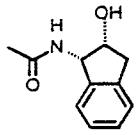
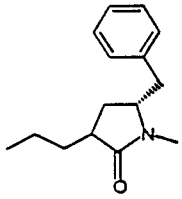
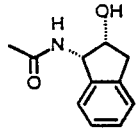
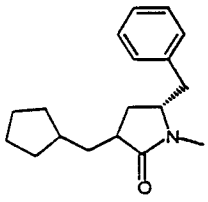
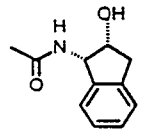
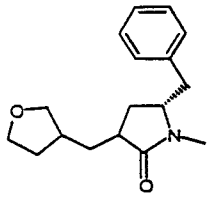
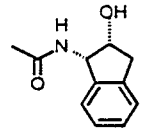
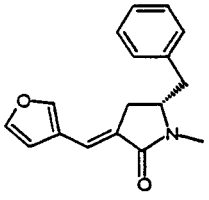
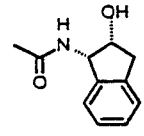
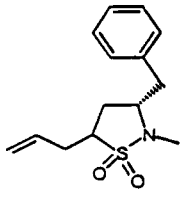
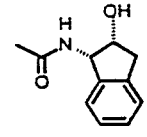
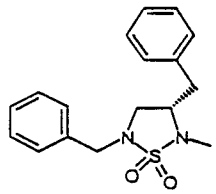
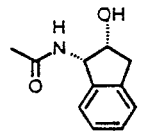
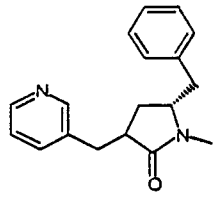
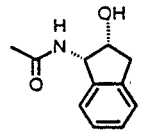
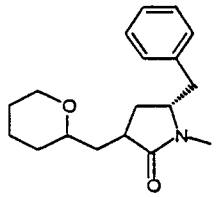
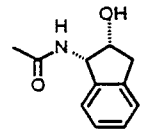
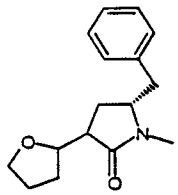
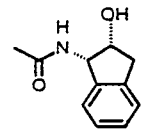
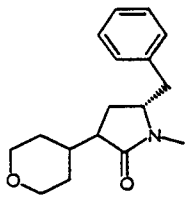
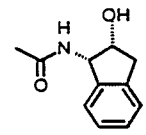
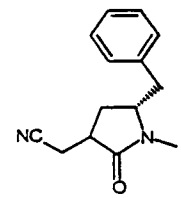
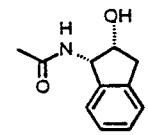
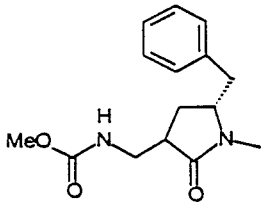
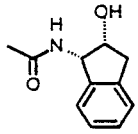
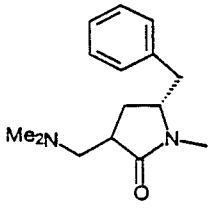
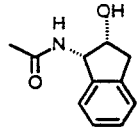
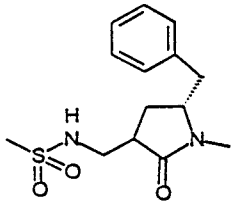
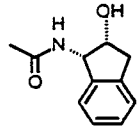
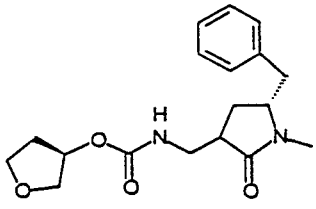
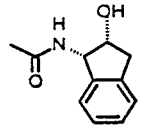
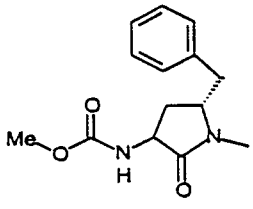
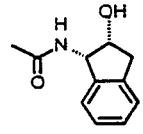
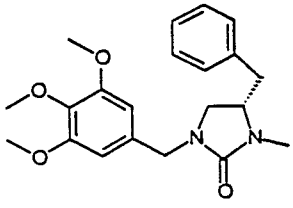
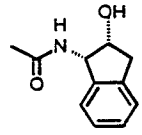
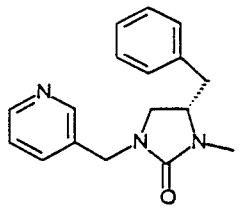
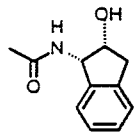
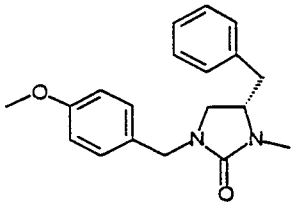
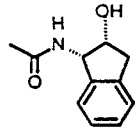
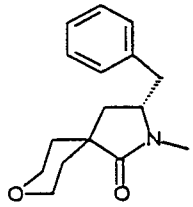
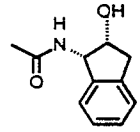
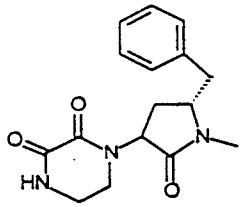
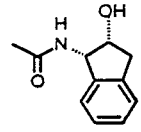
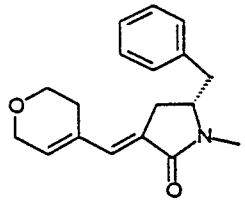
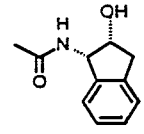
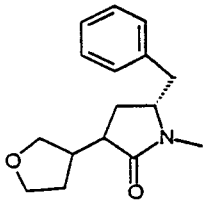
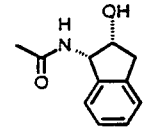
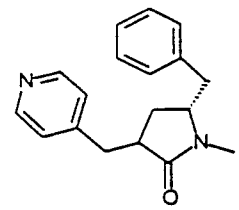
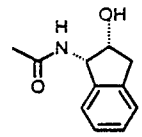
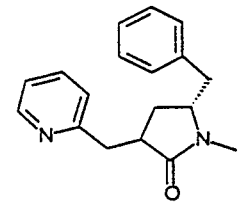
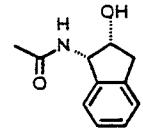
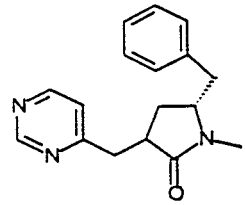
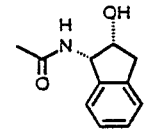
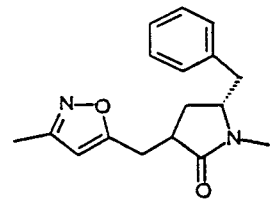
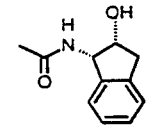
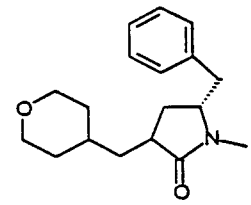
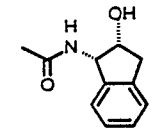
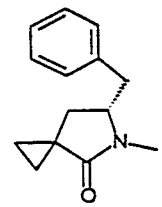
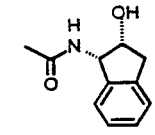
78		Bn	
79		Bn	
80		Bn	
81		Bn	
82		Bn	
83		Bn	
84		Bn	

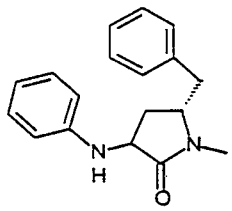
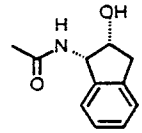
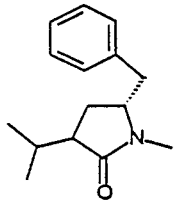
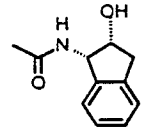
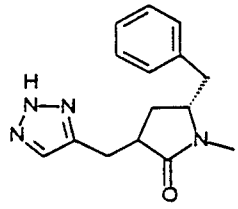
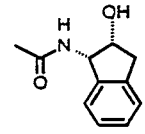
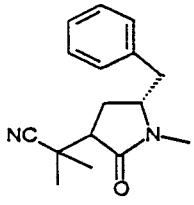
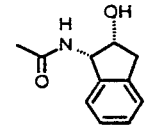
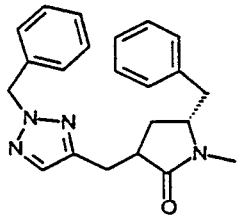
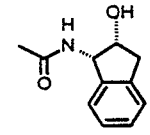
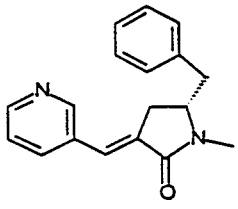
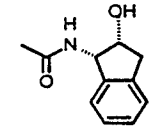
85		Bn	
86		Bn	
87		Bn	
88		Bn	
89		Bn	
90		Bn	

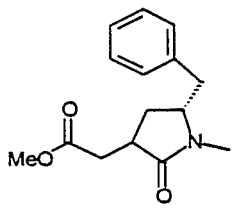
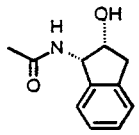
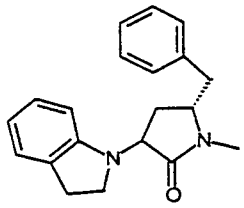
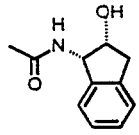
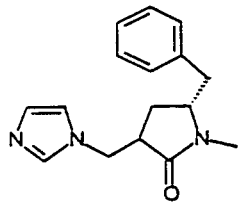
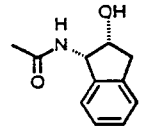
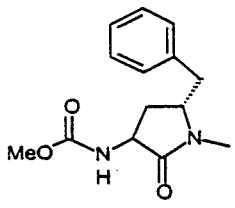
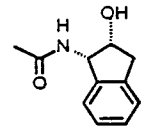
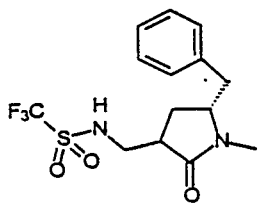
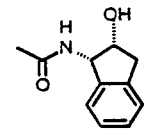
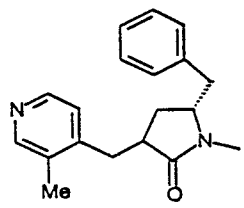
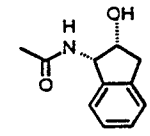
91		Bn	
92		Bn	
93		Bn	
94		Bn	
95		Bn	
96		Bn	

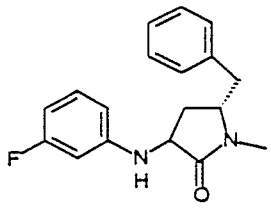
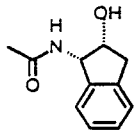
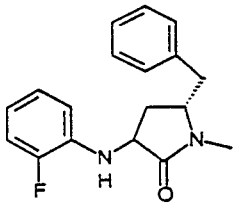
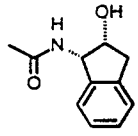
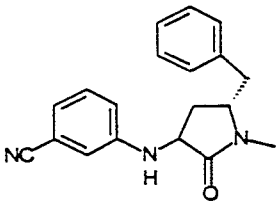
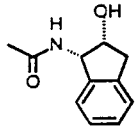
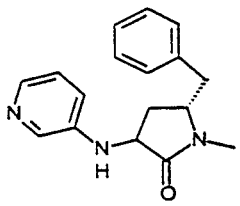
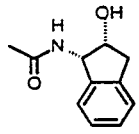
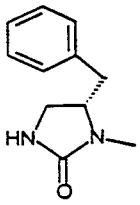
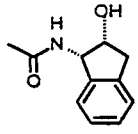
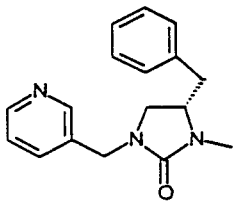
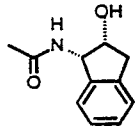
208		Bn	
209		Bn	
210		Bn	
211		Bn	
212		Bn	
213		Bn	

214		Bn	
215		Bn	
216		Bn	
217		Bn	
218		Bn	
219		Bn	

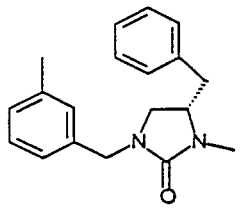
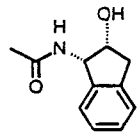
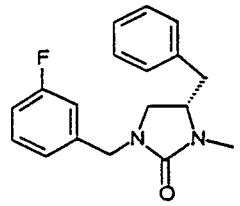
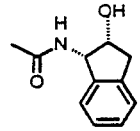
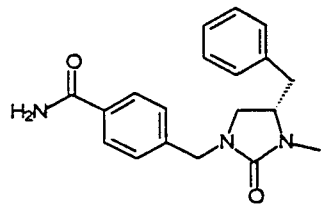
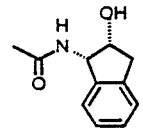
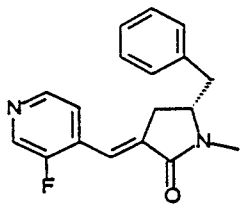
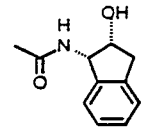
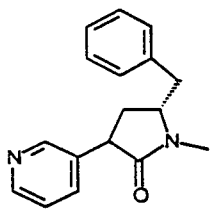
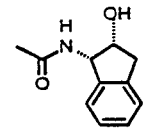
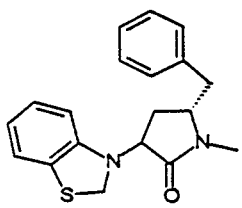
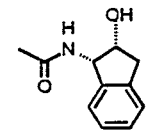
220		Bn	
221		Bn	
222		Bn	
223		Bn	
224		Bn	
225		Bn	

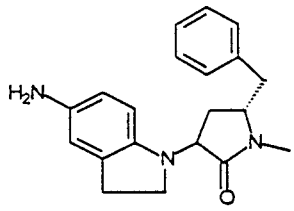
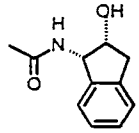
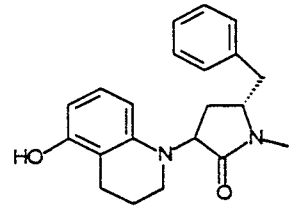
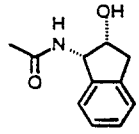
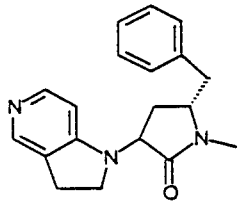
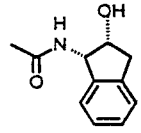
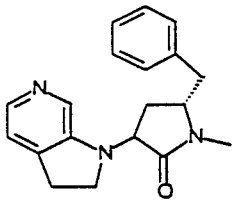
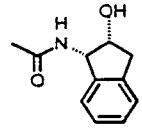
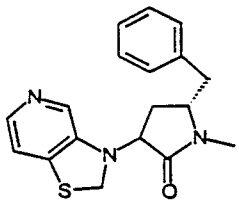
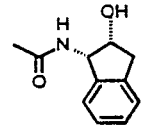
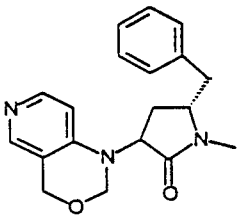
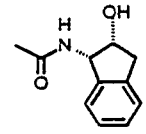
226		Bn	
227		Bn	
228		Bn	
229		Bn	
230		Bn	
231		Bn	

232		Bn	
233		Bn	
234		Bn	
235		Bn	
236		Bn	
237		Bn	

238		Bn	
239		Bn	
240		Bn	
241		Bn	
242		Bn	
243		Bn	

AMENDED SHEET

244		Bn	
245		Bn	
246		Bn	
247		Bn	
248		Bn	
249		Bn	

250		Bn	
251		Bn	
252		Bn	
253		Bn	
254		Bn	
255		Bn	

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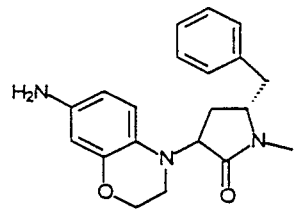
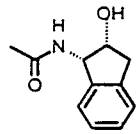
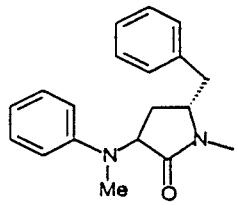
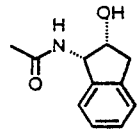
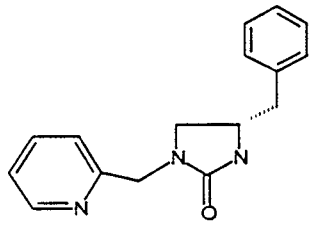
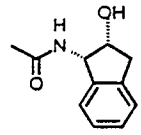
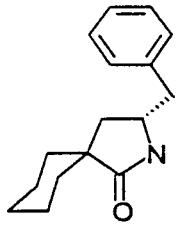
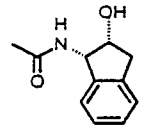
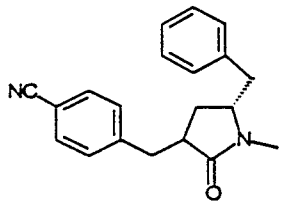
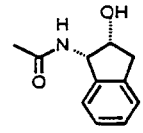
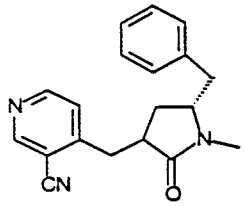
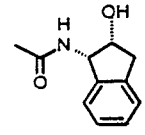
256		Bn	
261		Bn	
262		Bn	
263		Bn	
264		Bn	
265		Bn	

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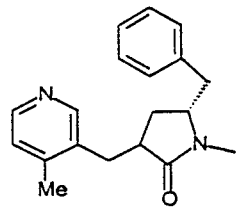
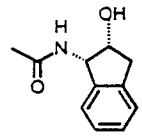
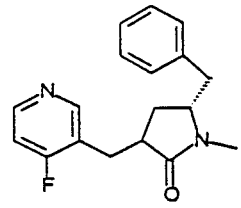
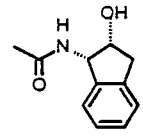
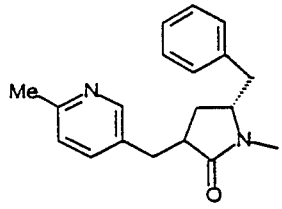
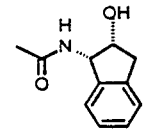
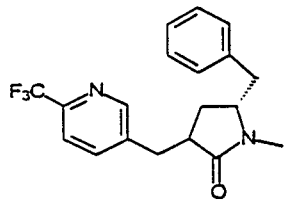
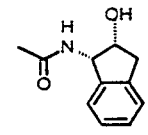
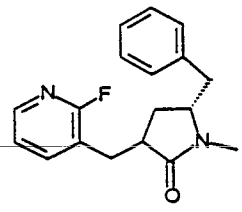
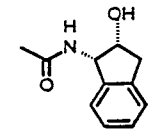
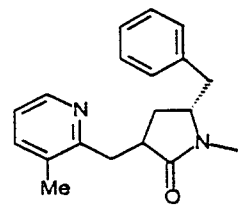
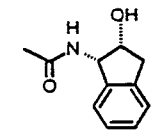
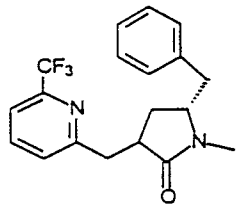
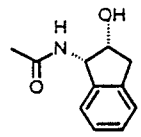
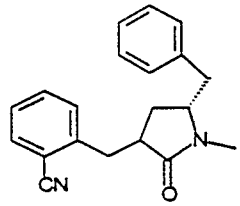
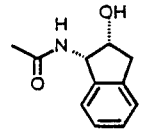
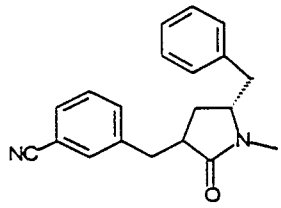
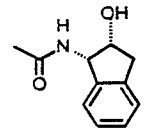
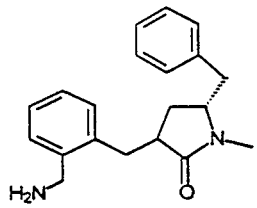
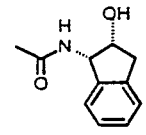
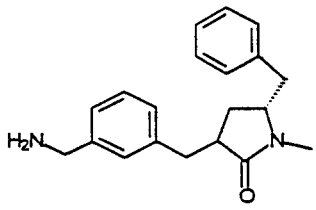
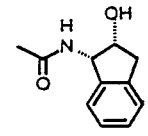
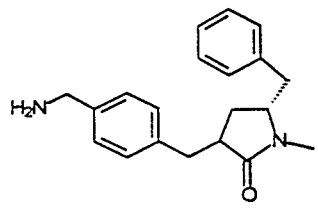
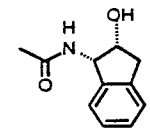
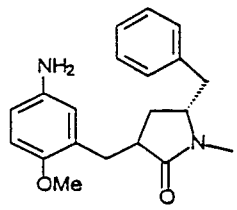
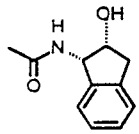
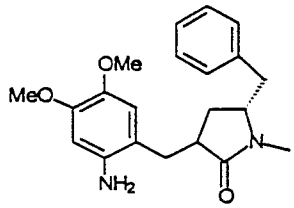
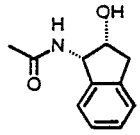
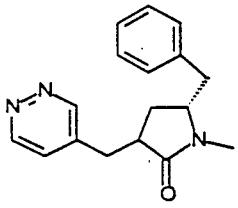
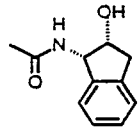
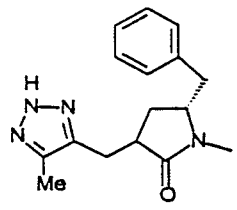
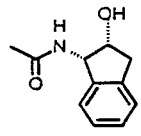
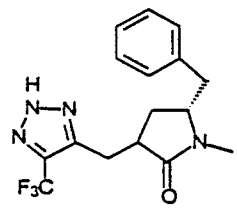
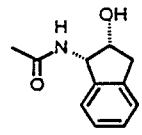
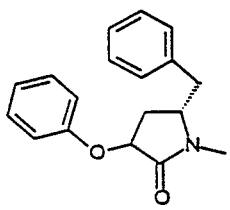
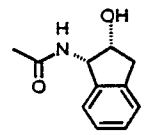
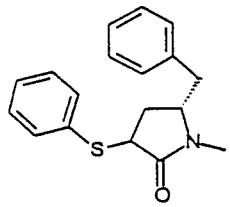
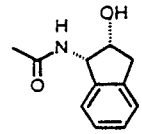
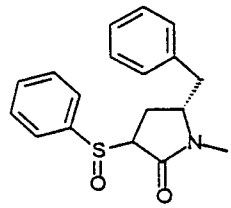
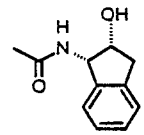
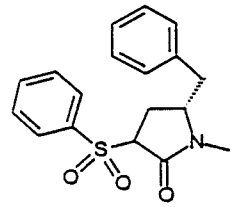
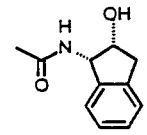
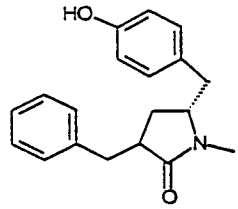
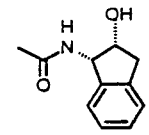
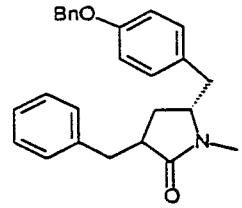
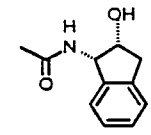
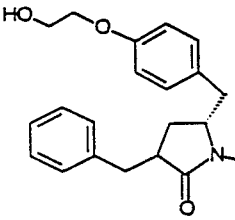
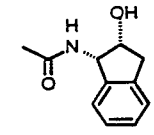
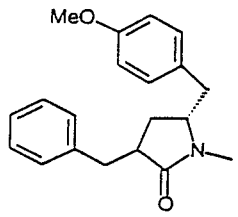
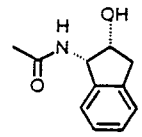
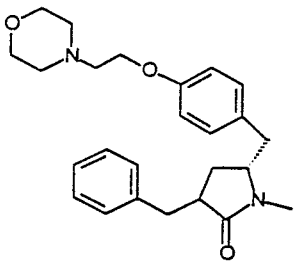
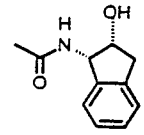
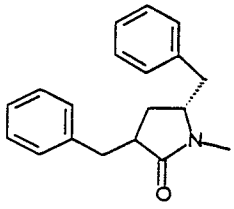
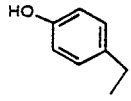
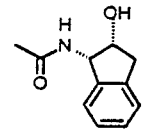
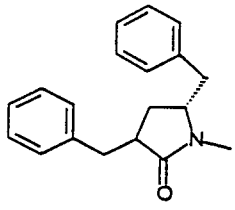
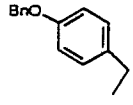
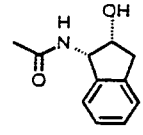
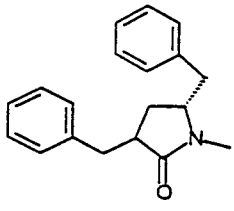
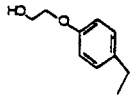
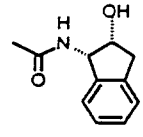
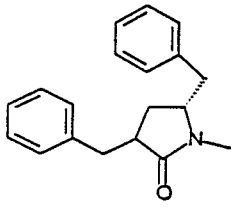
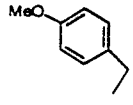
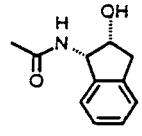
266		Bn	
267		Bn	
268		Bn	
269		Bn	
270		Bn	
271		Bn	

272		Bn	
273		Bn	
274		Bn	
275		Bn	
276		Bn	
277		Bn	

278		Bn	
279		Bn	
280		Bn	
281		Bn	
282		Bn	
283		Bn	

284		Bn	
285		Bn	
286		Bn	
287		Bn	
288		Bn	
289		Bn	

290		Bn	
291		Bn	
292			
293			
294			
295			

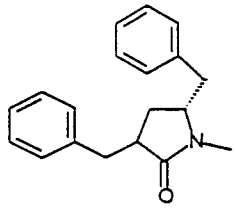
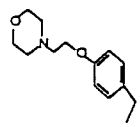
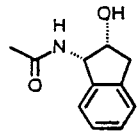
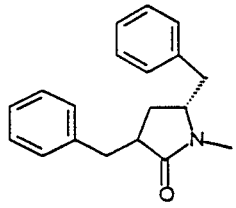
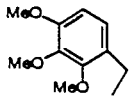
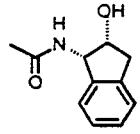
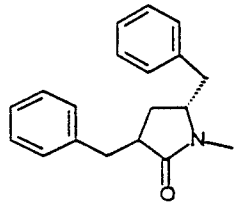
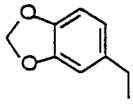
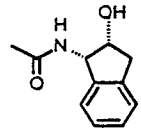
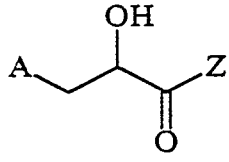
296			
297			
298			

TABLE 3



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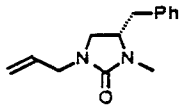
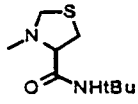
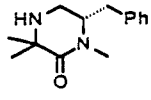
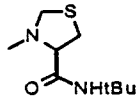
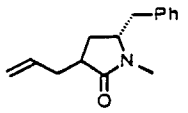
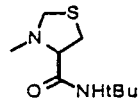
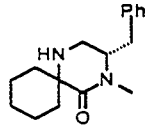
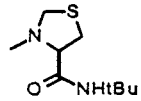
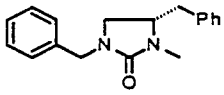
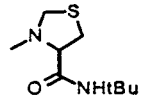
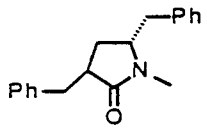
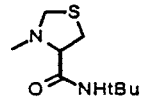
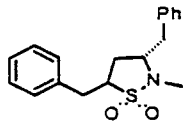
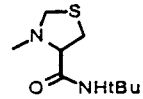
97		
98		

99		
100		
101		
102		
103		

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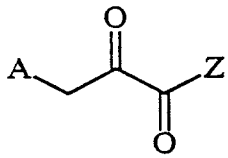

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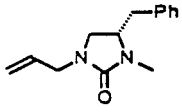
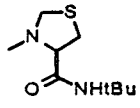
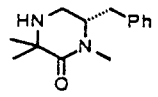
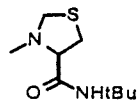
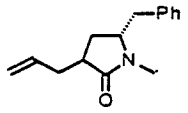
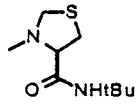
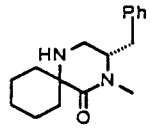
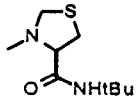
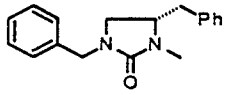
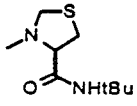
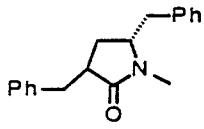
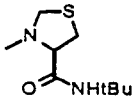
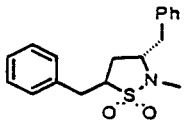
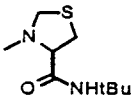
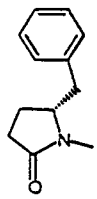
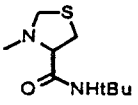
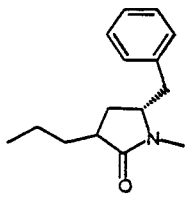
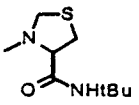
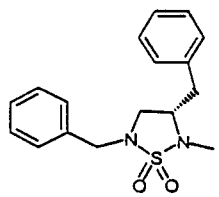
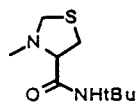
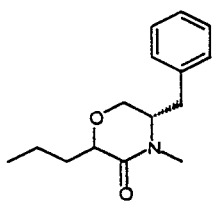
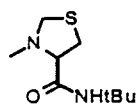
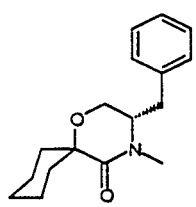
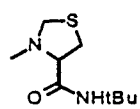
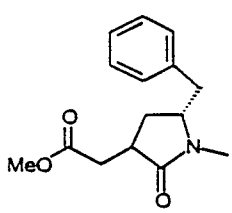
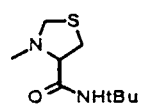
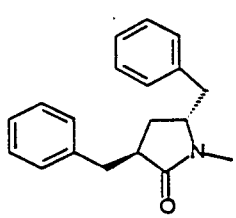
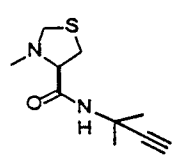
104		

105		
106		
107		
108		
109		
110		
111		
112		

113		
114		
115		
257		
258		

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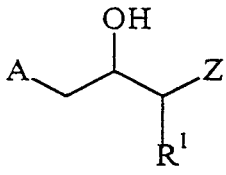

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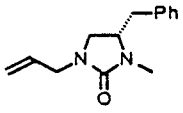
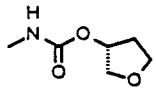
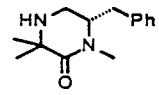
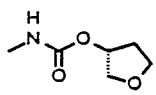
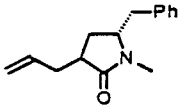
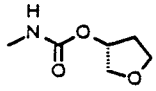
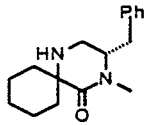
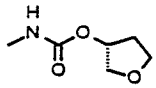
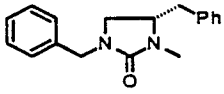
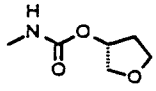
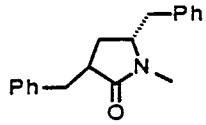
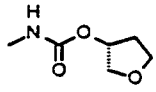
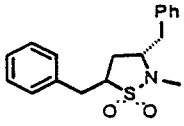
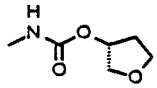
116		Bn	
117		Bn	
118		Bn	
119		Bn	
120		Bn	
121		Bn	
122		Bn	

The preferred compounds of this invention are compound numbers (as in Tables 1-5): 1, 2, 3, 4, 7, 8, 9, 13, 14, 16, 17, 18, 20, 23, 24, 25, 26, 32, 35, 38, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 62, 63, 72, 75, 76, 78, 80, 82, 83, 91, 92, 94, 95, 96, 101, 102, 109, 121, 122, 123, 124, 126, 127, 128, 129, 131, 132, 133, 134, 135, 137, 138, 140, 141, 145, 146, 147, 149, 150, 155, 156, 160, 161, 162, 164, 165, 170, 171, 175, 176, 177, 179, 180, 185, 186, 190, 191, 192, 194, 195, 200, 201, 208, 219, 220, 228 and 264. More preferred are compound numbers: 2, 7, 8, 9, 14, 18, 20, 25, 26, 32, 38, 45, 47, 48, 49, 50, 51, 53, 54, 62, 63, 72, 82, 83, 91, 92, 94, 95, 96, 123, 126, 140, 141, 219, 220, 228 and 264. Even more preferred are compound numbers: 7, 8, 9, 20, 45, 50, 51, 53, 54, 82, 83, 92, 94, 96, 219, 220, 228 and 264.

In an alternate embodiment, this invention also relates to novel methods for preparing compounds and intermediates of the following structures.

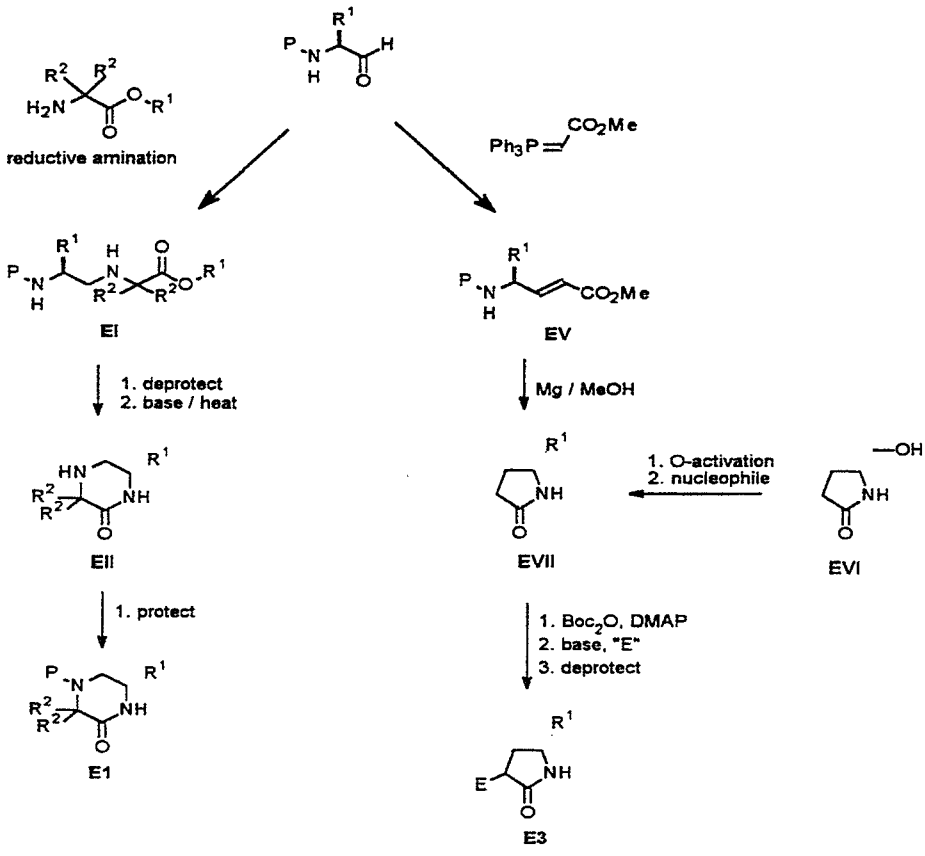
One embodiment relates to a process

The compounds of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

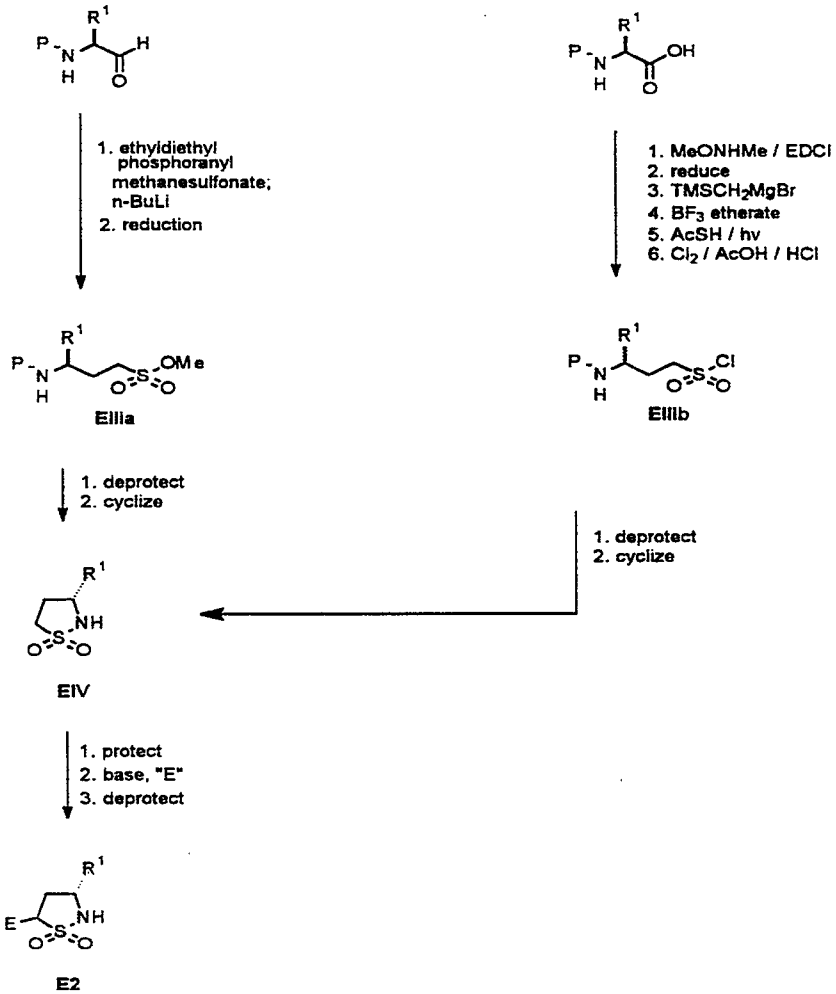
Although the syntheses of the compounds of this invention are known to those of skill in the art, the following general schemes are set forth to illustrate these methods. These schemes should not be viewed as limiting the scope of this invention in any way.

Using standard techniques, compounds of the present invention having the general formula I may be obtained as described in the following schemes:

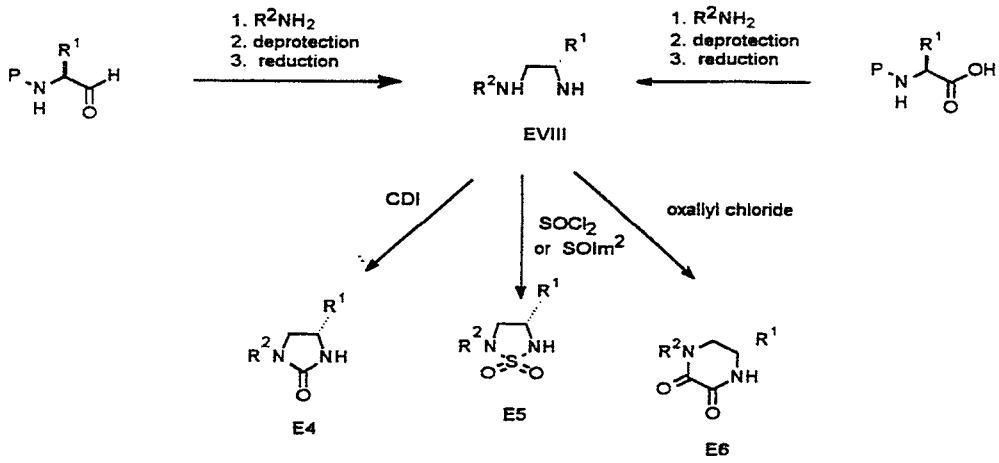
SCHEME 1


reductive amination
Ph3P=CHCO2Me
EI
EV
1. deprotect
2. base / heat
Mg / MeOH
EII
EVII
1. O-activation
2. nucleophile
EVI
1. protect
1. Boc2O, DMAP
2. base, "E"
3. deprotect
E1
E3

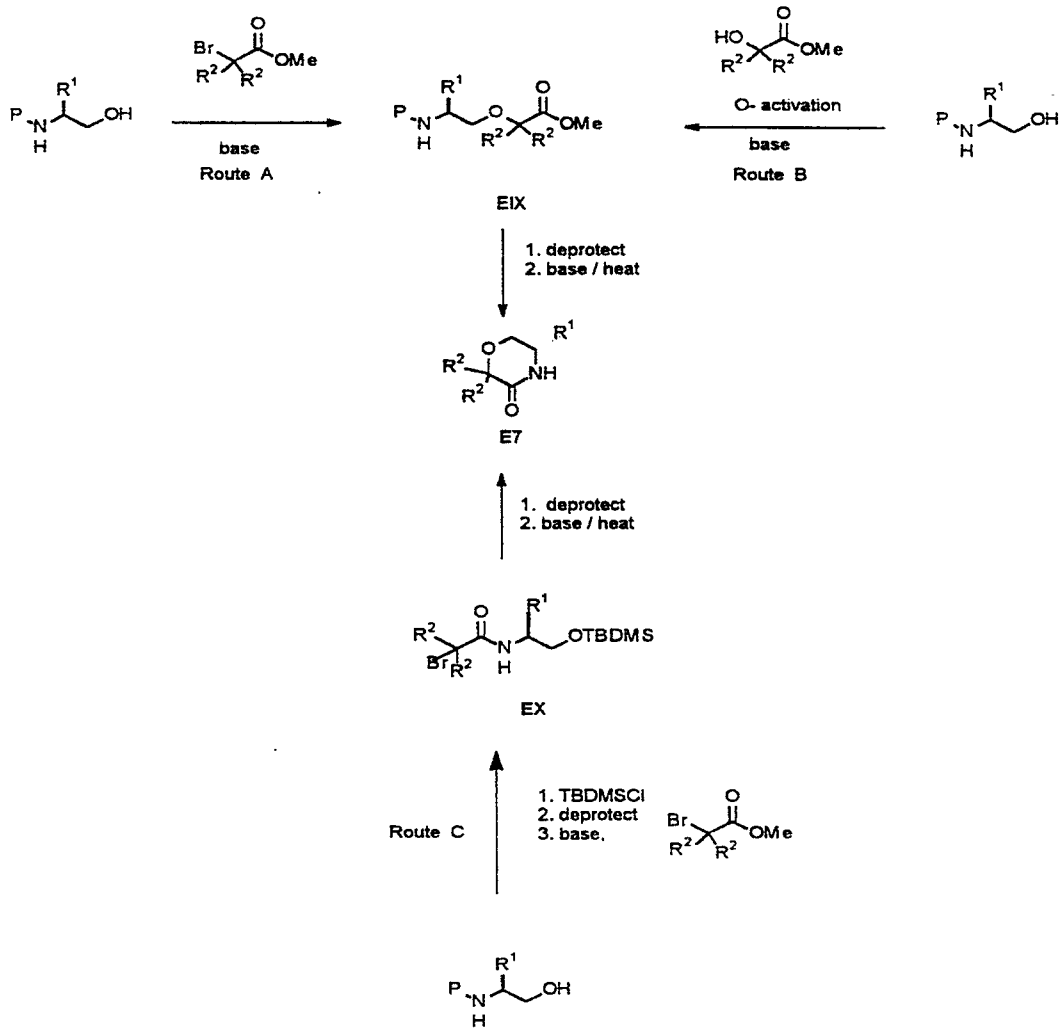
SCHEME 1 (cont'd)



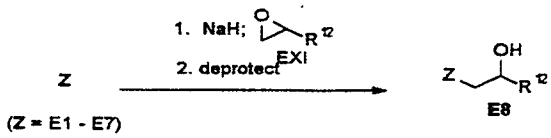
SCHEME 2


1. R2NH2
2. deprotection
3. reduction
1. R2NH2
2. deprotection
3. reduction
EVIII
CDI
SOCl2
or SOIm2
oxallyl chloride
E4
E5
E6

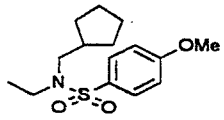
SCHEME 3

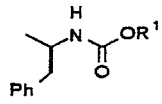

base
Route A
O- activation
base
Route B
EIX
1. deprotect
2. base / heat
E7
1. deprotect
2. base / heat
EX
Route C
1. TBDMSCl
2. deprotect
3. base.

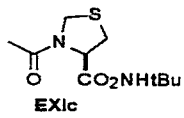
SCHEME IV

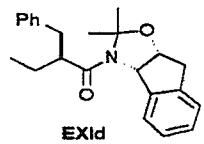


R^{12} =

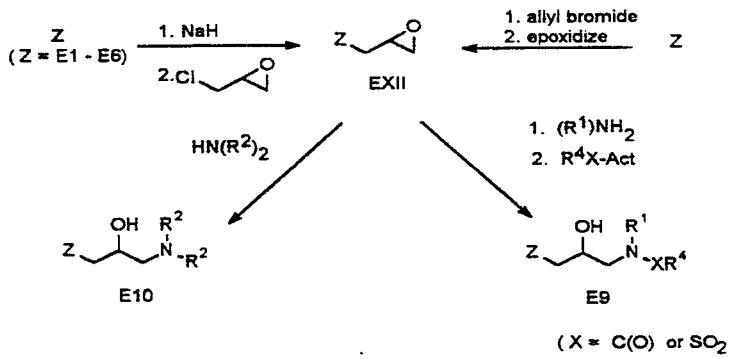




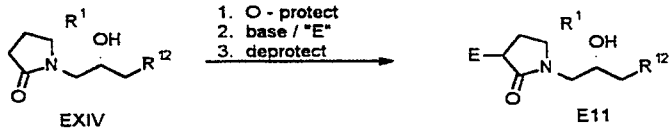




SCHEME 5



SCHEME 6



Methods for producing the compounds of this invention are well known in the art of organic synthesis. Several intermediates are commercially available, e.g. from Aldrich Chemical Company, Inc., Milwaukee, WI. The synthesis of heterocycles **E1-E6** (Schemes 1 and 2) begins with any protected amino aldehyde, the preparations for which are well known in the art from suitably protected amino acids, esters or alcohols. In the case of the this intermediate, transient protection of the amino group may be accomplished by means known in the art (see, e.g. T.W. Greene and P.G.M. Wuts "Protective Groups in Organic Synthesis", Second Edition, pp. 309-405 ©1991 John Wiley and Sons, Inc. New York, NY and E. Gross and J.

Meinhofer "The Peptides, Vol. 3: Protection of Functional Groups in Peptide Synthesis" pp. 3-88; ©1981 Academic Press, Inc. New York, NY). Carbamates such as Boc, Fmoc, Alloc and Cbz are particularly convenient protecting groups, the introduction and removal of are described in the above references.

The synthesis of **E1** is illustrated in Scheme 1. The protected amino aldehyde is treated with an alpha substituted or alpha, alpha disubstituted amino ester under typical reductive amination conditions well known in the art, such as sodium cyanoborohydride in a solvent mixture of DMF/Acetic acid. The resulting compound **EI** is then deprotected and free based with either a tertiary amine base or potasium carbonate in methanol to effect cyclization to form **EII** The resulting secondary amine may the be protected with groups (detailed in the references above) such as benzyl or t-butyloxycarbonyl (Boc) utilizing conditions well known in the art to form analogs of **E1**.

Preparation of **E2** is achieved by reaction of a starting aldehyde with ethyl diethylphosphoranylmethanesulfonate and subsequent reduction of the double bond (see: Gennari et al., Angew. Chem. Int. Ed. Engl., 33, pp. 2067-69 (1994)) to yield compound **EIIIa**. Cyclization may then be achieved by deesterification and activation of the sulfonate moiety as described in Gennari, followed by deprotection of the nitrogen protection group to yield the cyclized product **EIV**. Alternatively, an amino acid may be converted to compound **EIIIb** using standard synthetic methods illustrated in Scheme 1. Compound **EIIIb** can be cyclized to afford compound **EIV**. Compound **EIV** may then be N-protected, for example, in the presence of Boc anhydride and DMAP (see: Flynn et al.,

J. Org. Chem. 48, pp. 2424-26 (1983)), and treated with a non-nucleophilic base such as LDA or hexamethyldisilazane to generate the anion at the center alpha to the SO_2 moiety. This anion may then be quenched with a variety of electrophiles and subsequently deprotected to form the desired analogs of **E2**. Alternatively, this anion may be quenched with an aldehyde to form (after subsequent dehydration, i.e., an aldol-type condensation) an exo-methylene compound which may then be reduced (i.e., hydrogenation) to form the desired analogs of **E2**. Analogously, preparation of **E3** results from a Wittig reaction using methyl(triphenylposphoranylidene) acetate followed by simultaneous reduction of the double bond and cyclization using magnesium metal in methanol (Wei et al., Tetrahedron Lett., 34(28), pp. 4439-42 (1993)). A similar N-protection, deprotonation, quench and N-deprotection scheme, or condensation-reduction scheme, as described in the preparation of **E2**, results in desired analogs of **E3**. Alternatively, **E3** may be prepared from commercially available **EVI**. The hydroxyl group may be activated using commonly available reagents such as methanesulfonyl chloride or para-toluenesulfonyl chloride in the presence of a tertiary amine base. The addition of a nucleophile to displace the mesylate or tosylate yields **EVII** (Ackermann et al., Helv. Chim. Acta, 73, pp. 122-32 (1990)) which may be treated as described above to obtain **E3**.

Methods for the preparation of compounds **E4-E6** are also well known in the art and stem from readily available protected amino aldehydes. Treatment of these aldehydes with a variety of amines under reductive amination conditions well known in the art, such as sodium cyanoborohydride using DMF/Acetic acid

as a solvent mixture, followed by deprotection of the primary amine yields diamine **EVIII**. Intramolecular cyclization with a variety of activated carbonyl, dicarbonyl or sulfuryl equivalents in the presence of a tertiary amine base yields compounds **E4-E6**. Examples of activating reagents include but are not limited to carbonyldiimidazole, phosgene, sulfuryldichloride, sulfuryldiimidazole, sulfonyl diimide, and oxalyl chloride.

Methods leading to the production of analogs of compound **E7** are also known in the art (McManus et al., J. Med. Chem., 8, pp. 766-76 (1965)). Scheme 3 exemplifies several potential routes to the synthesis of compound **E7**. Any protected amino alcohol may be deprotonated to form the alkoxide which may be reacted with a substituted alpha bromo ester to form ether **EIX** (route A). Alternatively (route B), **EIX** may be formed from activation of a protected amino alcohol with, for example, methanesulfonyl chloride or para-toluenesulfonyl chloride in the presence on a tertiary amine base and subsequent addition of a nucleophile such as an alkoxide from an alpha hydroxy acid to displace mesylate or tosylate to yield **EIX**. Compound **EIX** can then be deprotected, free based with a tertiary amine base or potassium carbonate in methanol, and heated to effect cyclization to form **E7**. Alternatively (route C), **E7** may be prepared from a protected amino alcohol by protection of the hydroxyl group with, for example, t-butyldimethyl silyl chloride/imidazole to afford the silyl ether. Subsequent nitrogen deprotection and acylation with a alpha bromo acid in the presence of any number of available coupling agents (for example dicylcohexylcarbodiimide, other related carbodiimide reagents or isobutyl chloroformate) or

acylation with an alpha bromo acid chloride provides compound **EX**. Desilylation using, for example, tetrabutylammonium formate in THF followed by formation of the alkoxide with base affords cyclization to **E7**. Alternatively, **E7** may be prepared from the corresponding a-methylene compound (i.e., both R^2 are H in **E7**, the nitrogen may be protected if necessary) by a multiple deprotonation-alkylation sequence to give an **E7** wherein each R^2 is inserted in an independent alkylation step and each R^2 may be attached to form a spirocyclic product (i.e., alkylation with a dihaloalkane).

Schemes 4-6 describe methods for converting the cyclic compounds **E1-E7** into compounds of this invention. For example, compounds of the type **Z**, exemplified by compounds **E1-E7**, may be deprotonated and reacted with a functionalized epoxide to generate the desired compounds as described in Scheme 4. Several of the described epoxides are readily synthesized via methods well known in the art (Maligres et al,, Tetrahedron Lett., 36, pp. 2195-98 (1995)). Optionally, further modification of the compounds may be performed subsequent to epoxide opening using reactions and materials well known in the art. For example, subsequent to epoxide opening utilizing example **EXIb** deprotection of the carbamate allows further modification of the unmasked amine.

Alternatively, as shown in Scheme 5, compounds **EZ** may be converted to the desired products in a more stepwise fashion. Compounds **EZ** may be deprotonated using, for example, sodium hydride in DMF and treated with a three carbon based epoxide to generate epoxide **EXII**. Examples of such reagents include, but are not limited to, epibromohydrin,

epichlorohydrin and glycidyl tosylate. Several other potential methods for preparing compounds of the type **EXII** are well known in the art, for example, the anion of **Z** may be reacted with allyl bromide or allyl iodide to form an allyl intermediate, which may subsequently be oxidized to form the desired epoxide. Several epoxidation conditions for the generation of either racemic or chiral epoxides are well known in the art. Epoxide **EXII** may then treated with an amine and susequently carbonylated or sulfonated using activated species well known in the art to generate final compounds of the type **E9**. Alternatively **EXII** may be reacted with a functionalized secondary amine followed by optional manipulation of R^2 to produce compounds of the type **E10**. One example of such manipulation is reaction of **EXII** with the known Boc piperazine **EXIII** (Dorsey et al., J. Med. Chem.,37, pp. 3443-51 (1994)). Subsequent to epoxide opening, the Boc group may be removed and the unmasked secondary amine may be further manipulated by reaction with various electrophiles to form the desired product.

Scheme 6 describes a method for introduction of electrophiles into comounds of the type **EXIV**. Said compounds may be protected with a variety of protecting groups, for example t-butyldimethylsilyl triflate, to mask the secondary hydroxyl group followed by treatment with a non-nucleophilic base such as lithium diisopropylamide or hexamethyldisilyzane to generate the anion alpha to the carbonyl. Various electrophiles may then be added to substitute the position alpha to the carbonyl, or alternatively an aldol-type condensation-reduction scheme may be employed. Deprotection of the secondary hydroxyl then yields the desired product.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art.

Moreover, the determination of the optimum overall scheme, as well as the choice of reagents and reactions used to carry out the various steps in a given scheme will be based upon factors that are readily apparent to those of skill in the art. These factors include the identity of the compound to be produced, the efficiency of the individual steps and schemes in producing that compound in terms of overall yield, time, and cost and availability of reagents. It will therefore be apparent that some routine experimentation may be required in determining the optimum scheme to produce certain compounds of this invention.

It should be understood that the compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds of this invention are characterized by a superior ability to inhibit protease activity and viral replication, particularly aspartyl protease activity. These compounds are especially well suited for inhibiting HIV aspartyl protease. We

believe that this activity is due to specific steric and electronic interactions between the protease and compounds of this invention. This belief stems from our analysis of the structural basis for the activity of compounds of this invention, in view of the known crystal structures of HIV protease and bound inhibitors, such as the structure reported in Miller et al. "Structure of Complex of Synthetic HIV-1 Protease with a Substrate-Based Inhibitor at 2.3 Å Resolution", Science, vol. 246, pp. 1149-1152 (1989), which is incorporated herein by reference, as well as structures determined in our laboratories.

The novel compounds of the present invention are excellent ligands for aspartyl proteases, particularly HIV-1 and HIV-2 proteases. Accordingly, these compounds are capable of targeting and inhibiting late stage events in HIV replication, i.e., the processing of the viral polyproteins by HIV encoded proteases. Such compounds inhibit the proteolytic processing of viral polyprotein precursors by inhibiting aspartyl protease. Because aspartyl protease is essential for the production of mature virions, inhibition of that processing effectively blocks the spread of virus by inhibiting the production of infectious virions, particularly from chronically infected cells. Compounds according to this invention advantageously inhibit the ability of the HIV-1 virus to infect immortalized human T cells over a period of days, as determined by an assay of extracellular p24 antigen -- a specific marker of viral replication. Other anti-viral assays have confirmed the potency of these compounds.

The compounds of this invention may be employed in a conventional manner for the treatment of

viruses, such as HIV and HTLV, which depend on aspartyl proteases for obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection or to alleviate pathological effects associated with HIV infection or immunosuppression such as opportunistic infections or various cancers, tumors, CMV retinitis, candida infections, maternal fetal transmission, and AIDS related dementia,.

Alternatively, the compounds of this invention may be used in prophylactics and methods for protecting individuals against viral infection during a specific event, such as childbirth, or over an extended period of time. The compounds may be employed in such prophylactics either alone or together with other antiretroviral agents to enhance the efficacy of each agent. As such, the novel protease inhibitors of this invention can be administered as agents for treating or preventing HIV infection in a mammal.

The compounds of formula I, especially those having a molecular weight of less than about 700 g/mole, may be readily absorbed into the bloodstream of mammals upon oral administration. Compounds of formula I having a molecular weight of less than about 600 g/mole and aqueous solubility of greater than or equal to 0.1 mg/mL are most likely to demonstrate high and consistent oral availability. This surprisingly impressive oral availability makes such compounds

excellent agents for orally-administered treatment and prevention regimens against HIV infection.

The compounds of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other anti-viral agents which target different events in the viral life cycle and which target different viral substrains with varying susceptability to specific agents, the therapeutic effect of these compounds is potentiated. For instance, the co-administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early life cycle events include, didanosine (ddI), dideoxycytidine (ddC), d4T, zidovudine (AZT), 3TC, 935U83, 1592U89, 524W91, polysulfated polysaccharides, sT4 (soluble CD4), ganiclovir, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and tri-methotrexate. Additionally, non-nucleoside inhibitors of reverse transcriptase, delavirdine (U90) or nevirapine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral integrase.

Combination therapies according to this invention exert an additive or synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication or on different strains of virus present in

an infectious population. The use of such combination therapies may also advantageously reduce the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect, as compared to when that agent is administered as a monotherapy. Such combinations may reduce or eliminate the side effects of conventional single anti-retroviral agent therapies, while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity.

Advantages of combining HIV protease inhibitors may include viral population effects, whereby certain members of a virus population which show reduced sensitivity to one protease inhibitor may be fully sensitive to another inhibitor or may in fact have enhanced sensitivity to the second inhibitor. Alternatively or in addition, administration of two or more different inhibitors may be used to reduce specific toxicities associated with a single agent. This advantage of combination therapy also applies to co-administration of the protease inhibitor of this invention with other antiviral agents. Alternatively or in addition, co-administration of more than one protease inhibitor may lower the rate of metabolic inactivation of the compounds of this invention, for instance, by inhibiting enzymatic systems such as cytochrome P_{450}, or esterases or the like. In particular, co-administration of compounds of this invention with protease inhibitors such as ritonavir or other agents such as ketoconazole, grapefruit juice and antiulcer medications such as H_2-blockers, which

inhibits cytochrome P_{450} $3A_4$, may advantageously enhance their biological half-life.

These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. Compounds of this invention in combination with other anti-HIV agents may act in an additive or synergistical manner in preventing the replication of HIV in human T cells. Preferred combination therapies include the administration of a compound of this invention with AZT, ddI, ddC, d4T, 3TC, 935U83, 1592U89, 524W91 or a combination thereof.

Alternatively, the compounds of this invention may also be co-administered with other HIV protease inhibitors such as VX-478 (Vertex, also known as 141W94 (Glaxo-Wellcome) and KVX-478 (Kissei)), saquinavir (Ro 31-8959, Roche), indinavir (L-735,524, Merck)), ritonavir (ABT 538, Abbott), nelfinavir (AG 1343, Agouron), palinavir (Bila 2011 BS), U-103017 (Upjohn), XM 412 (DuPont Merck), XM 450 (DuPont Merck), BMS 186318 (Bristol-Meyers Squibb), CPG 53,437 (Ciba Geigy), CPG 61,755 (Ciba Geigy), CPG 70,726 (Ciba Geigy), ABT 378 (Abbott), GS 3333 (Gilead Sciences), GS 3403 (Gilead Sciences), GS 4023 (Gilead Sciences), GS 4035 (Gilead Sciences), GS 4145 (Gilead Sciences), GS 4234 (Gilead Sciences), and GS 4263 (Gilead Sciences) or prodrugs of these or related compounds to increase the effect of therapy or prophylaxis against various viral mutants or members of HIV quasi species.

We prefer administering the compounds of this invention as single agents or in combination with retroviral reverse transcriptase inhibitors, such as nucleoside derivatives, or other HIV aspartyl protease inhibitors, including multiple combinations comprising from 3-5 agents. We believe that the co-administration

of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial additive or synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral replication or infection or both, and symptoms associated therewith. Particularly preferred is administration of a combination of a compound of formula I, 3TC and zidovudine (AZT). Also preferred are administrations of combinations of a compound of formula I and 1592U89, or of compounds of formula I with VX-478, optionally with one or more reverse transcriptase inhibitors, paarticularly, AZT, 3TC and 1592U89.

The compounds of this invention can also be administered in combination with immunomodulators and immunostimulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone, tuscarasol, and rEPO); and antibiotics (e.g., pentamidine isethiorate) to prevent or combat infection and disease associated with HIV infections, such as AIDS, ARC and HIV-associated cancers.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition. The pharmaceutical compositions according to this invention may comprise a combination of an aspartyl protease inhibitor of this

invention and one or more therapeutic or prophylactic agents.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include other AIDS-like diseases caused by retroviruses, such as simian immunodeficiency viruses, HTLV-I and HTLV-II. In addition, the compounds of this invention may also be used to inhibit other aspartyl proteases, such as renin, pepsin, cymosin, RSV protease, AMV protease, SIV protease and FIV protease, and in particular, other human aspartyl proteases, including renin, and aspartyl proteases that process endothelin precursors.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, polyethyleneglycol polymers such as PEG-400, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty

acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, ß-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-ß-cyclodextrins, or other solublized derivatives may also be advantageously used to enhance delivery of compounds of formula I.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated

according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens and Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, hard or soft gelatin capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the

case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier with suitable emulsifying agents. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A

typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

The compounds of this invention are also useful as commercial reagents which effectively bind to aspartyl proteases, particularly HIV aspartyl protease. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for

affinity chromatography applications. For example, a compound of formula I may be tethered to an affinity column to purify recombinantly produced HIV protease. Derivatization of the compounds of this invention to produce affinity chromatography resins and the methods used to purify proteases using such resins are well known and within the skill of the art. These and other uses which characterize commercial aspartyl protease inhibitors will be evident to those of ordinary skill in the art. (See: Rittenhouse, J. et al. Biochem. Biophys. Res. Commun. 171, p. 60 (1990) and Heimbach, J.C. et al. Ibid 164, p. 955 (1989)).

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

General Materials and Methods

All temperatures are recorded in degrees Celsius. Thin layer chromatography (TLC) was carried out using 0.25 mm thick E. Merck silica gel 60 F_{254} plates and elution with the indicated solvent system. Detection of the compounds was carried out by treating the plate with an appropriate visualizing agent, such as 10% solution of phosphomolybdic acid in ethanol or a 0.1% solution of ninhydrin in ethanol, followed by heating, and/or by exposure to UV light or iodine vapors when appropriate. Thick layer silica gel chromatography was also carried out using E. Merck 60 F_{254} plates ("prep plates") of 0.5, 1.0, or 2.0 mm thickness. Following development of the plate, the

band of silica containing the desired compound was isolated and eluted with an appropriate solvent. Analytical HPLC was carried out using a Water's Delta Pak, 5 µM silica, C18 reversed-phase column, 3.9 mm ID x 15 cm L with a flow rate of 1.5 mL/min using the following table:

Mobile phase:	A = 0.1% CF_3CO_2H in H_2O
	B = 0.1% CF_3CO_2H in CH_3CN
Gradient:	T = 0 min., A (95%), B (5%)
	T = 20 min., A (0%), B (100%)
	T = 22.5 min., A (0%), B (100%)

Preparative HPLC was also carried out using C_{18} reversed-phase media. HPLC retention times were recorded in minutes. NMR spectral data was recorded using a Bruker AMX500, equipped with either a reverse or QNP probe, at 500 MHz, and was taken in the indicated solvent.

We have measured the inhibition constants of each compound against HIV-1 protease using the method described essentially by M.W. Pennington et al., Peptides 1990, Giralt, E. and D. Andreu, Eds., Escom, Leiden, Netherlands (1991); and the method described essentially by Partaledis et al., J. Virol., 69, pp. 5228-35 (1995).

Compounds of invention were tested for their antiviral potency in several virological assays. In the first assay, the compounds were added as a solution in dimethylsulfoxide (DMSO) to a test cell culture of CCRM-CEM cells, a strain of $CD4^+$ human T-cell lymphoma cells, previously acutely infected with HIV_{IIIb} using

standard protocols (see Meek, T. D. et al., "Inhibition of HIV-1 protease in infected T-lymphocytes by synthetic peptide analogues", Nature, 343, p. 90 (1990).

The effect of the compounds on inhibiting the replication of the virus was measured by determining the HIV extracellular p24 antigen concentration using a commercial enzyme immunoassay (obtained from Coulter Corporation, Hialeah, FL).

Antiviral activity may also be measured in a separate assay in MT4 cells. Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a propidium iodide based procedure in the human T-cell lymphotropicvirus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 minutes in a Jouan centrifuge (model CR 4 12). Cell pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of 5 x 105 cells/ml. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of 100 x TCID50. A similar cell aliquot was diluted with medium to provide a mockinfected control. Cell infection was allowed to proceed for 1 hour at 37 °C in a tissue culture incubator with humidified 5% CO_2 atmosphere. After the 1 hour incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 μl of the cell suspension was added to each well of the plate

containing prediluted compound. Plates were then placed in a tissue culture incubator with humidified 5% CO_2 for 5 days. At the end of the incubation period, 27 ul of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multitip pipetter, 60 ul of the mixture was transferred to filter-bottomed 96-wellplates. The plates were analyzed in an automated assay instrument (Pandex Screen Machine, Baxter Biotechnology Systems). The assay makes use of a propidium iodide dye to estimate the DNA content of each well. The antiviral effect of a test compound is reported as an IC_{50}, i.e. the inhibitory concentration that would produce a 50% decrease in the HIV induced cytopathic effect. This effect is measured by the amount of test compound required to restore 50% of the cell growth of HIV-infected MT-4 cells compared to uninfected MT-4 cell controls.

References:

1. Averett, D.R. 1989. Anti-HIV compound assessment by two novel high capacity assays. J. Virol. Methods 23: 263-276.

2. Schwartz, O., et al. 1988. A rapid and simple colorimetric test for the study of anti-HIV agents. AIDS Res. and Human Retroviruses, 4 (6): 441-447.

3. Daluge, S.M., et al. 1994. 5-chloro-2',3'-dedeoxy-3'fluorouridine (935U83), a selective anti-human immunodeficiency virus agent with an improved

metabolic and toxicological profile. Antimicro. Agents and Chemother., 38(7):1590-1603.

4. Dornsife, R.E., et al. 1991. Anti-human immunodeficiency virus synergism by zidovudine (3'-azidothymidine) and didanosine (dideoxyinosine) contrasts with their additive inhibition of normal human marrow progenitor cells. Antimicro. Agents and Chemother., 35(2): 322-328.

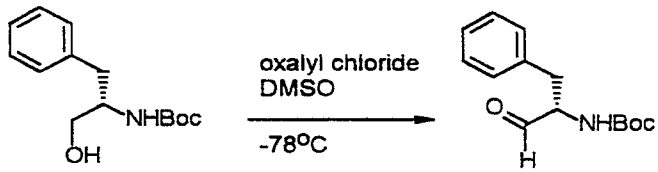
Depending on the cell type and the desired readout, syncytia formation, reverse-transcriptase (RT) activity, or cytopathic effect as assayed by a dye uptake method may also be used as readouts of antiviral activity. See H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphoadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides", Proc. Natl. Acad. Sci. USA, vol. 83, pp. 1911-1915 (1986).

Insofar as the compounds of this invention are able to inhibit the replication of the HIV virus in CD_4^+ cells of human lineage, they are of evident clinical utility for the treatment of HIV infection. These tests are predictive of the compounds ability to inhibit HIV protease in vivo.

Synthetic Examples

Example 1

A.



1 2

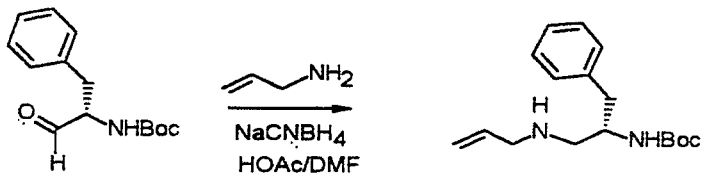
N-(t-butoxycarbonyl)-L-phenylalaninol;

	251.3 g/Mol	10.0g	39.8 mmol
DMSO	78 g/Mol	3.80mL	49.0 mmol
oxalyl chloride	126.9 g/Mol	3.82mL	43.8mmol
triethylamine	101 g/Mol	23.0mL	160mmol
methylene chloride		200 mL	

The oxalyl chloride was added dropwise to a solution of DMSO in methylene chloride at -78 °C. After stirring for 10 minutes, the alcohol was added as a solution in methylene chloride. The reaction was then stirred at -78 °C for 45 minutes. At this time the triethylamine was added and a white precipitate formed. The reaction was then stirred 45 minutes at -78 °C and 45 minutes at 0 °C. The reaction was then quenched by the addition of a solution of 90g of citric acid in 300 mL of water. The organic portion of the reaction was then washed by (2 x 80 mL) of both saturated sodium bicarbonate and brine. The combined

organic layers were then dried over sodium sulfate, filtered and concentrated in vacuo to leave a white solid. The aldehyde was then used without further purification in the reductive amination.

B.



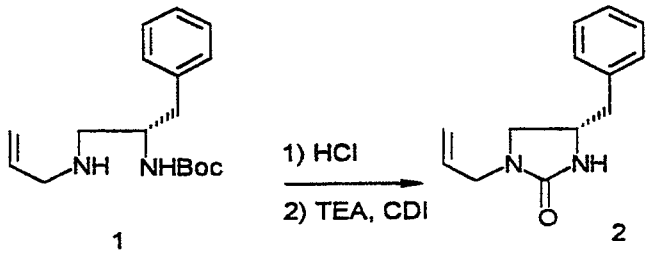
1 2

allyl amine	57 g/Mol	6.0 mL	160 mmol
aldehyde		est.	39.8 mmol
sodium cyanoborohydride	62.8g/Mol	4.0g	6.4 mmol
DMF			180 mL
acetic acid (glacial)			1.8 mL

The aldehyde of Example 1A was dissolved in 180 mL of DMF at 25 °C. This was followed by addition of the aldehyde and 1.8 mL of acetic acid respectively. After 2 hours sodium cyanoborohydride was added, as a solid. The reaction was then stirred at 25 °C for 12 hours. The reaction was then quenched by the addition of 50 mL of saturated sodium bicarbonate, and after 10 min. diluted by 100 mL of diethyl ether. The organic portion was then washed by (2 x 50 mL) of both saturated sodium bicarbonate and brine. The combined organic layers were then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude oil was

purified by silica gel chromatography eluting with 30 % ethyl acetate: hexane to provide 8.8 g of product (29.8 mmol, 75%).

C.



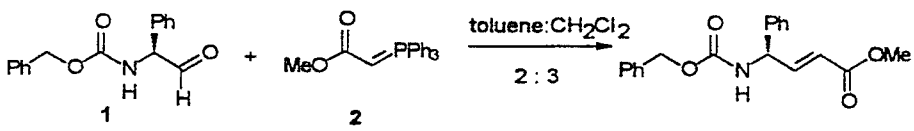
1 2

Boc amine	291 g/Mol	6.8g	23.4 mmol
HCl/dioxane	4 N HCl	15 mL	
deprotected diamine-2HCl		3.83g	14.7 mmol
carbonyl diimidazole	162.15g/Mol	2.77g	17.1 mmol
triethylamine		12.7mL	179 mmol
methylene chloride		550mL	0.03 M

The Boc amine of Example 1B was stirred in 15 mL of 4N HCl at 25 °C for 1.5 hours. The reaction mixture was then concentrated in vacuo to provide a white foaming solid. 3.83 mg of the deprotected diamine was dissolved in 500 mL of methylene chloride. To this, triethyl amine was added. After stirring for 20 minutes, CDI was added (solid). The reaction was then stirred for 24 hours. This was followed by concentration in vacuo. The crude material was purified by silica gel chromatography, eluting with ethyl acetate, to provide 2.15 g (67 %) of the desired allyl urea.

Example 2

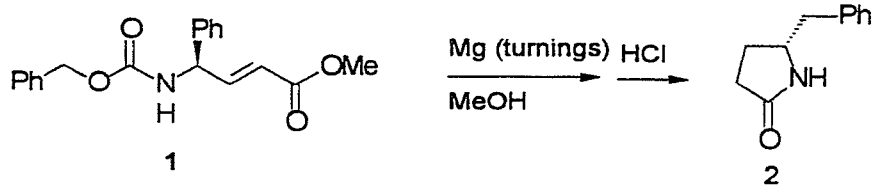
A.



1	aldehyde	1.0 equiv.,
2	methyl (triphenylphosphoranylidene)acetate	1.05 eq.
3	toluene	80mL
4	methylene chloride	120mL

Combine 7.9g of (S)-N-Boc-amino-3-phenyl-1-propanal, 40mL of anhydrous toluene and 60mL of anhydrous methylene chloride. Add 9.8g of the ylide followed by 20mL of toluene and 60mL of methylene chloride. Stir overnight at room temperature. After approximatly 18 hours the solvent was removed *in vacuo* and the residue was purified by flash chromatography (EtOAc/Hexane) to give 7.1g(77%) of the desired ester.

B.

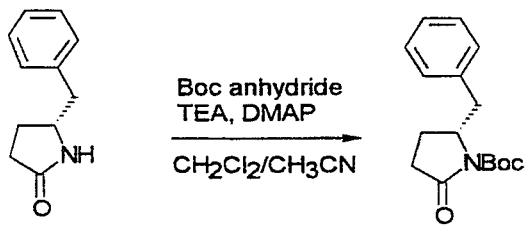


1	ester	4.5g, 1.0 equiv.
2	magnesium turnings (Aldrich)	3.2g 10.0 eq..
3	2N HCl	@ 10 eq.

To a solution of ester **1** in anhydrous methanol at 0 °C was added Mg turnings with stirring under N_2. Bubbling became evident within 1 hour. The reaction was then stirred at 0 °C for ~2.5 hours then allowed to warm to RT overnight (TLC (95:5, CH_2Cl_2:MeOH) showed reaction complete. st. mat. Rf = .84, prod. Rf = .25). The reaction was cooled to 0 °C, neutralized with 2 N HCl, diluted with water, and the volume reduced *in vacuo*. The remaining aqueous layer was extracted with 3 portions of methylene chloride and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.. The residue was then purified by silica get flash chromatography (CH_2Cl_2 -- >3% MeOH/CH_2Cl_2) to yield desired lactam product (1.74g,75% yield).

Literature reference: *Tetrahedron. Lett.*, **1993**, 34 (28), pp. 4439-4442.

C.



1 2

1	lactam from 2B	1.0 equiv., 1.7g
2	BOC anhydride	2.5 equiv., 5.2g
3	triethylamine	2.0 equiv, 2.7mL
4	DMAP	1.2 equiv, 1.4g

Lactam **1** was dissolved in methylene chloride (20mL) and to this solution was added a solution of Boc anhydride 2 in CH_2Cl_2 (10 ml) followed by triethylamine (2 eq) and DMAP (1.2 eq). After stirring for 4 hours at room temperature the reaction was refluxed for 4 hours and after this time, an additional 1.0g of Boc anhydride in acetonitrile (20mL) and 700uL of triethylamine were added. The reaction was stirred for 15 hours at room temperature. (TLC (95:5, CH_2Cl_2 : MeOH) Rf (st mat.) = .31. Rf(prod) = .66.) The solvent was then removed *in vacuo* and the residue was partitioned between methylene chloride and water. The organic layer was washed with water and brine, dried ($MgSO_4$) and filtered. The dried organic layer was then concentrated *in vacuo* and the residue was purified by silica gel chromatagraphy (CH_2Cl_2) to yield desired boc lactam 2 (2.3g, 86%).

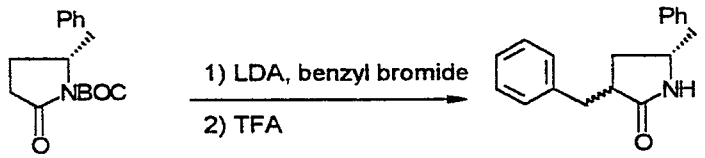
D.

1 2

1	BOC-lactam from 2C	1.0 equiv.,85 mg
2	Allyl Bromide, (Aldrich)	1.8 equiv. , 51uL
3	LDA, 1.29M (Aldrich)	2.0 equiv , 420 uL

Boc-lactam 1 was dissolved in dry THF and cooled to -78 °C and to this solution was added LDA via syringe. After stirring for 40 min. at -78 °C, allyl bromide was added via syringe and the reaction was stirred for 3 hours after which time an additional amount of allyl bromide (17 ul) was added. The reaction was then stirred at -78 °C for 4 hours (TLC (5:95, MeOH:CH_2Cl_2) Rf (st mat.) = .34. Rf(2 diast.) = .55 and.61). The reaction was then quenched with 1mL saturated NaCl solution, and partitioned between saturated sodium bicarbonate and ethyl acetate. The organic layer was then washed with water and brine, dried (MgSO4), filtered and concentrated *in vacuo*. The residue was purified by silica get chromatography to yield allylated product 2 (47mg, 48% yield).

E.



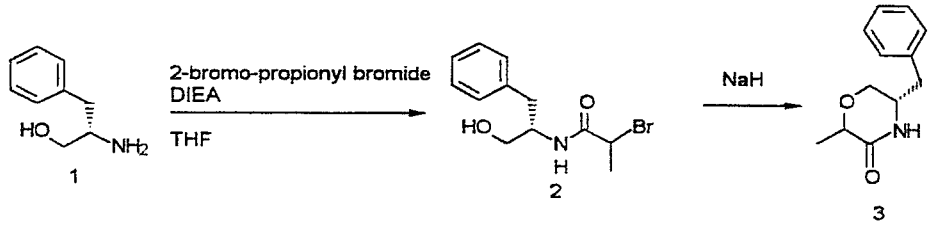
1 2

A mixture of diisopropylamine (4.6 mL, 3 eq) and THF (10 mL) was cooled to -78 °C, and to this solution was added n-butyl lithium (1.4 eq) via syringe. This

mixture was warmed to -10 °C and stirred for 40 min, after which time the mixture was cooled back to -78 °C. A solution of Boc lactam 1 (3.0 g, 1 eq) in THF (15 mL total) was added. The reaction mixture was then stirred at -78 °C for 40 min followed by the addition of benzyl bromide (1..45 mL, 1.1 eq) via syringe . After stirring for 2.5 hours at -78 °C, the reaction was warmed to -45 °C and stirred an additional 1 hour. The reaction was then quenched at -78 °C, with 0.5 mL saturated NaCl solution. The reaction was warmed to room temperature, diluted with ethyl acetate and the organic layer was washed with water and satuated NaCl, dried ($MgSO_4$) and concentrated in vacuo. The residue was then dissolved in methylene chloride (50 mL) and to this solution was added triflouroacetic acid (8 mL, excess). After 4 hours the reaction was concentrated *in vacuo*, and partitioned between a saturated solution of sodium bicarbonate and ethyl acetate. The organic layer was washed with water and brine and then dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was purified by flash silica get chromatography to give 726 mg (30%) of the desired benzyl lactam product 2 as a mixture of diastereomers.

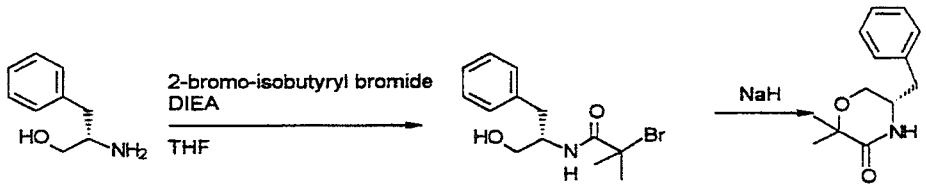
Example 3

A.



Synthesis of 2-oxo-3-methyl-6-phenylmethylmorpholine. Dissolve S-(-)-2-Amino-3-phenyl-1-propanol (1.51 g, 10 mmol) in THF (10 ml). To 0 °C solution add (rac)-2--bromopropionyl bromide (1.04 ml, 10 mmol), followed by a dropwise addition of diisopropylethylamine (1.73 ml, 10 mmol). Warm up to rt and continue stirring for 90 min. Remove solvents *in vacuo* and remove salts by ethyl acetate/water extraction (3X). Following magnesium sulfate drying, the ethyl acetate layer is evaporated and residue redissolved in anhydrous THF. To 0 °C solution of intermediate 2 add 13 mM of NaH (from 60% mineral oil dispersion, removed by washing, with hexane). Solution was warmed up to rt and reaction terminated (MeOH) after 1 hr. Residue left after solvents removal was again partitioned between ethyl acetate/water (2X), organic phases combined, dried with magnesium sulfate, filtered and evaporated, resulting in 1.20 g crude product. Silica gel chromatography (ethyl acetate) yielded 0.70 g of pure product, 34% yield. ^{1}H NMR (CDC13): 7.25 (m, 5H), 6.75 (broad s, 1H), 4.19 (q, 1H, J=7.0 Hz), 3.76 (2H, d, J=7.5 Hz), 3.57 (1H, m), 2.90 (2H, m), 1.49+1.46 (both s, total integration 3H). CHN: 70.0 (calc: 70.2), 7.3 (7.4), 6.8 (6.8). Mass Spec. (API-)=204 (M-1). Silica gel plates: Rf=0.19 (1/1 ethyl acetate/hexane). HPLC at 220 nm (YMC 0.46 cm x 25 cm C_{18} reverse phase) t=11.47 min (single peak), gradient: 0-100%B/30 min, 1.5 ml/min, A=O.I% TFA in water, B=0.1% TFA in acetonitrile.

B.



1 2 3

Synthesis of 2-oxo-3,3-dimethyl6-phenylmethylmorpholine.

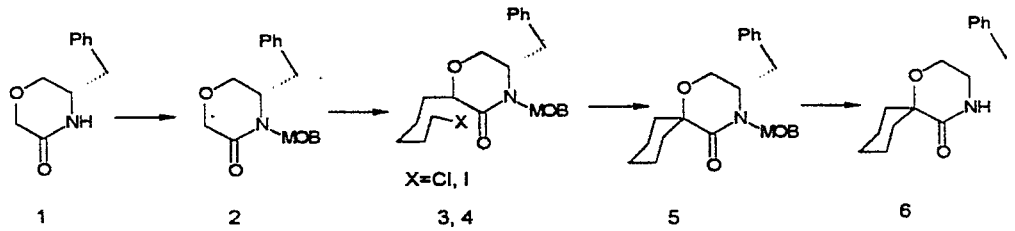
Dissolve 3.02g (20 mM) of S-(-)-2-Amino-3-phenyl-1-propanol in 10 ml THF. To 0 °C solution add 2-Bromoisobutyryl bromide (2.47 ml, 20 mmol), followed by dropwise addition of diisopropylethylamine (3.47 ml, 20 mmol). Warm up to rt and continue stirring for 90 min. Remove solvents *in vacuo* and remove salts by ethyl acetate/water extraction (3X). Following magnesium sulfate drying, the ethyl acetate layer is evaporated and residue redissolved in anhydrous THF. Following silica gel chromatography (1/1 ethyl acetate/hexane), 1.20 g of intermediate **2** is isolated from mixture containing overacylation product.

To 0 °C solution of **2** in 4 ml of anhydrous DMF add 4 mM of NaH (from 60% mineral oil dispersion, removed by washing with hexane).

After 14 hrs at rt, the solvent was removed and solid residue partitioned between ethyl acetate/water (2X), organic phases combined, filtered, evaporated and (silica gel) chromatographed with ethyl acetate,

resulting in 0.20 g of product homogenous by TLC, but heterogeneous by HPLC.

C.



Synthesis of 2-oxo-3,3-spirocyclohexyl6-phenylmethylmorpholine via multiple deprotonation-alkylation route.

A solution of **1** (5.73 g) was dissolved in 5 ml of anhydrous DMF, cooled down to 0° C and 0.72 g of NaH was added portionwise. After stirring for 15 min at room temperature, the solution was cooled to 0° C and 4.70 g of p-methoxy-benzyl chloride was added. The reaction was then stirred at room temperature for two hours, followed by silica gel purification, yielding 4.72 g (51%) of **2**.

M (AP+) =312.1 (M+1). 1H NMR (CDCl3)=7.26-6.87 (9H,m), 5.42 (1H,d), 3.85 (1H,d), 4.34 (1H,d), 4.20 (d,1H), 3.79 (s,3H), 3.68 (1H,d), 3.42 (1H,d), 3.26 (1H,m), 2.95 (2H, m).

4.70 g of **2** was dissolved in 10 ml of anhydrous THF, cooled to -78 °C and 9.8 ml of 2M LDA in heptane/THF/ethylbenzene was added. After 15 min, 4.56g of 1-chloro-5-iodopentane was added dropwise and the

reaction carried out at -78 °C for 1 hr and then quenched. The solvents were removed and the material was purified by silica gel (2.6g, 41.4%). The resulting compound (**3**) was ca 1:1 mixture of two diastereomers. MS (API+)=416.2 (M+1). 1H NMR (CDCl3)= 7.4-6.9 (9H, m), 5.40 (1H), 4.23 (1H), 3.83 (1H), 3.80 (s,3H), 3.75 (1H), 3.55 (3H), 3.36 (1H), 3.12 (1H), 2.96 (1H), 1.88 (m,4H), 1.58 (m,4H).

2.6 g of **3** was dissolved in 5 ml of acetone. 1.87 g of sodium iodide was added and refluxed overnight. Acetone was then removed in vacuo and the crude material purified by ethyl acetate/aqueous extraction, resulting in 2.8g of **4** (88.3%).
MS (API+)=508.1 (M+1), 530.1 (M+Na).

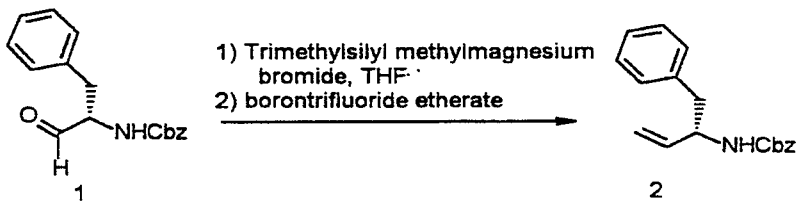
2.8g of **4** was dissolved in 40 ml of anhydrous THF, cooled down to -78 °C, and 3.6 ml of 2M LDA was added. The reaction was allowed to progress for 2 hrs, with gradual temperature increase to room temperature. The residue was quenched with water, THF was evaporated and the crude material desalted between ethyl acetate/water, resulting in 1.90 g of **5**.
1H NMR (CDCl3)=7.35-6.83 (m,9H), 5.35 (d,1H), 3.79 (s,3H), 3.76 (d,1H), 3.55 (m,2H), 3.23 (m,1H), 3.0 (m,2H), 2.0-1.05 (m,10H).

1.90g of **5** was deprotected by 9.61 g of CAN in 3/1 (v/v) acetonitrile/water overnight at room temperature. The product **6** (0.50g) was purified on silica using EtOAc/hexane/methanol gradient.

M (AP+) =259 (M+1). 1H NMR (CDCl3)=7.22 (m,5H), 6.96 (s,1H), 3.82 (m,1H), 3.67 (m,1H), 3.60 (m,1H), 2.83 (m,2H), 2.0-1.20 (m,10H).

Example 4

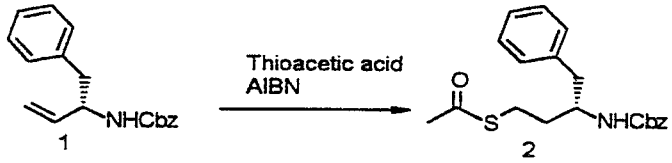
A.



1 2

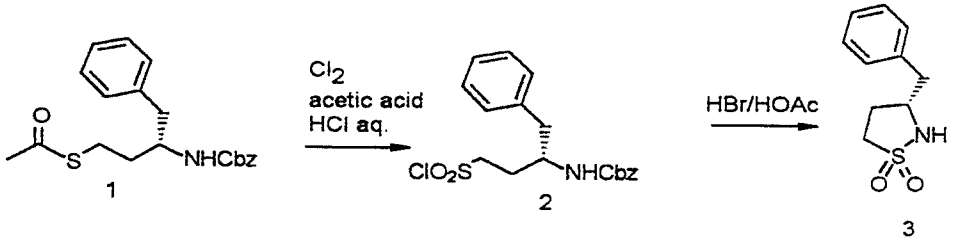
7.0g of the aldehyde 1 was dissolved in 40 mL of THF and added dropwise to a cooled (-78°) solution of 128 mL (128mMol) of 1M trimethylsilyl methylmagnesium bromide in ether. The resulting mixture was allowed to warm to rt and poured into water. After diluting with ethyl acetate and 1N HCl, the layers were separated and the organic layer was washed with 10% aqueous sodium bicarbonate. Drying over magnesium sulfate and removal of the solvent *in vacuo* gave a viscous oil, which was re-dissolved in 150 mL of dichloromethane and treated dropwise with 15.6 mL of borontrifluoride etherate. The resulting mixture was stirred for 5 days at rt and then quenched with 10% NaOH. The organic layer was dried and evaporated and the residue was chromatographed on silica gel (20% ethyl acetate/hexanes) to give 5.2g of a yellow solid. Recrystallization from hexane yielded 4.6g of the desired alkene as a white solid in three crops.

B.



2.0g (7.1mMol) of the alkene from the previous step were mixed with 10 mL of carbon tetrachloride and 1.4 mL (20mMol) of thioacetic acid. A spatula tip of AIBN was added and the mixture was irradiated in a quartz vessel at 254nm for 2h. The resulting mixture was diluted with dichloromethane and extracted with satd. aqueous sodium bicarbonate. Drying and removal of the solvent, followed by chromatography on silica gel (15% ethyl acetate/hexane) gave the desired thioacetate (2.0g) as a pale yellow liquid which solidified on standing.

C.



A solution of 0.85g of the thioacetate from the previous step in 30 mL of acetic acid and 15 mL of 1N HCl was cooled on ice and exposed to a stream of chlorine gas for 2h. Ethyl acetate was added and the organic layer was separated, dried and co-evaporated

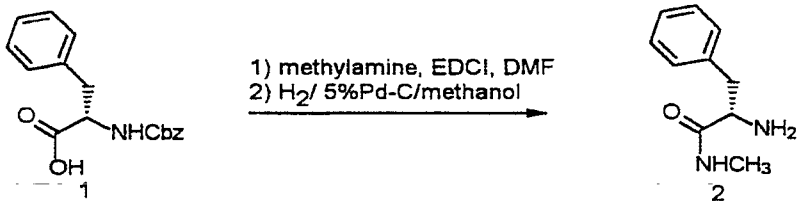
with toluene to give the desired sulfonyl chloride as a white solid (1.05g).

0.7g of the sulfonyl chloride 2 obtained in the previous step were dissolved in 30 mL of 30% HBr in acetic acid. After 2h, the volatiles were removed *in vacuo*, the gummy residue was redissolved in 100mL of chloroform and the solution was treated with 1mL of triethylamine. The mixture was stirred for 1h and then extracted with 1N HCl and 10% aqueous sodium bicarbonate. Drying over magnesium sulfate and removal of the solvent gave a brown oil which was chromatographed on silica gel (2% MeOH/dichloromethane) to give the desired sulfonamide as an off-white solid (0.305g). 1H-NMR (CDC13): 2.20 (1H,m), 2.48 (1H,m), 2.89 (2H,m), 3.10 (1H,m), 3.23 1H,m), 3.84 (1H, m), 4.18 (1H, bs), 7.30 (5H,m). 13C-NMR (CDC13): 28.8, 42.0, 47.8, 56.2, 127.8, 129.1, 129.3, 136.6.

Example 5

Synthesis of Sulfamate

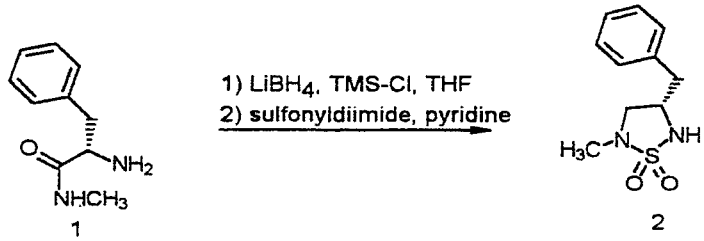
A.



A solution of 30g of Cbz-(L)-phenylalanine, 6.8g of methylamine hydrochloride, 14.8g of hydroxybenzotriazole and 22 mL of N-methylmorpholine in

300 mL of dimethylformamide was cooled on an ice-bath and treated with 19.2g of EDCI. The mixture was allowed to reach rt overnight and then poured into 2000 mL of water. The product was collected by filtration, dried and redissolved in 500mL of methanol and 300 mL of THF. 1g of 5% palladium on carbon was added and the mixture was stirred under hydrogen for 36h. Filtration and removal of the solvent, followed by short plug filtration through silica gel (5% MeOH(2M NH3)/ dichloromethane) gave the desire amine as a pale yellow solid (17g).

B.



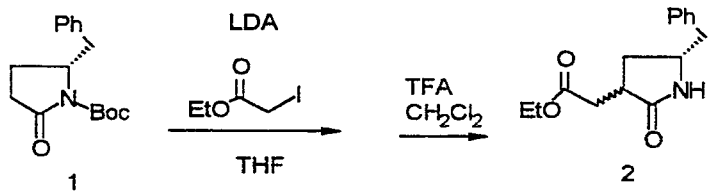
1 2

A solution of 1.22g (56 mMol) of lithiumborohydride in 28 mL of THF was treated with 14.2 mL (112mMol) of chlorotrimethyl silane. The resulting mixture was treated scoopwise with 5g (28mMol) of the amide from the previous step. After stirring at rt for 24h, 40 mL of methanol were added carefully, followed by 10 mL of acetic acid. Repeated evaporation from methanol gave a colorless glass, which was dissolved in 100mL of 20% NaOH. Extraction with 4x50mL of chloroform, followed by drying and removal of the solvent gave a yellow oil which was chromatographed on silica gel (20% methanol(2M ammonia)/dichloromethane to give 1.5g of

the desired diamine as a colorless oil, and 2.0g of recovered starting material.

0.15g of the diamine from the previous step were dissolved in 0.5 mL of pyridine and added dropwise to a refluxing solution of 0.1g of sulfonyldiimide in 1.5mL of pyridine. Reflux was continued for 24h and the volatiles were removed *in vacuo*. The resulting brown oil was chromatographed on silica gel (20% methanol(2M ammonia)/dichloromethane) to give the desired sulfonylurea as a yellow oil (0.04g). ^{1}H-NMR (CD_3OD): 2.60 (3H,s), 2.86 (1H,dd), 2.96 (1H,dd), 3.15 (1H,dd), 3.47 (1H,dd), 4.18 (1H, m), 7.22 (5H,m), 7.38 (1H,d). ^{13}C-NMR (CD_3OD): 31.8, 39.9, 50.0, 57.8, 126.5, 128.2, 129.0, 136.6

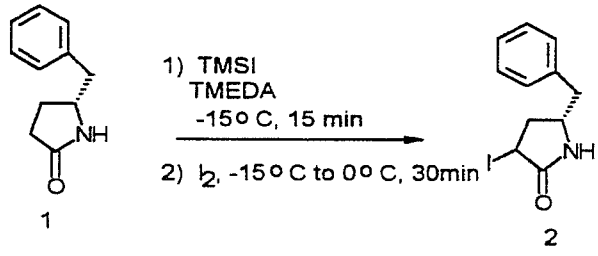
Example 6



Boc lactam 1 (1.27 g, 1eq) was dissolved in THF (27 mL) and cooled to -78 °C. To this solution was added LDA (Aldrich, 1.5 M in hexane, 3.7 mL, 1.2 eq) via syringe over 3 minutes. After stirring for 85 minutes at -78 °C, a solution of ethyl iodoacetate (600 uL, 1.1 eq) in THF (13 mL) was added via syringe over 6 minutes. The reaction was then stirred at -78 °C for 4.5 hours, then at 1.5 hours at -40 °C. The reaction was then cooled back to -78 °C and quenched with 2.5 mL

saturated NaCl solution, and partitioned between saturated sodium bicarbonate and ethyl acetate. The organic layer was then washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash silica get chromatography eluting with 5% EtOAc/ CH_2Cl_2 to give 1.67g of substituted lactam product 2 contaminated with a minor amount of lactam starting material 1. HPLC showed 52% product and 28% starting material. This mixture was then dissolved in methylene chloride (45 mL) and cooled to 0 °C. To this solution was added trifluoroacetic acid (2 mL) and the reaction was stirred at room temperature for 1.5 hr. TLC showed no BOC material and the reaction was concentrate *in vacuo* and partitioned between saturated bicarbonate solution and ethyl acetate. The organic was washed with water, brine and dried ($MgSO_4$). The organic layer was evaporated in vacuo, and the residue was purified by flash chromatography eluting with 3:1 EtOAc/ hexane to give 770mg of pure lactam product 2.

Example 7

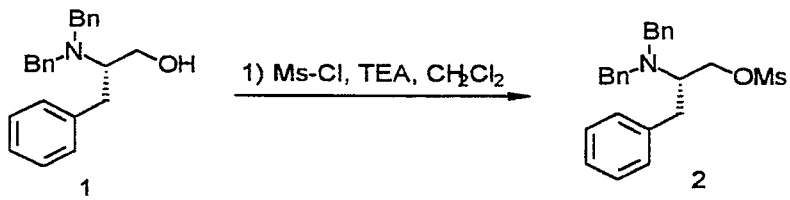


A solution of 5-benzyl-pyrrolidinone 1 (1.5 gr, 8.86 mmol) was dissolved at ambient temperature under

nitrogen in anhydrous dichloromethane (40 mL). TMEDA (6.5 mL, 42.8 mmol) was added via pipette and the solution was cooled and maintained at -20 °C. TMSI (2.33 mL, 17.12 mmol) was added via pipette and the mixture was stirred for 15 min. Solid iodine (4.345 g, 17.12 mmol) was added and the mixture was stirred vigorously for 15 minutes and then quenched by rapid addition of the reaction mixture into aqueous 10% sodium sulfite solution (100 mL). The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1N $NaHSO_4$, water, and then dried over $MgSO_4$. The solution was then diluted in half with methanol and stirred overnight under a nitrogen atmosphere. The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with ethyl acetate : hexane (7:3). Pure iodo lactam product 2 was recovered as a solid (2.11 g).

Example 8

A.

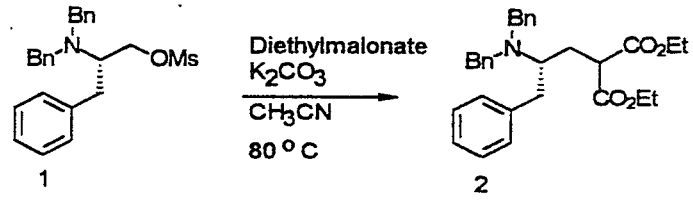


1 2

To a solution of dibenzylphenylalinol 1 (100 mmol) in methylene chloride (100mL), was added triethylamine (150 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (110 mmol) was slowly added. The mixture was stirred at 0 °C for one hour and then

poured into a beaker containing diethyl ether (400mL). The mixture was filtered and washed with more diethyl ether and the filtrate was washed with water, saturated $NaHCO_3$ and saturated brine. The organic layer was then dried ($MgSO_4$), filtered and concentrated to yield 41 g of crude mesylate product 2 as a light yellow-brown thick oil, which was used as is in subsequent steps.

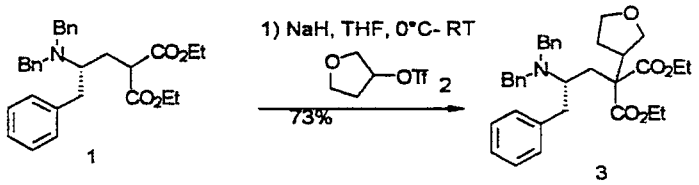
B.



1 2

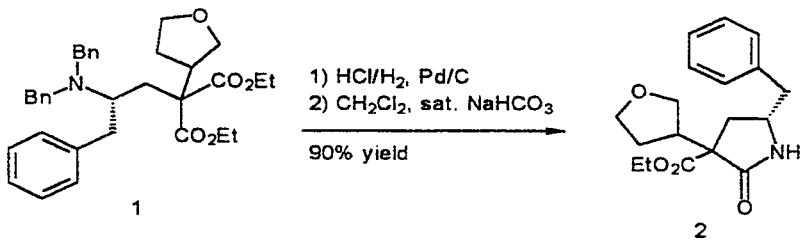
Diethyl malonate (300 mmol) was dissolved in acetonitrile (250 mL) and to this solution was added potassium carbonate (300 mmol); the suspension was stirred overnight at room temperature. Mesylate 1 (100 mmol) in acetonitrile (60mL) was then added to the reaction mixture which was then heated to 80 °C and stirred overnight. The reaction mixture was then filtered and concentrated in vacuo. Addition of hexane to the residue formed a precipitate, which was filtered as pure malonate product 2 (19.5 g). Material was used as is.

C.



Malonate 1 (10.6 mmol) was dissolved in dry THF (40 mL) and cooled to 0 °C. To this solution, sodium hydride (17 mmol) was added in portions and the suspension was stirred for 1.5 hr at 0 °C. The triflate 2 (12 mmol) in dry THF (10mL) was then slowly added to the reaction mixture and after complete addition the reaction was allowed to warm to room temperature and was stirred overnight. The reaction was then diluted with water (100mL) and extracted with diethyl ether (3x50 mL). The combined organic layers were then washed with saturated brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by mplc (eluted with a gradient of 9:1 hexane:ethyl acetate up to 4:1 hexane:ethyl acetate to yield product 3 (4.2 g, 73 %).

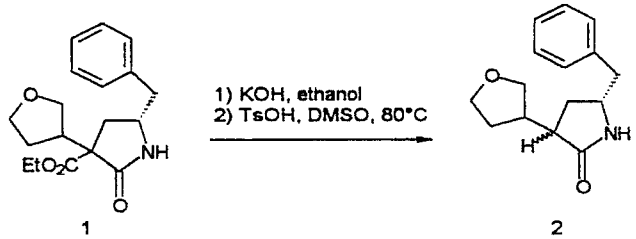
D.



The subsituted malonate 1 (1.62 mmol) was suspended in ethanol and to this was added conc. HCl (0.24 mL, 2.4

mmol) and 10% palladium on Carbon (0.162 mmol). This mixture was then stirred under a balloon of hydrogen gas at room temperature overnight. The reaction was then filtered through Celite and to the filtrate was added triethylamine (10 mL, excess) followed by solid sodium bicarbonate (excess). The mixture was stirred for 0.5 hr, filtered and concentrated to yield a yellow solid. This residue was then dissolved in ethyl acetate and washed with water, 0.5N HCl, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered, and dried to yield crude lactam product 2, which was used as is.

E.



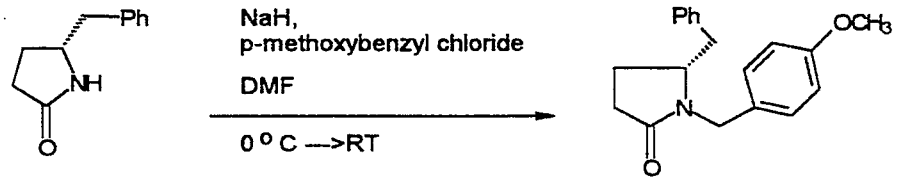
1 2

Lactam 1 (1.18 mmol) was dissolved in ethanol (5mL) and to this solution was added KOH (10 mmol). The mixture was stirred for 3 hr at room temperature and then concentrated to dryness. The residue was dissolved in water and washed with diethyl ether. The aqueous layer was then acidified with HCl and extracted with ethyl acetate. The organic layer was dried (MgSO4), filtered and concentrated in vacuo to yield 341 mg of a light yellow solid. The residue was dissolved in DMSO (3mL) and to this solution was added p-toluenesulfonic acid mono- hydrate, and the mixture was heated to 80 °C

overnight. The mixture was diluted with water (15 mL) and extracted with ethyl acetate. The organic layer was washed with saturated sodium carbonate and brine followed by drying with $MgSO_4$. The organic layer was then filtered and concentrated in vacuo to yield the THF substituted lactam product (245 mg, 77% from ester) which was used as is in the next step without further purification.

Example 9

A.

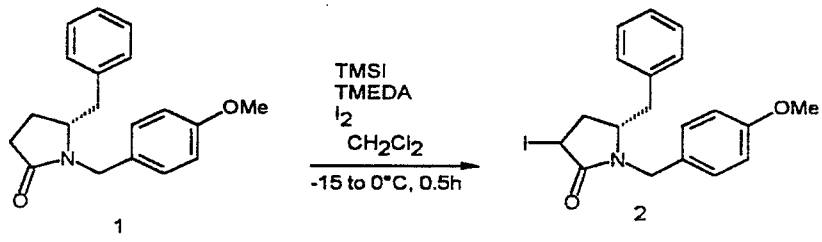


1 2

Sodium hydride (60% dispersion in mineral oil, 4.0 g, 1.17 eq) was washed with 4 x 25 mL portions of hexanes to remove the mineral oil, then suspended in 25 mL of DMF and cooled to 0 °C. A solution of lactam 1 (15g, 1 eq) in dry DMF (25 mL) was then added dropwise via canula into the cold NaH suspension over 40 min. An additional 65 mL of DMF was then added to aid stirring. After stirring the anion for 1 hour, p-methoxybenzyl chloride (14.5 mL, 1.26 eq) was added over 5 min at 0 °C. The reaction was then allowed to warm to room temp. An additional amount of p-methoxybenzyl chloride was added to drive the reaction to completion. TLC (EtOAC) Rf lactam 1 = 0.21. Rf product 2 = 0.43.

After 3.5 hours, the reaction was poured into cold water and extracted twice with ethyl acetate. The combined organic layers were washed with water (5X), brine, dried ($MgSO_4$) and filtered. Concentration *in vacuo* , afforded a crude solid which was purified by crystallization(7:1 hexane:EtOAc) to yield the protected lactam product 2 (19g, 75%).

B.

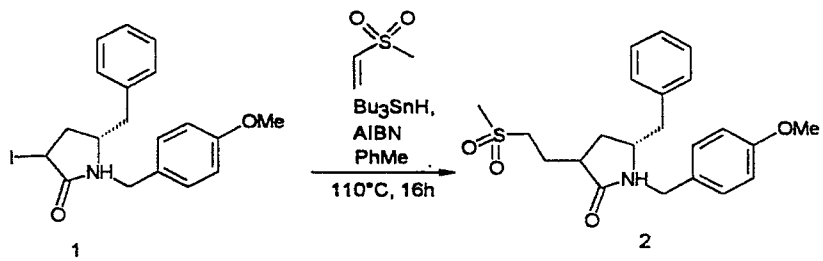


1 2

To protected lactam **1** (328 mg, 1.11 mmol) and N,N,N^1,N^1-tetramethylethylenediamine (Aldrich, 5.0 equiv., 5.55 mmol, 645 mg, 838 ml) in 15 ml dichloromethane at -15 °C, was added iodotrimethylsilane (Aldrich, 1.0 equiv., 1.11 mmol, 222 mg, 158 ml). After 15 min, iodine (Aldrich, 1.2 equiv., 1.33 mmol, 338 mg) was added in one portion and the reaction warmed to 0 °C. After 30 min the reaction was quenched with 5 ml each of 10% aqueous sodium sulfite and saturated aqueous sodium chloride. The orgnic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 2.5 x 10 cm, 2.5% diethylether in dichloromethane)

yielded 322 mg of diastereomeric iodolactam **2** as a white solid.

C.

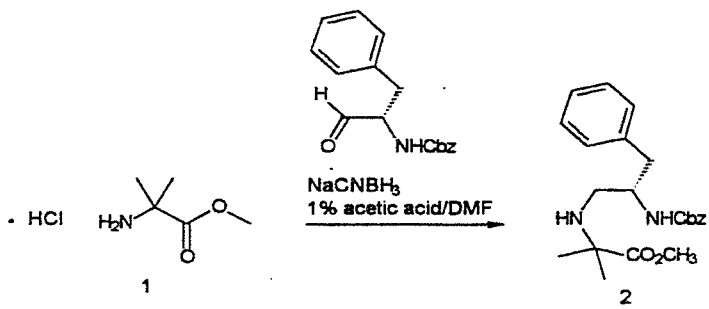


1 2

To iodolactam **1** (1.18g, 2.91 mmol) and methyl vinyl sulfone (Aldrich, 6.0 equiv., 17 mmol, 1.82 g, 1.5 ml) in 25 ml refluxing toluene was added tributyltin hydride (Aldrich, 1.3 equiv., 3.79 mmol, 1.10 g, 1.0 ml) and AIBN (Pfaltz & Bauer, 0.12 equiv., 0.35 mmol, 57 mg) as a solution in 5 ml toluene over 1.2 h. After 16 h the solvent was removed *in vacuo*, and the residue taken up in 200 ml diethyl ether and stirred with 20 ml 10% aqueous potassium fluoride (wt/v) at ambient temperature. After 3 h the orgnic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo* . Purification by flash column chromatography (silica gel, 5 x 20 cm, 2:1 ethyl acetate/hexanes) yielded 0.31g of diastereomeric sulfone **2** as a white solid.

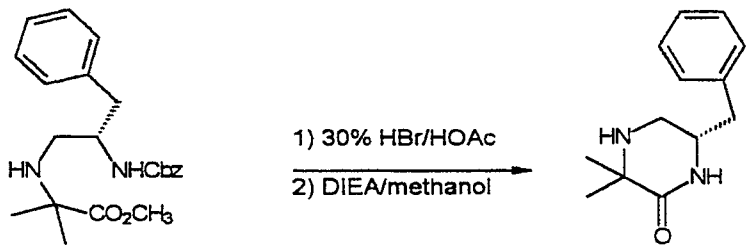
Example 10

A.



To a solution of solution of Cbz-L-phenylalinal (13 g, 45.9 mmol) in 1%AcOH/DMF (200 mL) mL was added aminoisobutyic acid methyl ester hydrochloride 1 (8.5 g, 55.1 mmol) with stirring at room temperature. Once homogeneous, solid sodium cyanoborohydride (8.6 g, 137.6 mmol) was added in one portion. Some bubbling was evident and the reaction was stirred overnight at room temperature. The reaction was quenched with water (20 mL) and concentrated in vacuo to about 100 mL. The concentrate was diluted with ethyl acetate and washed with water and brine followed by drying ($MgSO_4$). The organic layer was evaporated in vacuo to yield a yellow residue which was purified by MPLC (elutant 1:2 ethyl acetate : hexane) to afford amine product 2 (11.6 g, 66%).

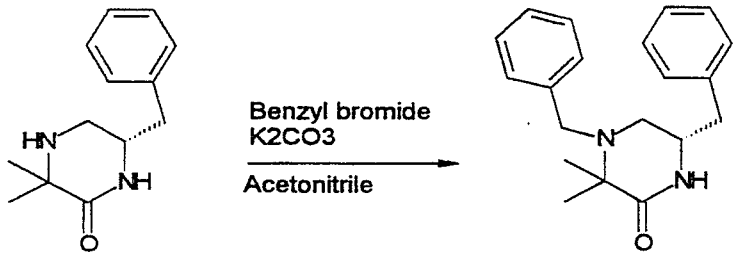
B.



1 2

To a solution of amine 1 (1.41 gr, 3.7 mmol) in methylene chloride (25 mL) was added 30% HBr in acetic acid (6 mL) via pipet. Vigorous gas evolution occurred and the reaction was allowed to stir overnight at room temperature. The mixture was then evaporated in vacuo and dried under high vacuum. The residue was then dissolved in methanol (25 mL) and to this solution was added diisopropylethylamine (5eq) and the reaction was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was taken up in ethyl acetate and washed with water, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) filtered and concentrated in vacuo to yield crude product . Flash silica gel chromatography (8% methanol / methylene chloride) afforded pure piperazinone product 2 (556 mg, 70 %).

C.

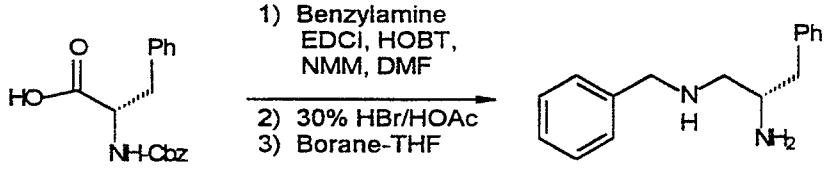


1 2

To a solution of piperazinone 1 (556 mg, 2.55 mmol) and potassium carbonate (1.06 g, 7.6 mmol) in acetonitrile was added benzyl bromide (364 uL, 3 mmol) and the reaction was stirred at room temperature overnight. The reaction was then filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with water and brine and dried ($MgSO_4$). The organic layer was then removed in vacuo and the residue was flash chromatographed (3% methanol in methylene chloride) to yield pure benzyl protected piperazinone product 2 (589 mg, 75%).

Example 11

A.

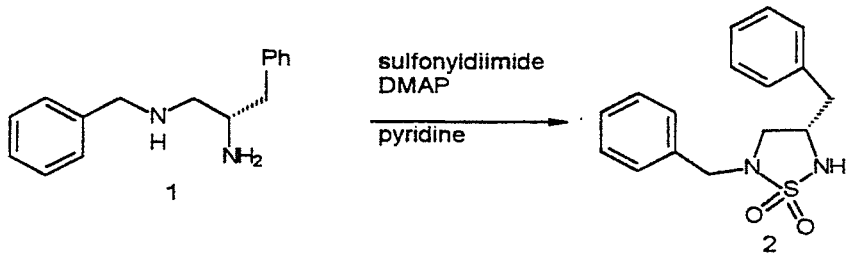


A solution of Cbz-(l)-Phenylalanine (15 gr, 50 mmol), HOBT (7.4g, 50mmol), N-methyl morpholine (5.5 mL, 50 mmol) and benzylamine (6 mL, 55 mmol) in 250 mL of DMF

was cooled to 0 °C and treated with EDCI (9.6 g, 50 mmol). The resulting mixture was stirred at 25 °C for 12h and the volatiles were removed in vacuo. Partitioning between ethyl acetate and 1N hydrochloric acid, followed by extraction with 10% sodium bicarbonate, drying over magnesium sulfate and evaporation of the solvent afforded the desired amide as a white solid (19.5g).

19g of the above material were dissolved in 280mL of 30% hydrogen bromide in acetic acid and stirred at 25 °C for 3h. The volatiles were removed and the residue was partitioned between water and ether. The aqueous layer was treated with excess 6N sodium hydroxide and extracted twice with ethyl acetate. Drying over magnesium sulfate and evaporation of the solvent afforded the desired amine as a pale yellow oil (14.0g), which was redissloved in 200 mL of tetrahydrofuran and treated with 200 mL of 1M borane-THF in tetrahydrofuran. The mixture was stirred at 25 °C for 72h and then heated to reflux for 4h. The solution was cooled and treated with 100 mL of methanol under vigorous gas evolution. The volatiles were removed and the resulting residue was dissolved in 150 mL of concentrated hydrochloric acid. After refluxing for 1h, the volatiles were removed and the residue was dissolved in 300 mL of 3N sodium hydroxide. Extraction with 3 times 250 mL of dichloromethane, drying over magnesium sulfate and chromatography on 2 inches of silica gel (2% methanol-dichloromethane) gave the desired diamine as a pale yellow honey (9.2g).

B.



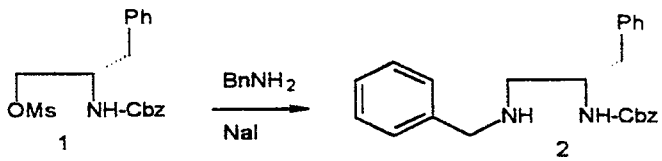
A solution of sulfonyldiimide (3.6 g, 36 mmol) in 100 mL of pyridine was heated to reflux and treated dropwise with a solution of the diamine 1 (7.2 g, 30 mmol) from the previous step in 20 mL of pyridine. After 2h of reflux, 15 mL of triethylamine and 0.4g of 4-dimethylaminopyridine were added and heating was continued for 12h. The volatiles were evaporated and the residue was partitioned between 1N hydrochloric acid and ethyl acetate. Extraction of the organic layer with saturated sodium bicarbonate, drying over magnesium sulfate and chromatography on silica gel (1:1 ethylacetate - hexanes) afforded the desired cyclic sulfamate 2 as a white solid (6.0g).

1H-HMR (CDCl3): 2.80(1H,dd), 2.96(1H,dd), 2.98(1H,dd), 3.32(1H,dd), 3.95(1H,m), 4.04(1H,d), 4.24(1H,d), 4.40(1H,d), 7.18(2H,d), 7.2-7.4(8H)

13C-NMR(CDCl3): 41.5, 50.0, 52.7, 53.8, 127.5, 128.0, 128.2, 128.3, 28.4, 128.5, 135.5, 136.0

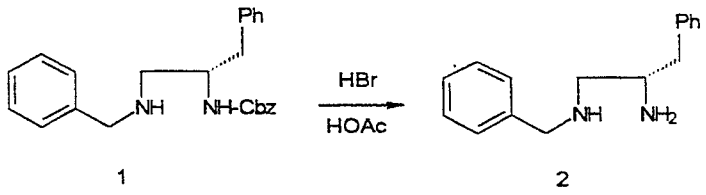
Example 12

A.



The Cbz-phenylalaninol mesylate 1 (280 mg, 0.77 mmol) was stirred in acetonitrile (5 mL) containing benzyl amine (413 mg, 3.85 mmol) and sodium iodide (115 mg, 0.77 mmol). The reaction was then refluxed for 24 hours. The reaction was then cooled to 25 °C and concentrated in vacuo. The crude oil was then purified by silica gel chromatography, eluting with CH_2Cl_2 with a gradient up to 1:1 CH_2Cl_2:EtOAc to provide 120 mg of the desired diamine 2.

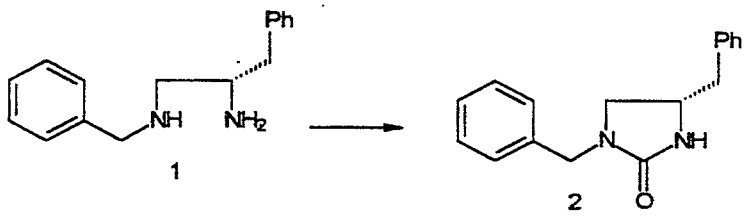
B.



The Cbz protected diamine 1 (120 mg, 0.32 mmol) was stirred in 2.0 mL of 30 % HBr in acetic acid for one hour. This was followed by concentration in vacuo. The crude oil was then dissolved into toluene and concentrated in vacuo two times followed by evacuation at approx. 1 mm Hg. The crude diamine was then purified by silica gel chromatography, eluting with

95:5:1, CH_2Cl_2:MeOH:NH_4OH to provide 71 mg (90 %) of the desired diamine 2.

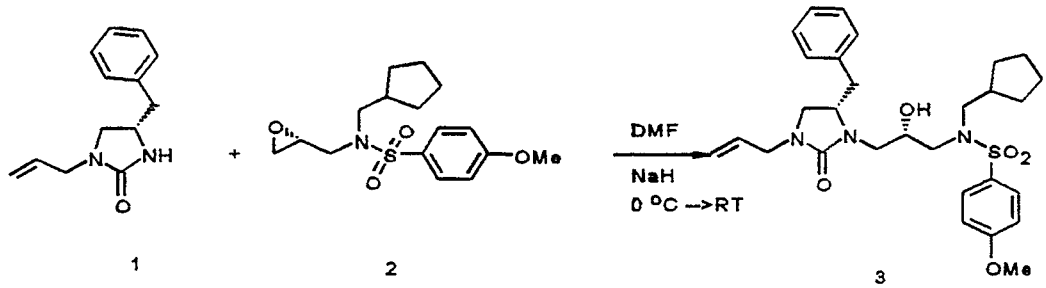
C.



The diamine 1 (56 mg, 0.23 mmol) was dissolved in 3.0 mL of CH_2Cl_2. This was followed by the addition of TEA (66 uL, 0.25 mmol) and then CDI (32 mg, 0.25 mmol). A new spot was observed by tlc after 2-3 hours (Rf = 0.29 in EtOAc on SiO_2). The reaction mixture was then concentrated and the residue was purified by silica gel chromatography, eluting with EtOAc, to provide 32 mg (52%) of the desired benzyl urea 2.

Example 13

Synthesis of Compound 1



1 2 3

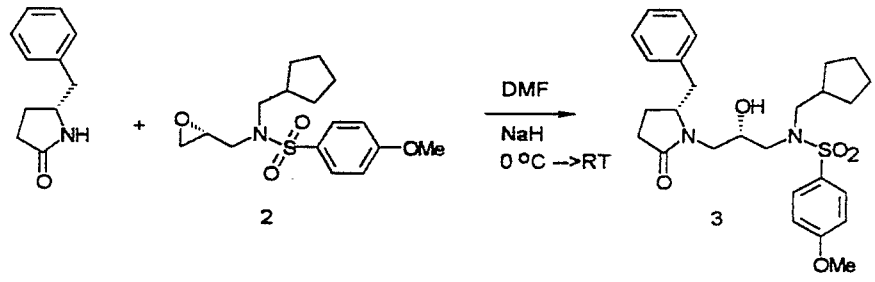
allyl urea	216 g/Mol	100mg	0.46 mmol
NaH, (60% in oil)	24 g/Mol	140.0 mg	9.7 mmol
epoxide	325.4 g/Mol	150.0 mg	0.46 mmol
DMF		2.0 mL	

The urea of Example 1C was dissolved in 1.0 mL of anhydrous DMF and cooled to 0 °C. This was followed by the addition of 140 mg NaH. The reaction turned darker over the next hour at 0 °C. This was followed by the dropwise addition of the epoxide as a solution in DMF (0.6 mL), washing with 300 uL of DMF. The reaction was then stirred one hour at 0 °C, followed by warming to 25 °C. Tlc indicated nearly complete conversion to two new products (Rf = 0.4 and 0.45 on SiO_2 with 2:1 hexane: ethyl acetate, between that of the epoxide and the urea). The reaction was then cooled to 25 °C and quenched by the addition of 3 mL of saturated sodium bicarbonate. The reaction mixture was then diluted by 15 mL of methylene chloride and washed by both saturated sodium bicarbonate and brine, (2 x 15 mL each). The organic portions were then dried over

sodium sulfate, filtered and concentrated in vacuo. The crude product was then purified by silica gel chromatography, eluting with 80% ethyl acetate: hexane to provide 35.0 mg of the desired alcohol.

Example 14

A.



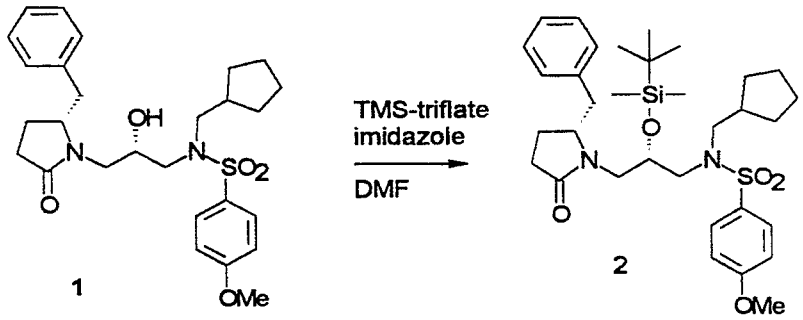
1	lactam	1.0 equiv., 295mgg
2	sulfonamide epoxide	1.1 equiv., 520mg
3	NaH, 60% in oil (Aldrich)	1.5 equiv, 102mg
4	DMF	8 mL

Lactam 1 was dissolved in 3mL of DMF and cooled to 0° C. To this solution was then added sodium hydride as a solid and the reaction was stirred for 40 min. at 0 °C. The anion solution was canulated into a solution of epoxide 2 in 3 mL of DMF. The reaction was stirred at 0 °C for 5 minutes, then warm to room temperature and stirred overnight (TLC (95:5, CH_2Cl_2 : MeOH) Rf (st mat.) = .26. Rf(prod) = .46). After 22 hours, the reaction was cooled to 0 °C, and quenched with H_20/EtOAc. The organic layer was washed with water(5X) and brine, dried ($MgSO_4$), filtered, and concentrated *in*

vacuo. The residue was then purified by silica gel chromatography (40% ether/ CH_2Cl_2) to yield product 3 (310mg, 37%).

Example 15

A.



1 2

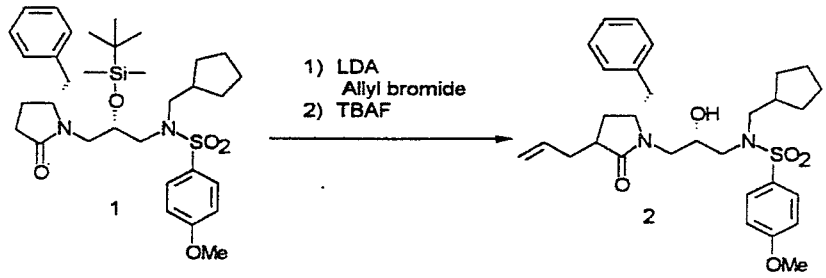
1	lactam	1.15g, 1.0 equiv.
	t-butyldimethylsilyl trifluoromethanesulfonate	1.5 equiv. + .5 eq., (1.06mL)
	imidazole	2.5 equiv + .5 eq, (470mg)

Lactam 1 was dissolved in 5mL of DMF and cooled to 0 °C. To this solution was then added imidazole followed by TBDMS-triflate. The reaction was then allowed to warm to room temperature. After approximatly 2 hours, an additional .5 eq.(80mg) of TBDMS-triflate and .5 eq.(265uL) of imidazole was added and the reaction was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and partitioned between H_2O/EtOAc. The organic layer was washed with water(5X) and brine, dried ($MgSO_4$),

filtered, and concentrated *in vacuo* to yield product 2 (1.5 gr,37%) which was used as is.

Example 16

Synthesis of Compound 7



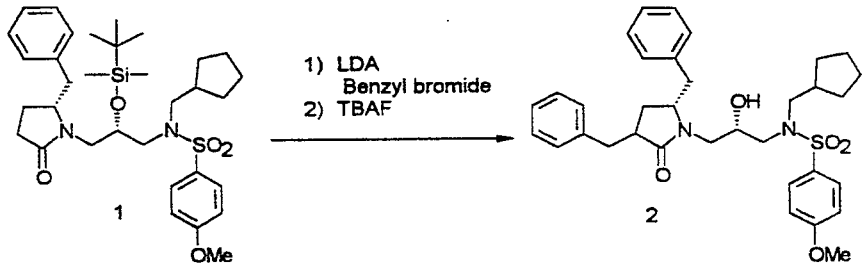
1	silyl-lactam	1.0 equiv.,23mg
	Allyl Bromide, (Aldrich)	2.1 equiv. , 7 uL
	LDA, 1.29M (Aldrich)	1.25 equiv , 36uL
	TBAF, 1.0M, (Aldrich)	2.5 equiv., 95uL:

Silyl protected lactam 1 was dissolved in THF and cooled to -78 °C. To this solution, was added LDA (1.25 eq) via syringe. After stirring for 30 minutes at -78 °C, allyl bromide was added via syringe. After 2 hours an additional 2ul of allyl bromide was added and the reaction was stirred at -78 °C for 2.5 hours, then warmed to room temp for 17 hours (TLC (2:8, ether:CH_2Cl_2) Rf (st mat.) = .56. Rf(silyl-prod) = .72). After this time, TBAF (1M in THF) was added and the reaction was stirred at room temperature for 7 hours (TLC (1:9, ether:CH_2Cl_2) Rf(prod) = .20). The reaction mixture was then partitioned between H_20/EtOAc

and the organic layer was washed with water and brine, dried (MgSO4) and filtered concentrated *in vacuo*. The residue was then purified by silica gel chromatography (10% ether/methylene chloride) to yield product 2 (6mg, 30% yield).

Example 17

Synthesis of Compound 20



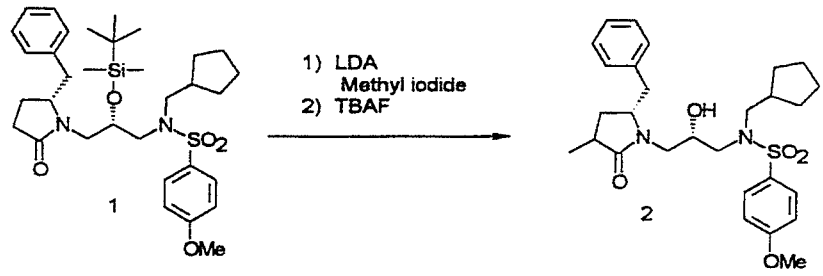
1	silyl-lactam	1.0 equiv., 122mg
	benzyl bromide, (Aldrich)	1.5 equiv. 42uL
	LDA, 1.29M (Aldrich)	1.4 equiv , 275ul
	TBAF, 1.0M, (Aldrich)	2.5 equiv., 625uL

Silyl lactam 1 was dissolved in dry THF (6mL) and cooled to -78 °C. To this solution was then added LDA and the reaction was stirred for 30 minutes at -78 °C after which time benzyl bromide was added via syringe. The reaction was stirred at -78°C until reaction was complete (1.5 hours, TLC (1:9, ether:CH_2Cl_2) Rf (st mat.) = .29. Rf(silyl-prod) = .62. Rf(BzBr) = .79). The reaction was then quenched at -78 °C with 6uL water and then TBAF (1M in THF was added and the reaction was warmed to room temperature and stirred for 3 hours (TLC

(1:9, ether:CH_2Cl_2) Rf(prod) = .28). The reaction was partition betweem H_20/EtOAc and the organic layer was washed with with water and brine, dried ($MgSO_4$) and filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (10% ether/ CH_2Cl_2) to yield benzyl product 2 (71mg, 48%).

Example 18

Synthesis of Compound 16

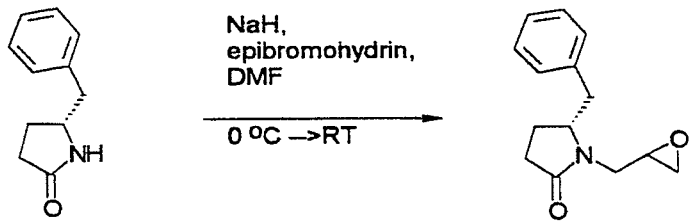


1	silyl-lactam	1.0 equiv.,66mg
	Methyl iodide, (Aldrich)	1.6 equiv., 16uL
	LDA, 1.29M (Aldrich)	1.3 equiv , 110uL
	TBAF, 1.0M, (Aldrich)	3.0 equiv., 325uL:

The reaction for the above methylated compound was carried out as per the procedure described for compound 20 (Example 17) substituting methyl iodide for benzyl bromide on the scale described in the above table. The final compound was purified by silica gel chromatography using 10% ether/ CH_2Cl_2 to yield methylated product 2 (33mg, 60% yield).

Example 19

A.

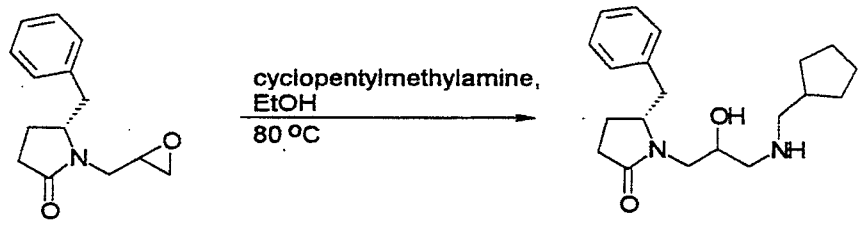


1 2

1	lactam	1.0 equiv., 400mg
	epibromohydrin	1.5 equiv., 280uL
	sodium hydride, 80% oil disp.	2.0 equiv, 126mg
	DMF	15mL

Lactam 1 was dissolved in dry DMF (15 mL) and cooled to 0 °C under a nitrogen atmosphere. To this solution was added sodium hydride (2 eq) in one portion and the reaction was stirred at 0 °C for 1 hour after which, epibromohydrin was added via syringe. After stirring for 5 min. at 0 °C the reaction was warmed to room temperature (TLC (EtOAc) Rf (st mat.) = .16. Rf(prod) = .23). After 1.5 hours at room temperature the reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was then washed with water(4X) and brine, dried (MgSO4) and filtered, and concentrate *in vacuo*. The residue was then purified by silica gel chromatagraphy (3:1 EtOAC:hexane) to yield 315mg(60%) of epoxide product 2 which was used as is in the next step.

B.

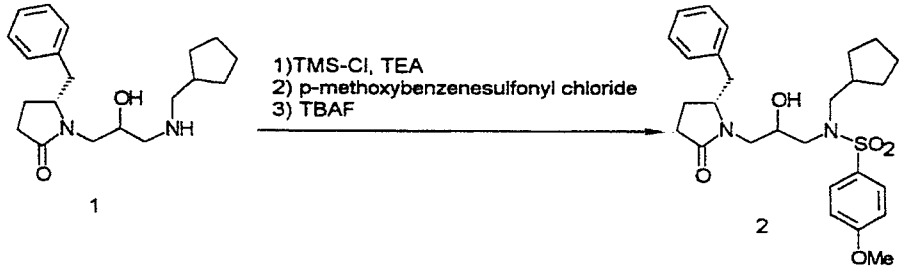


1 2

1	lactam	1.0 equiv., 315mg
	cyclopentylmethylamine	5.75 equiv., 775mg
	anhy. EtOH	3mL

Epoxide 1 was dissolved in 3 mL of EtOH and to this solution was added cylcopentylmethylamine. The reaction was heated to 80 °C for 2.5 hours (TLC (9:1,CH_2Cl_2:MeOH) Rf (st mat.) = .56. Rf(prod) = .13). The solvent was removed *in vacuo* and the residue was purified by silica gel chromatagraphy (3%MeOH/ CH_2Cl_2 to 10%MeOH/ CH_2Cl_2) to yield 224mg(50%) of amine product 2.

C. Synthesis of Compound 15



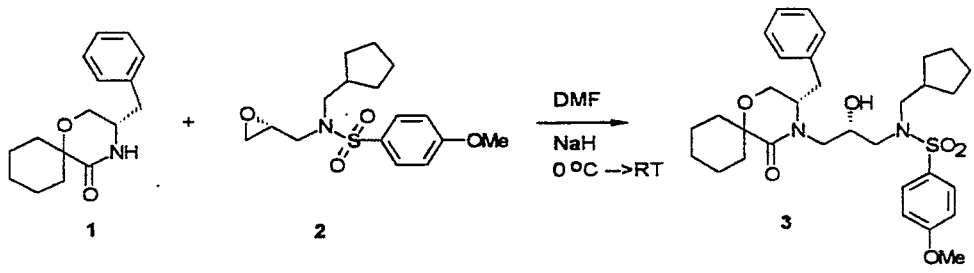
1 2

1	lactam	1.0 equiv., 315mg
	chlorotrimethylsilane	2.2 equiv., 112uL
	triethylamine	5.0 equiv., 280uL
	4-methoxybenzenesulfonylchloride	1.5 equiv., 124 mg
	TBAF, 1.0M	4.4 equiv., 1.78mL

Amine 1 from Example 19B was dissolved in methylene chloride and cooled to 0 °C. To this solution was added triethylamine (2.5 eq) followed by chlorotrimethylsilane. The reaction was then warmed to room temperature and stirred under nitrogen for 2.0 hours. An additional amount of triethylamine was added (2.5 eq) and 4-methoxybenzenesulfonyl chloride was added. The reaction was stirred at room temperature for 3 hours. After this time, TBAF (1M in THF) was added and the reaction stirred at room temperature for 1 hour. The solvent was removed *in vacuo*. and the residue partitioned between ethyl acetate and aqueous saturated bicarbonate solution. The organic layer was washed with water, brine, dried $MgSO_4$, filtered and the solvent removed *in vacuo*. (TLC (8:2, CH_2Cl_2: ether), Rf(upper diast.) = .21 Rf(lower diast.) = .12). The residue was purified by silica gel chromatagraphy (25% ether/CH_2Cl_2) to yield 52 mg(26%) of (upper diastereomer). The lower diastereomer was further purified by preperative TLC (1:1, ether:CH_2Cl_2) to give 23mg(12%) of the lower diastereomer.

Example 20

Synthesis of compound 47

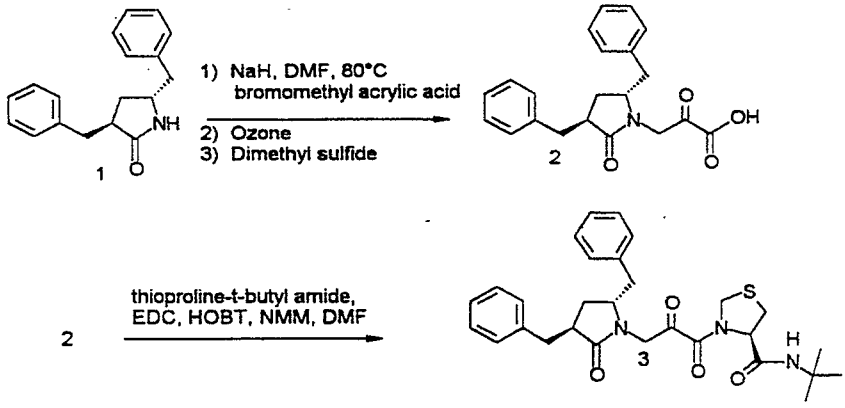


1 2 3

Morpholinone 1 was dissolved in 1 ml of anhydrous DMF, cooled to 0 C and to this solution was added 4.4 mg of NaH. The solution was brought to room temperature for 30 min and then cooled down to 0C before adding 0.20 g of epoxide 2. After heating for 5 hrs at 45 °C, the solvent was removed in vacuo and purified on silica gel yielding 111 mg of final product 2 (compound 47). M (ES+) =585 (M+1), 607.1 (M+Na). 1H NMR (CDCl3)= 7.52 (d, 2H), 7.30 (m, 5H), 6.95 (d, 2H), 4.05 (m, 1H), 3.87 (3H, s), 3.60 (m, 2H), 3.16 (m, 4H), 3.0 (m, 4H), 2.18 (1H, m), 1.97 (m, 2H), 1.60 (m, 14H), 1.23 (m, 4H).

Example 21

Synthesis of Compound 109

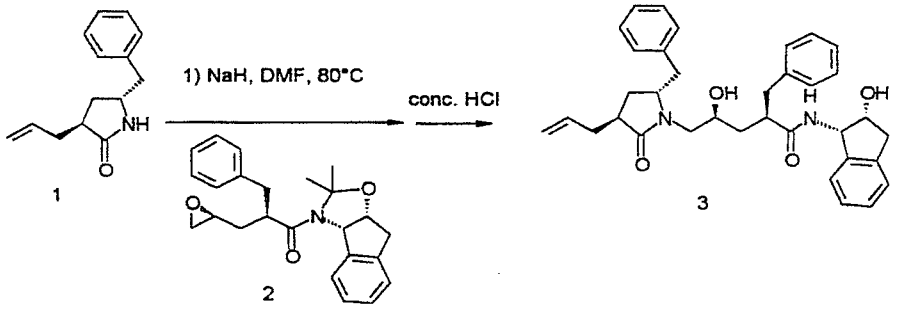


To a cooled solution (-78 °C) of benzyl lactam 1 (0.150g, 0.57 mmol) and bromomethyl acrylic acid (0.094g, 0.57mmol) in anhydrous THF (4.0mL) was added NaH (60%, 0.046g, 1.14 mmol) with stirring. The solution was allowed to gradually warm to room temperature and stir for 1.5h. The reaction mixture was then diluted with ethyl acetate (60mL) and washed with 1.0N HCl (2 x 10mL) and brine (2 x10mL). The organic layer was dried (magnesium sulfate), filtered, and evaporated to give an off white solid. This solid was dissolved in methylene chloride/methanol (80/20, 10mL) and through the cooled solution(-78 °C) was bubbled ozone for 10min. The solution was flushed with oxygen, warmed to 0 °C, and methyl sulfide (2.0mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stand for 1.0h. Evaporation of the solvent afforded crude product 2 as a yellow oil. To a solution of the acid 2 in anhydrous DMF (3.0mL) was added thioproline-t-butylamide (0.11g, 0.57mmol), hydroxybenzotriazole (0.77g, 0.57 mmol), N- methyl-

morpholine (0.62mL, 0.57mmol) and EDCI (0.11g, 0.57 mmol) respectively with stirring at room temperature. After 24h. at room temperature, the reaction mixture was evaporated and the residue was dissolved in ethyl acetate (100mL). The solution was washed with 1.0N HCl (2 x 20mL), 10% sodium carbonate (2 x 20mL), water (1 x 10mL), brine(1 x 10mL), filtered and evaporated to give 0.210g of a yellow oil. The oil was purified by column chromatography; hexane/ethyl acetate (60/40) to give compound 3 (0.050g, 18%) MS: M+1= 522; H NMR (chloroform-d) 1.35(d, 9H); 1.85(m,2H); 2.6(m, 3H); 2.85(m,1H); 3.15(m,2H); 3.40(m,1H); 3.8(m,1H); 4.1(m, 2H); 4.4(m,1H); 4.70(m,1H); 4.95(m, 1H); 6.1(d, 1H); 7.1(m,4H); 7.25(m,6H).

Example 22

Synthesis of Compound 80

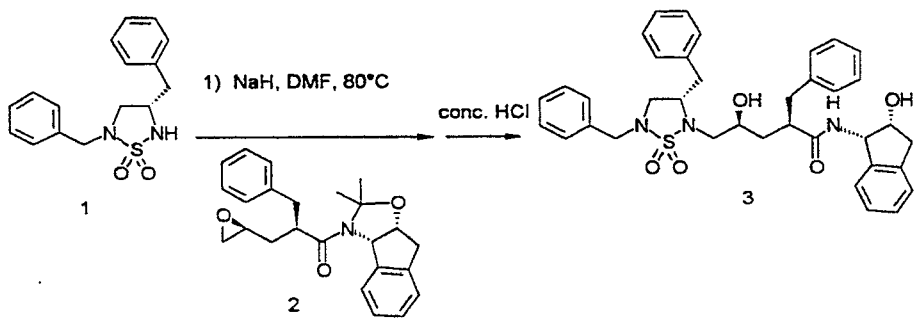


0.80g of allyl lactam 1 was dissolved in 1 ml of DMF, cooled to 0 °C and 89.5 mg of sodium hydride was then added. The solution was then brought up to ambient temperature for 30 min, again cooled down to 0 °C and 1.4 g of epoxide 2 was added. The reaction was warmed to 50 °C under N_2 blanket for 3 hrs. The resulting crude mixture was then chromatographed on silica gel

yielding 1.4g of 3 (63.7%). This amount was treated with 12 ml of 4N HCl in dioxane and 2 ml water for 30 min. The product was then chromatographed on C18rphplc, yielding 0.36g of two diastereomers, subjected to chiral separation, which resulted in 138 mg of pure diastereomer 3. MS (ES- 551.3 (M-1)), ES+, 553.3 (M+1) and 575.3 (M+Na). 1H NMR (CDCl3)= 7.20 (m, 14H), 6.26 (m, 1H), 5.62 (m, 1H), 5.24 (m, 1H), 4.97 (m, 2H), 4.23 (m, 1H), 3.83 (m. 2H), 3.61 (m, 1H), 2.95 (m, 10H), 2.40 (m, 1H), 2.24 (m, 1H), 2.04 (m, 1H), 1.95 (m, 2H), 1.70 (m, 2H).

Example 23

Synthesis of Compound 91



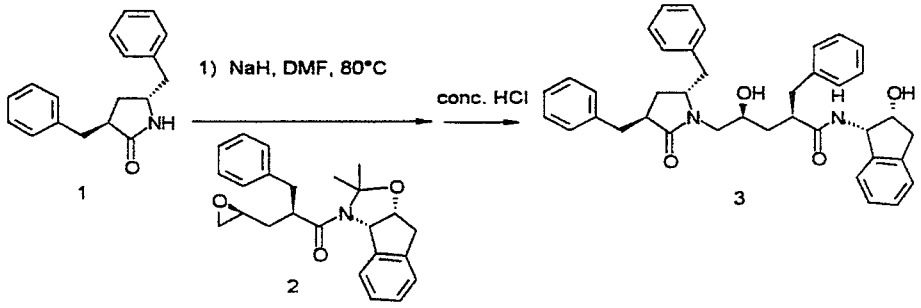
A solution of cyclic sulfamate 1 (0.1g, 0.33mmol) in 2 mL of dimethyl formamide was cooled to 0 °C and treated with of 60% sodium hydride (0.005g, 0.13 mmol) in oil. The mixture was stirred at 25 °C for 1.5h and treated with of epoxide 2 (0.125g, 0.33mmol) The resulting mixture was stirred at 60 °C for 3h, more sodium hydride (0.005g) was added and heating was continued over night. The volatiles were removed in vacuo and the residue was dissolved in 2 mL of 4M hydrogen

chloride in 1,4-dioxane. Water (0.5 mL) was added and the mixture was stirred for 6h at 25 °C. The reaction mixture was diluted with ethyl acetate and extracted with 10% soduim bicarbonate. Drying over magnesium sulfate and removal of the solvents gave a yellow gum, which was subjected to C-18 preparative HPLC (acetonitrile-water gradient). The desired material 3 was isolated as a minor fraction (9 mg) as a white solid

1H-NMR(CDCl3): 2.10(2H), 2.70(2H), 2.8-3.2(8H), 3.4(1H), 3.58(1H), 4.02(1H), 4.15(1H), 4.22(2H), 5.30(1H), 5.86(1H), 7.06(2H), 7.1-7.4(16H).

Example 24

Synthesis of Compound 83



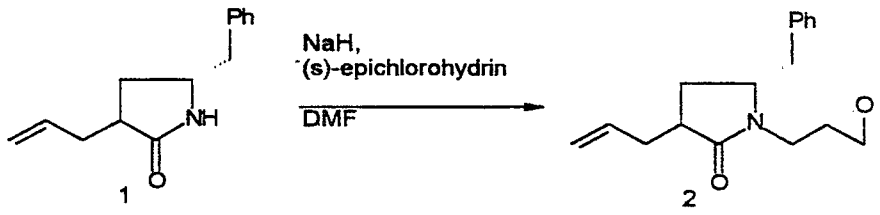
To a cooled solution (0 °C) of compound 1 (0.190g, 0.72mmol) in anhydrous DMF (10mL) was added NaH(60%, 0.028g, 0.72mmol) with stirring. The solution was allowed to warm to room temperature and stir for 1.0h. Compound 2 (0.275g, 0.73mmol) was added at room temperature and the mixture was heated at 60 °C for 5.0h. The solution was evaporated and the reside was partioned between ethyl acetate (150mL) and water

(30mL). The organic layer was washed with water (2 x 10mL), brine (25mL), dried ($MgSO_4$), filtered, and evaporated to give a grey oil. The oil was purified by column chromatography: hexane/ethyl acetate (60/40) to give 0.23g (50%) of the acetonide protected product. The acetonide (0.185g, 0.29mmol) was dissolved in isopropanol (10mL) and treated with conc. HCl (3.0mL) at room temperature. After 1.5h., the solution was adjusted to pH 11 with 3.0N NaOH and then concentrated. The aqueous solution was extracted with ethyl acetate (3 x75mL). The ethyl acetate was dried ($MgSO_4$) and evaporatated to give a clear film. The crude product was purified by column chromatography: hexane/ethyl acetate (45/55) to give the product as a white solid (0.090g, 50%). Preparative HPLC on chiral phase (isopropanol-hexane gradient) yielded the desired diastereomer 3 (10mg) along with a 1:1 mixture of the desired diastereomer and an additional epimer (50mg). MS: M+1= 603 H NMR (chloroform-d) 1.80(m, 6H); 2.50(m,1H); 2.60(m, 2H); 3.0(m,8H); 3.60(m,1H); 3.70(m,1H); 3.95(m,1H); 4.25(m,1H); 5.30(m,1H); 6.00(m,1H); 7.05(m,4H); 7.25(m,15H).

Example 25

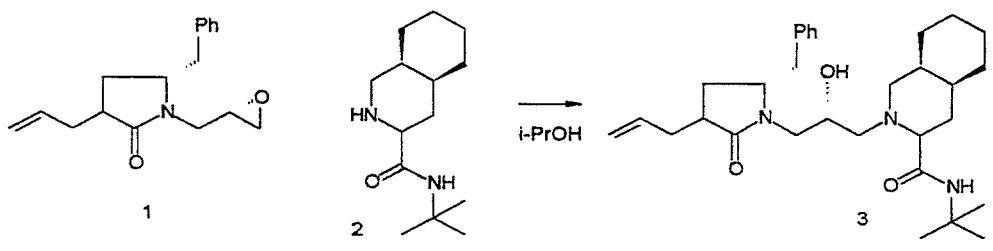
Synthesis of Compound 8

A.



Allyl lactam 1 (443 mg, 2.06 mmol) was dissolved in DMF (2 mL) and to this solution was added sodium hydride (2.2 mmol). The reaction mixture was stirred at room temperature for 1 hr after which (s)-epichlorohydrin (172 ul, 2.2 mmol) was added neat. The reaction was stirred at room temperature for 4 hr, diluted with water (20 mL) and extracted with ethyl acetate. The organic layer was then washed with water, brine and dried ($MgSO_4$) and filtered. Concentration in vacuo afforded crude epoxide product 2 which was used without further purification.

B.



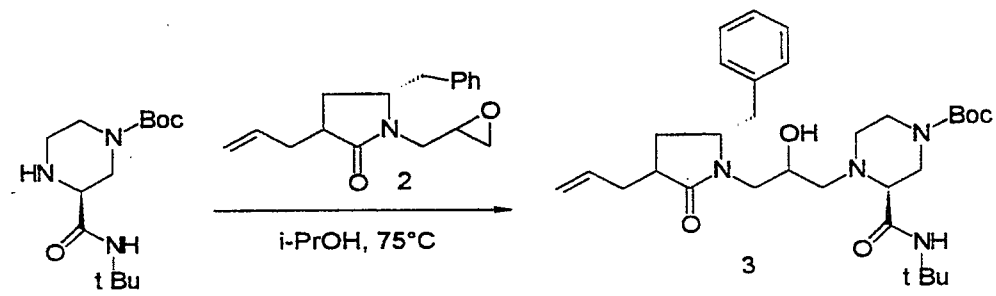
Lactam epoxide 1 (180 mg, 0.66 mmol) and decahydroisoquinoline 2 (160 mg, 0.66 mmol) were heated

to 80 °C in isopropanol. After three hours the reaction was cooled to 25 °C and stirred for 48 hours at room temperature. The reaction was then concentrated *in vacuo*. Purified by silica gel chromatography, eluting with 25 % EtOAc : Hexanes, providing 90 mg (90% pure by HPLC) of desired product 3.

Example 26

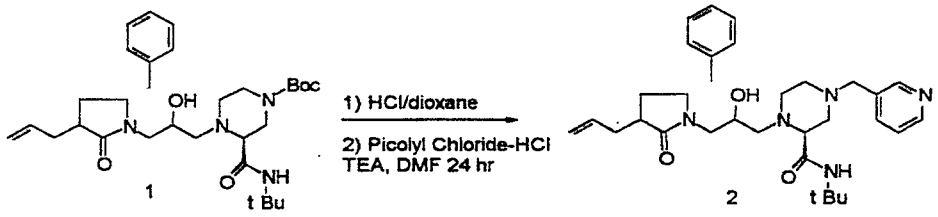
Synthesis of Compound 9

A.



The Boc protected piperazine 1 (21.4 mg, 0.081 mmol), was dissloved in 1.5 mL of i-PrOH. This was followed by the addition of the lactam epoxide 2 (18.3 mg, 0.068 mmol). The reaction vessel was then fitted with a reflux condenser and heated to 75 °C for 16 hours. TlC indicated complete consumption of both starting materials and formation of a new material. The reaction was then cooled to 25 °C and concentrated in vacuo. The complete consumption of epoxide was confirmed by both tlc and ^{1}H NMR. The crude addition product was then used without further purification.

B.



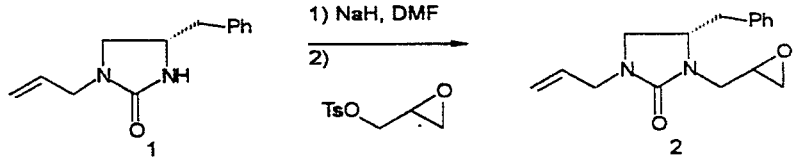
The Boc protected piperazine addition product 1 from the previous step was stirred for 2 hours in 1.0 mL of 4N HCl/dioxane. This was followed by concentration in vacuo. The crude solid was then dissolved in 10 mL of CH_2Cl_2 and washed by 2 x 10 mL of each saturated aqueous sodium bicarbonate and saturated aqueous brine. The combined organic portions were then dried over $MgSO_4$, filtred and concentrated in vacuo to provide the freebase of the desired intermediate. The crude amine was then dissolved in 1.0 mL of DMF at 25 °C. This was followed by the addition of the hydrochloride salt of 3-picolyl chloride (0.081 mmol). After stirring 5 minutes triethylamine (300 uL, mmol) was added. The reaction was then stirred for 36 hours the reaction was quenched by the addition of 1.0 mL of saturated aqueous sodium bicarbonate. The reaction mixture was then diluted by the addition of 10 mL of diethyl ether and washed by 2 x 10 mL of each saturated aqueous sodium bicarbonate and saturated aqueous brine. The combined organic portions were then dried over $MgSO_4$, filtered and concentrated in vacuo to provide the crude product. Purification of the crude solid was carried out by silica gel chromatography (1000 uM SiO_2 prep. plate) eluting with 20 % MeOH/CH_2Cl_2. This provided 3.1 mg of the desired product 2, with 96 % purity by HPLC. The

overall yield for addition, deprotection of N-Boc and coupling with 3-picolyl chloride was 9 %.

Example 27

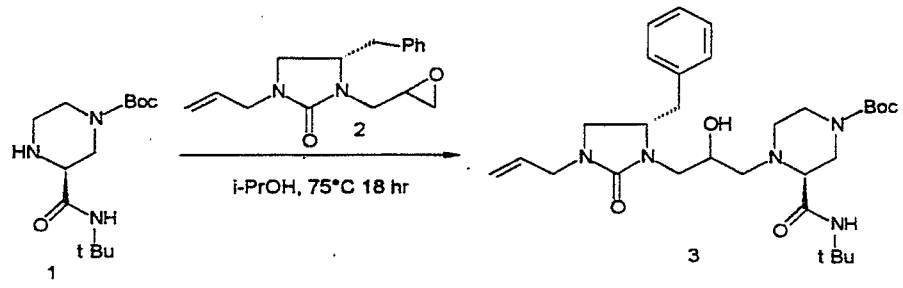
Synthesis of Compound 3

A.



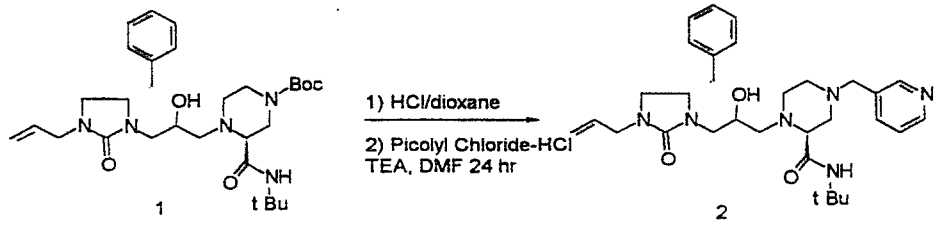
Allyl urea 1 (195.2 mg, 0.09 mmol) was dissolved in 6.0 mL of DMF and cooled to 0 °C. This was followed by the addition of NaH (54 mg, 1.0 mmol). The glycidyl tosylate (410 mg, mmol) was then added as a solid. The reaction was stirred for 4 hours at 25 °C and then quenched by the addition of 4 mL of saturated aqueous sodium bicarbonate. The reaction was then extracted by 10 mL of Et_2O. The organic layer was then washed by 10 mL of saturated aqueous sodium bicarbonate and 2 x 10 mL of saturated brine. The combined organic portions were then dried over MgSO4, filtered and concentrated in vacuo to provide the desired epoxide 2 (180 mg, 73 % yield). The epoxide was then used without further purification.

B.



Piperazine 1 (25.7 mg mmol) and epoxide 2 (22.6 mg, mmol) were heated to 75 °C in 1.5 mL of i-PrOH for 18 hours. After cooling to 25 °C the crude reaction mixture was concentrated in vacuo. Complete consumption of the epoxide was apparent by both tlc and ^1H NMR.

C.

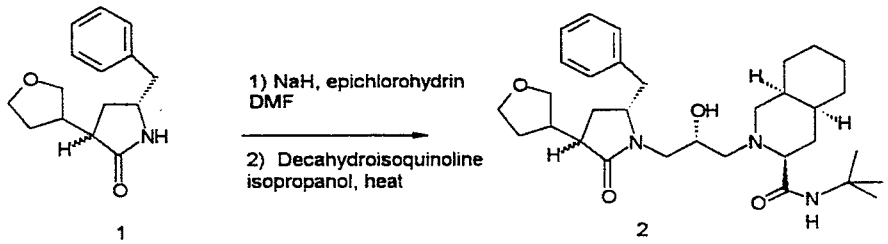


The Boc protected piperazine 1 from the previous step was stirred for 1.5 hours in 1.0 mL of 4 N HCl in dioxane. This was followed by concentration in vacuo. The crude hydrochloride salt was then dissolved in 10 mL of CH_2Cl_2 and washed by 10 mL of both saturated sodium bicarbonate and saturated brine. The organic portion was then dried over $MgSO_4$, filtered and concentrated in vacuo. The free amine was then taken up in 1 mL of DMF. This was followed by the addition of 3-picolyl chloride HCl salt (50 mg, mmol) and

triethyl amine (300 uL), respectively. The reaction was then stirred at 25 °C for 30 hours. The reaction was then quenched by the addition of 2 mL of saturated sodium bicarbonate and diluted by 10 mL of Et_2O. The organic portion was then washed by 10 mL of saturated sodium bicarbonate and 2 X 10 mL of saturated brine. The combined organic portions were then dried over $MgSO_4$, filtered and and concentrated in vacuo. The crude material was purified by silica gel chromatography (1000 uM prep. plate) eluting with 3:1, CH_2Cl_2:MeOH to provide 8.8 mg of the desired product 2. The overall yield for addition, deprotection of the N-Boc and reaction with 3-picolyl chloride was 19.3%.

Example 28

Synthesis of Compound 62



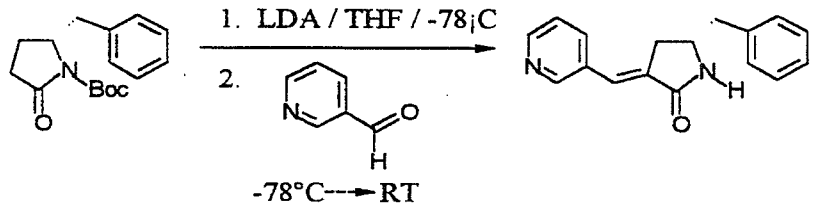
The THF lactam 1 (0.4 mmol) was dissolved in dry DMF at 0 °C and to this solution was added sodium hydride (0.47 mmol). After 30 min of stirring, (s)-epichlorohydrin (0.47 mmol) was added and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with 0.5N HCl, saturated $NaHCO_3$ and brine, followed by drying ($MgSO_4$), filtration and

concentration in vacuo to yield product (118 mg, crude) which was used as is. The lactam-epoxide (0.4 mmol, crude) was dissolved in isopropanol (2 mL), and to this solution was added decahydroisoquinoline t-butylamide (0.7 mmol). The mixture was then heated to 80 °C and stirred overnight. The reaction mixture was cooled and concentrated to dryness in vacuo, the residue of which was applied to a preperative TLC plate and eluted with 100% ethyl acetate to yield pure product (88 mg, 42%) as a mixture of diastereomers.

Example 29

Synthesis of Compound 92

A.

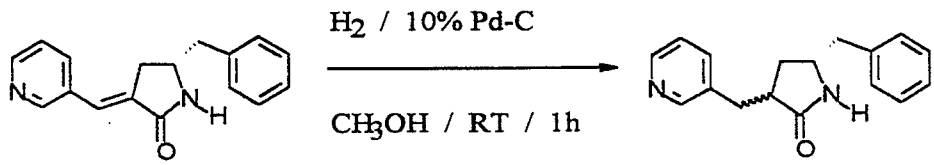


A stirred, cooled (-78 °C) solution of 1.4 g (5.0 mmol) of pyrrolidinone in 35 mL of anhydrous tetrahydrofuran was treated in a dropwise fashion with 3.6 mL (7.2 mmoL) of lithium diisopropylamide. The resultant solution was stirred for 70 min, and subsequently treated with 0.57 mL (6.0 mmoL) of 3-pyridine carboxaldehyde. The homogenous solution was allowed to ambiently warm to room temperature (RT), and stirring was continued overnight. The reaction mixture was diluted with 400 mL of dichloromethane, washed once

with 150 mL of water, dried (magnesium sulfate), filtered, concentrated, and purified on silica gel using 3:1 ethyl acetate/hexanes as the eluent, affording 0.6 g (46%) of the desired compound as a golden oil which solidified upon standing.

^{1}H NMR (d6-DMSO, 400MHz) 8.65 (s, 1H); 8.47 (m, 2H); 7.83 (d, J = 8.0 Hz, 1H); 7.41 (m, 1H); 7.23 (m, 5H); 7.03 (t, J = 2.7 Hz, 1H); 3.96 (m, 1H); 3.07 (m, 1H); 2.89 - 2.65 (series of m, 3H). M+H (265.2).

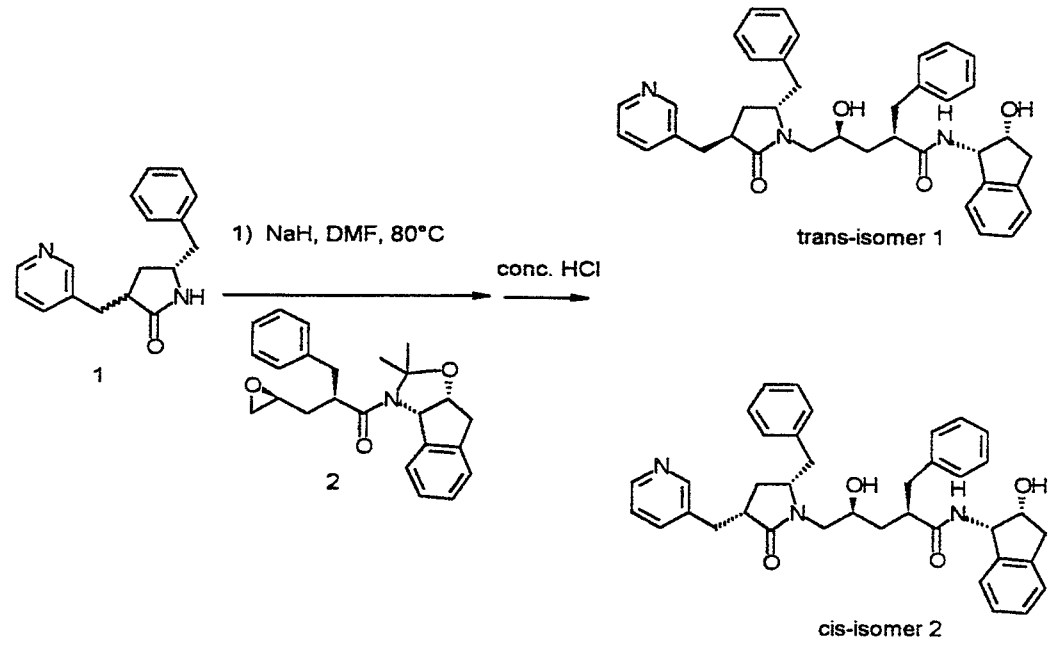
B.



A vigorously stirred suspension of 330 mg (1.25 mmoL) of eneamide and 80 mg of 10% palladium on carbon (Degussa) in 12mL of anhydrous methanol was hydrogenated (Hydrogen balloon) for 1 h. The mixture was diluted with 100 mL of methanol, carefully filtered, concentrated, and purified on silica gel using ethyl acetate as the eluent, affording 295 mg (89%) of an isomeric mixture of the desired compounds as a golden oil which solidified upon standing.

^{1}H NMR (d6-DMSO, 400MHz) 8.36 (s, 2H); 7.88 (s, 1H); 7.56 (d, J = 7.9 Hz, 1H); 7.27 - 7.12 (m, 7H); 3.66 (m, 1H); 2.96 - 2.37 (series of m, 7H). M+H (267.2); M+Na (289.2)

C.



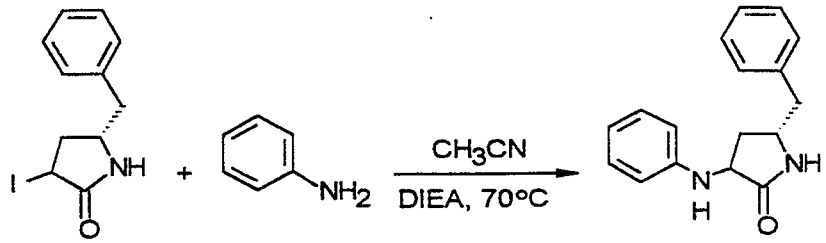
The lactam obtained above was coupled to the corresponding epoxide according to the protocol used for Example 24. The final purification was performed on silica gel (2% 2M ammonia-methanol in dichloromethane) to give the cis- and the trans-lactam diastereomers each as white solids.

trans-isomer 1: Rf: 0.20 ^{1}H NMR (CDCl3,. 400MHz) : 1.62(2H,m), 1.86(4H,m), 2.19(1H,m), 2.63(2H,m), 2.78-3.10(8H,m), 3.65(1H,m), 3.75(1H,bt), 3.95(1H,t), 4.27(1H,t), 5.24(1H,m), 6.32(1H,d), 7-7.4(14H,m), 8.22(1H,s), 8.34(1H,s). M+H (604)

cis-isomer 2: Rf: 0.18. ^{1}H NMR (CDCl3,. 400MHz) : 1.35(1H,m), 1.60(2H,m), 1.95(2H,m), 2.19(1H,dd),

2.48(1H,dd), 2.60(1H,m), 2.8-3.05(5H,m), 3.10(1H,dd), 3.26(1H,dd), 3.60(1H,m), 3.78(1H,m), 3.99(1H,m), 4.15(1H,bs), 4.24(1H,t), 5.24(1H,m), 6.18(1H,d), 7.02(2H,d), 7-7.3(10H,m), 7.41(1H,d), 8.25(1H,s), 8.40(1H,d). M+H (604)

Example 30

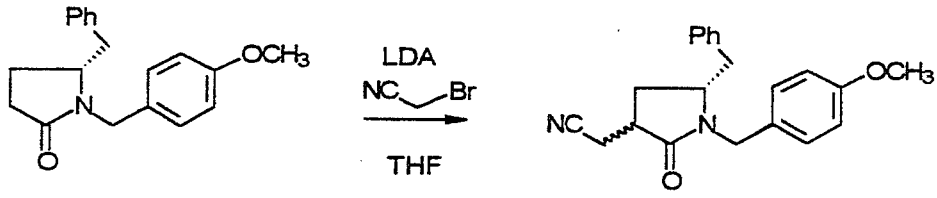


1 2 3

The iodolactam 1 (0.43 mmol) was dissolved in dry acetonitrile in a high pressure tube and to this solution was added diisopropylethylamine (Pierce, 0.65 mmol) followed by aniline 2 (Aldrich, 0.47 mmol). The tube was sealed and the reaction heated to 70 °C with stirring overnight. The reaction was cooled to ambient temperature, solvent removed *in vacuo*, and the residue taken up in ethyl acetate/water. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 1:1 ethyl acetate/hexanes to give 61 mg of product 3; TLC R_f = 0.29 (1:1 ethyl acetate/hexanes); HPLC Rt = 12.6 min (96%); MALDI-TOF MS *m/z* 267 (M^+).

Example 31

A.



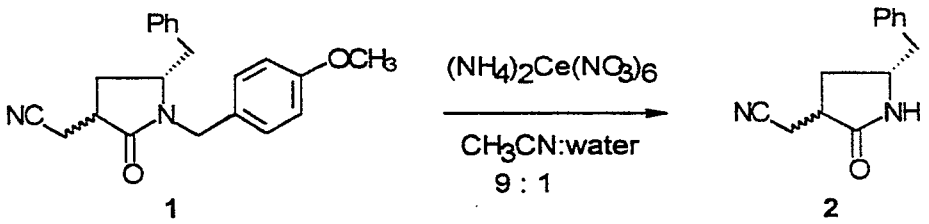
1 2

PMB lactam **1** (1.5 g, 5.07 mmol) was dissolved in THF (12 mL), cooled to -78 °C, and to this solution was added LDA (6.6 mmol , 1.3 eq.), over 7 minutes to give a greenish-brown anion. The reaction mixture was stirred at -78 °C for 55 minutes after which a solution of bromoacetonitrile (400 ul, 0.75 mmol, 1.1 eq.) was added over 2 minutes while keeping the internal reaction temperature at <-65 °C. The reaction was stirred at -78 °C for 2 hours, then warmed to room temperature and stirred for an additional 16 hours. The reaction was cooled to -50 °C and quenched with saturated ammonium chloride solution. The reaction was partitioned between ethyl acetate and a saturated bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with water, brine and dried (MgSO4) and filtered. Concentration *in vacuo* afforded 1.6g of crude material, which was purified by silica gel chromatography to give 640 mg (38%) of the desired material 2.

^{1}H NMR ($CDCl_3$) d 7.31 (m, 3H), 7.18 (d, 2 H), 7.09 (d, 2H), 6.90 (d, 2H), 5.08 (d, 1H), 3.92 (d, 1H), 3.81 (s,

3H), 3.70 (m, 1H), 2.92 (dd, 1H), 2.72 (m,2H), 2.55 (dd,1H), 2.42 (m,1H), 2.19 (dd,1H), 1.81 (m, 1H).

B.



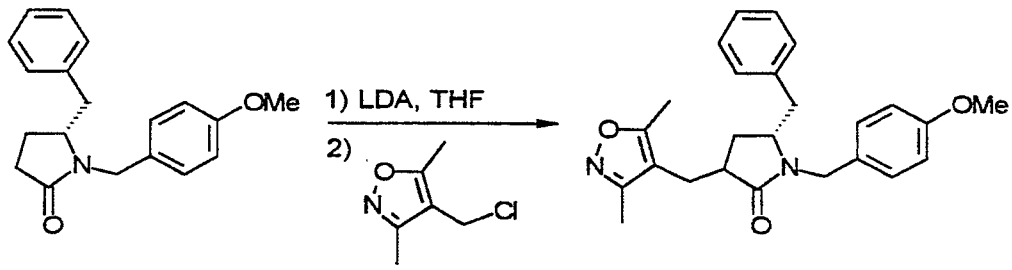
1 2

PMB lactam **1** (640mg, 1.9 mmol) was dissolved in CH_3CN (9 mL). 1 mL of water was added followed by 3.1 g of cerium ammonium nitrate. The reaction went from dark amber to light orange within 5 minutes and was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and a saturated bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with saturated bicarbonate solution, water, brine, dried (MgSO4) and filtered. Concentration *in vacuo* afforded 590 mg of crude material, which was purified by silica gel chromatography (9:1 CH_2Cl_2 : EtOAc) to give 285 mg (70%) of the desired material 2. HPLC suggests 2 diastereomers, retention time 9.95 min.(major) and 10.17 min. (minor).

^1H NMR ($CDCl_3$) d 7.37 (m, 2H), 7.28 (m, 1 H), 7.20 (m, 2H), 5.74 (br s, 1H), 3.95 (m, 1H), 2.85 (dd, 1H), 2.79-2.65 (m, 3H), 2.55 (dd, 1H), 2.27 (m,2H).

Example 32

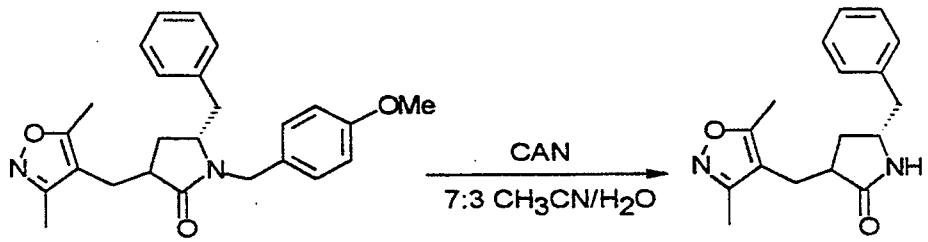
A.



1 2 3

The PMB lactam 1 (0.46 mmol) was dissolved in dry THF at -78 °C and to this solution was added lithium diisopropylamide (Aldrich, 1.5 M in cyclohexane, 0.65 mmol). The solution was stirred for 15 minutes at -78 °C and 4-(Chloromethyl)-3,5-dimethylisoxazole 2 (Acros Organics, 0.56 mmol) was added. The cooling bath was removed and the solution warmed to room temperature and stirred overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 10% diethyl ether/dichloromethane to give 53 mg of product 3 as a mixture of diastereomers.

B.

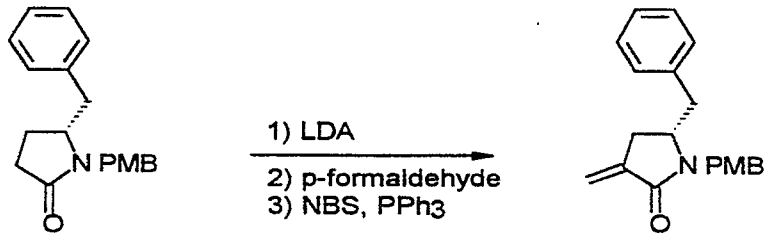


1 2

Lactam 1 (0.13 mmol) was dissolved in 7:3 acetonitrile/water. Ceric ammonium nitrate (Aldrich, 0.26 mmol) was added and the mixture was stirred at ambient temperature until the starting material was no longer evident by TLC. Acetonitrile was removed *in vacuo*, and the residue taken up in ethyl acetate/water. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 8% MeOH in dichloromethane to give 21 mg of product 2; TLC R_f = 0.47 (8% MeOH/CH_2Cl_2).

Example 33

A.



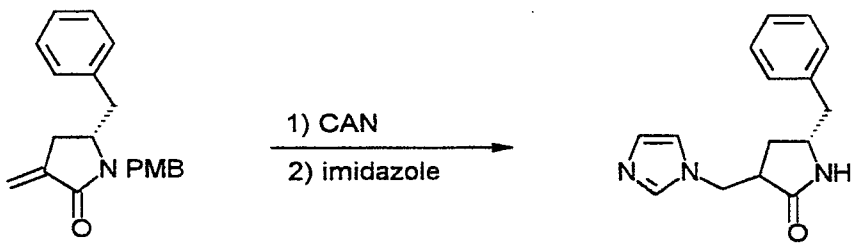
1 2

Lactam 1 (1.43 mg, 4.86 mmol) was dissolved in anhydrous THF (25 mL) and cooled to -78 °C. This was followed by the addition of 3.9 mL of LDA (5.83 mmol, 1.2 eq.). The anion solution was stirred at -78 °C for 45 minutes and then cannulated into a -78 °C solution of p-formaldehyde (437 mg) in 25 mL of THF, washing with 1 mL of THF. The reaction was warmed to room temperature over 4 hr and stirred overnight. The reaction was quenched by the addition of 10 mL of a saturated sodium bicarbonate, and concentrated *in vacuo* to remove the THF. The crude reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layers was then washed with water, brine and purified by silica gel chromatography (gradient of 50 to 75 % ethyl acetate: hexanes), to provide 584 mg (45%) of the desired alcohol, as well as 265 mg of recovered starting material.

The alcohol (316mg, 0.979 mmol) was then dissolved in 3 mls of CH_2Cl_2 and added to a 0 °C solution of triphenyl phosphine (734 mg, 2.8 EQ.) and NBS (534 mg, 3 EQ.) in 3 mls of CH_2Cl_2. After 1 hour the reaction was quenched by the addition of 10 mL of Et_2O. The organic layer was then filtered and the filtrate washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$) and filtered. Concentration *in vacuo* afforded the crude product which was purified by silica gel chromatography (CH_2Cl_2) to provide 151 mg (40% of the bromide.

The bromide (87.2 mg, 0.28 mmol) was dissolved in 2 mL of benzene and treated with imidazole (46mg, 3 EQ.). After heating to 125 °C for 20 hours the reaction was cooled to 25 °C and concentrated *in vacuo*. The crude product which was purified by silica gel chromatography (5 % MeOH/CH_2Cl_2), to provide the addition product (50%) and the elimination product (2) in a 50 % yield.

B.



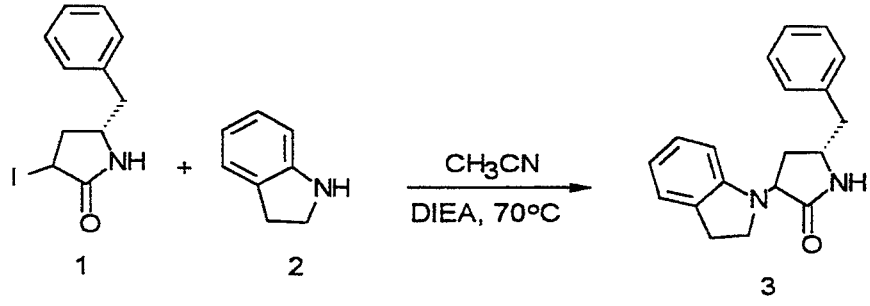
1 2

The lactam 1 (621 mg, 2.02 mmol) was dissolved in 7 mL acetonitrile, followed by the addition of H_2O (3 mL). This was followed by the addition of CAN, 3.32 g (6.06 mmol, 3 EQ.). The reaction was stirred at 25 °C for 1

hour. After concentrating the reaction *in vacuo*, the crude material was resuspended in ethyl acetate and washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$) and filtered. Concentration *in vacuo* afforded the crude product which was purified by silica gel chromatography (3% methanol:CH_2Cl_2) to procide the desired unprotected lactam (122 mg, 32 %)

The α,β-unsaturated lactam (55 mg, 0.29 mmol) was then heated to 130 °C in 2 mL of benzene containing imidazole (30 mg, 0.44 mmol) for 24 hours. After cooling to 25 °C, the reaction mixture was concentrate *in vacuo*. The crude material was purified by silica gel chromatography, eluting with 5% methanol:CH_2Cl_2 to provide 46.7 mg of the desired addition product (63 %) as well as 15.7 mg of recovered starting olefin (29 %).

Example 34

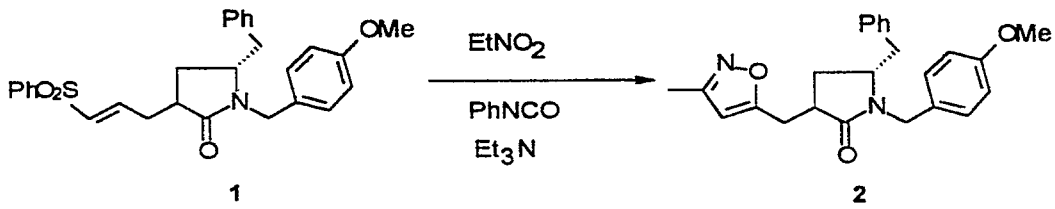


The iodolactam 1 (0.45 mmol) was dissolved in dry acetonitrile in a high pressure tube and to this solution was added diisopropylethylamine (Pierce, 1.35 mmol) followed by indoline 2 (Aldrich, 0.54 mmol). The

tube was sealed and the reaction heated to 70 °C with stirring overnight. The reaction was cooled to ambient temperature, solvent removed *in vacuo*, and the residue taken up in ethyl acetate/water. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with ethyl acetate to give 113 mg of product 3; TLC R_f = 0.39 (ethyl acetate); HPLC Rt = 13.1 min (92%); MALDI-TOF MS *m/z* 293 (M^+).

Example 35

A.

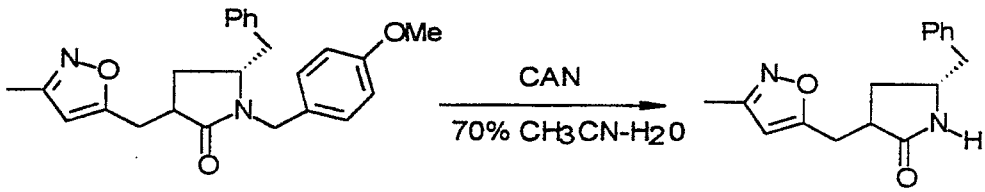


1 2

In an oven-dried 100 mL round-bottomed flask, the vinyl sulfone PMB lactam **1** (1.2126 g, 2.55 mmol) was dissolved in 50 mL of C_6H_6. Phenyl isocyanate (2.0 mL, 18.4 mmol) was added via syringe followed by the dropwise addition of nitroethane (0.4 mL, 5.56 mmol). Triethylamine (2.0 mL, 14.3 mmol) was added dropwise. The solution was refluxed for 15 minutes and cooled. A white solid precipitated during the heating period. The mixture was cooled, poured into water and extracted

with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to afford a brown oil that was chromatographed to afford the isoxazole PMB lactam 2 (901 mg, 90%) as a light yellow oil.

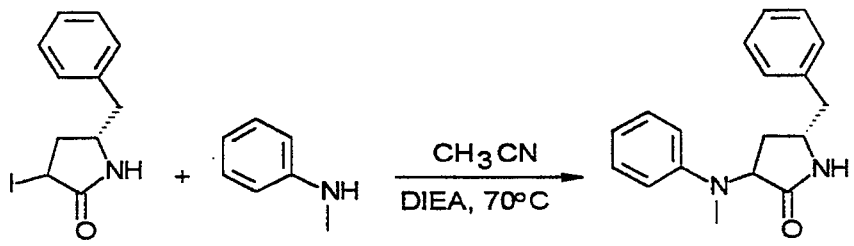
B.



1 2

In a 25 mL round-bottomed flask, isoxazole PMB lactam **1** (900 mg, 2.30 mmol) was dissolved in 14 mL of 70% CH_3CN-H_2O. Ceric ammonium nitrate (3.607 g, 6.58 mmol) was added forming a dark orange solution. The mixture was stirred until the starting material was no longer evident by TLC (10% EtOAc/CH_2Cl_2). The light yellow solution was diluted with CH_2Cl_2 and washed with water. The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to afford a brownish-red oil that was chromatographed (10% EtOAc/CH_2Cl_2) to produce the lactam **2** (300.3 mg, 48%) as a colorless oil.

Example 36

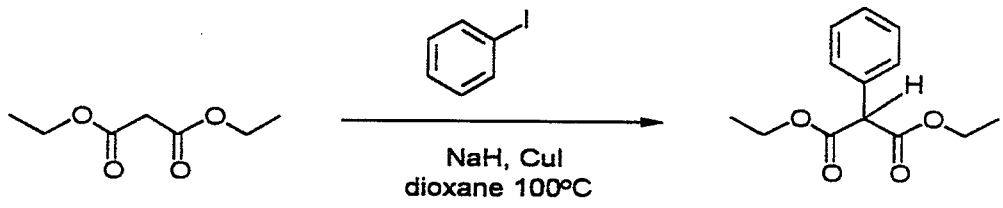


1 2 3

The iodolactam 1 (0.78 mmol) was dissolved in dry acetonitrile in a high pressure tube and to this solution was added diisopropylethylamine (Pierce, 2.35 mmol) followed by N-methylaniline 2 (Aldrich, 0.94 mmol). The tube was sealed and the reaction heated to 70 °C with stirring overnight. The reaction was cooled to ambient temperature, solvent removed *in vacuo*, and the residue taken up in ethyl acetate/water. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 2:1 ethyl acetate/hexanes to give 134 mg of product 3; TLC R_f = 0.24 (2:1 ethyl acetate/hexanes); HPLC Rt = 12.7 min (80%); MALDI-TOF MS *m/z* 282 (M^+).

Example 37

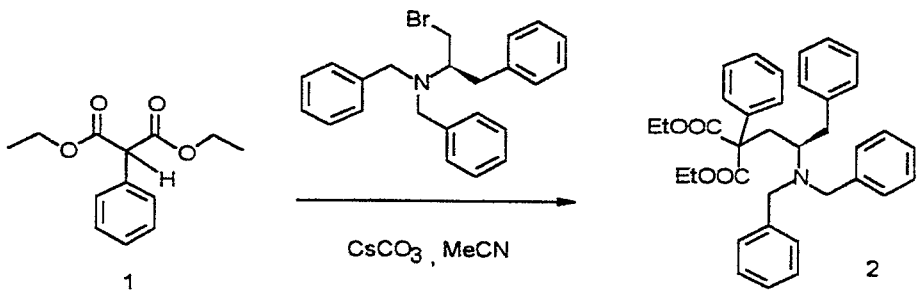
A.



1 2

NaH (0.96 g, 40 mmol) was suspended into 20 mL of dioxane. This was followed by the addition of diethyl malonate (4.6 mL, 40 mmol), then phenyl iodide (2.2 mL, 20 mmol) and finally copper (I) iodide (7.6g, 40 mmol). The reaction was then heated to 100 °C for 14 hours. The reaction was then quenched with water and diluted with ethyl acetate, the organic layer was washed with water and saturated NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was further purified by MPLC (SiO_2) eluting with 4:1, toluene: ethyl acetate to provide 1.21 g of product (29 % isolated yield).

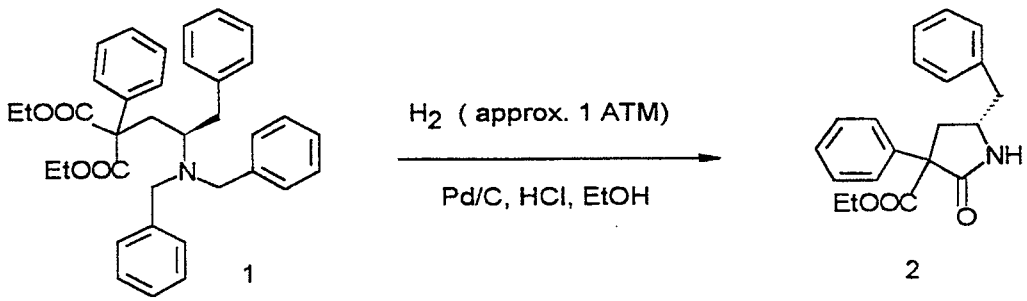
B.



1 2

The alkylated malonic ester (1, 227 mg, 1.09 mmol) was stirred for 14 hours in acetonitrile (2.5 mL) containing; cesium carbonate (710 mg, 2.18 mmol) and the bromide (516 mg, 1.31 mmol). The reaction was then concentrated to dryness *in vacuo*. After re-suspension of the reaction mixture in ethyl acetate, the reaction mixture was washed with water, saturated $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was further purified by MPLC (SiO_2) to provide 200 mg of the desired product 35.2 % yield).

C.

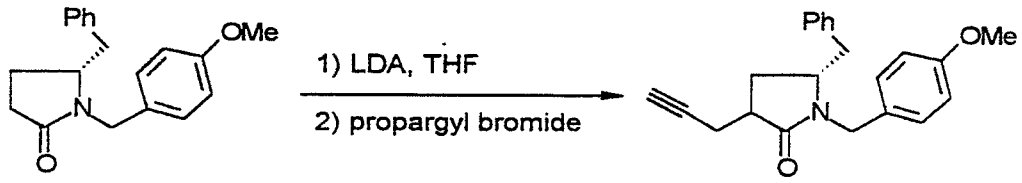


To the malonate (1, 200 mg) in ethanol (3 mL) was added concentrated HCl (100uL) and an excess of 5% Pd / C (approx. 50 mg). The reaction was then fitted with a balloon of H_2 and hydrogenated for 14 hours. After purging the reaction mixture of H_2, triethylamine (1 mL, 7 mmol, excess) and an excess of solid NaHCO3 was added. After stirring for 30 minutes the reaction was filtered and concentrated *in vacuo*. The yellow oil was

then re-dissolved in ethyl acetate and the reaction mixture was washed with water, saturated $NaHCO_3$ and saturated NaCl, dried (MgSO4) and concentrated *in vacuo* to provide the desired product. The ^1H NMR was consistent with the desired material.

Example 38

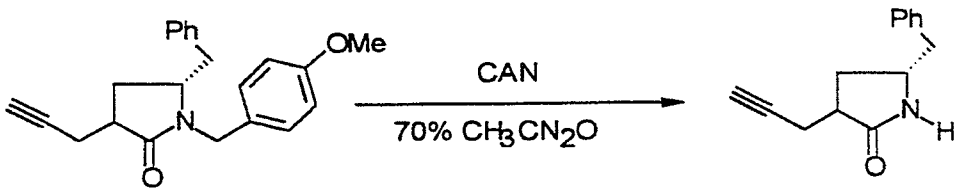
A.



1 2

In an oven-dried 25 mL round-bottomed flask, the PMB-lactam 1 (563.7 mg, 2.75 mmol) was dissolved in 10 mL of THF. The solution was cooled to -78 °C and 1.5M LDA (2.0 mL, 3.00 mmol) was added dropwise via syringe producing the yellow color of the enolate. The solution was stirred for 15 minutes at -78 °C and propargyl bromide (310 uL, 3.48 mmol) was added dissipating the yellow color. The cooling bath was removed and the solution was warmed to room temperature and stirred overnight. The solution was poured into 1N HCl and extracted with CH_2Cl_2. The organic extracts were combined and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo to afford a brown oil that was chromatographed (90% CH_2Cl_2/hexane) to produce the propargyl lactam 2 (577 mg, 86%) as a colorless oil.

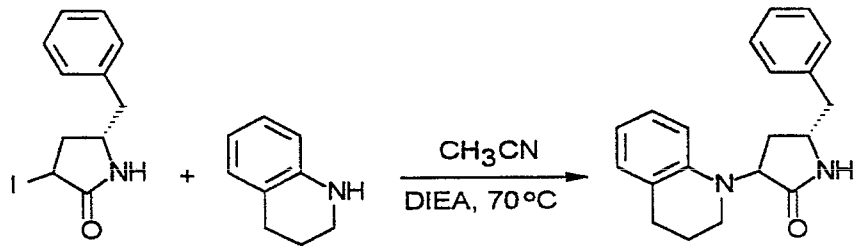
B.



1 2

In a 25 mL round-bottomed flask, propargyl PMB lactam **1** (358.2 mg, 1.08 mmol) was dissolved in 6 mL of 70% CH_3CN-H_2O. Ceric ammonium nitrate (1.321 g, 2.41 mmol) was added forming a dark orange solution. The mixture was stirred until the starting material was no longer evident by TLC (10% EtOAc/CH_2Cl_2). The light yellow solution was diluted with EtOAc and washed with water. The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to afford a yellow oil that was chromatographed (10% EtOAc/CH_2Cl_2) to produce the propargyl lactam **2** (145 mg, 63%) as a colorless oil.

Example 39.



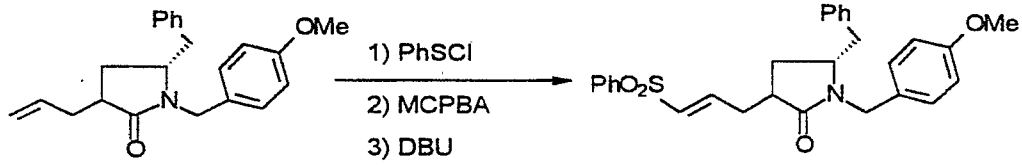
1 2 3

The iodolactam 1 (1.38 mmol) was dissolved in dry acetonitrile in a high pressure tube and to this

solution was added diisopropylethylamine (Pierce, 4.15 mmol) followed by tetrahydroquinoline 2 (Aldrich, 1.66 mmol). The tube was sealed and the reaction heated to 70 °C with stirring overnight. The reaction was cooled to ambient temperature, solvent removed *in vacuo*, and the residue taken up in ethyl acetate/water. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 1:1 ethyl acetate/hexanes to give 233 mg of product 3; TLC R_f = 0.21 (1:1 ethyl acetate/hexanes); HPLC Rt = 14.0 min (85%); MALDI-TOF MS *m/z* 307 (M^+).

Example 40

A.

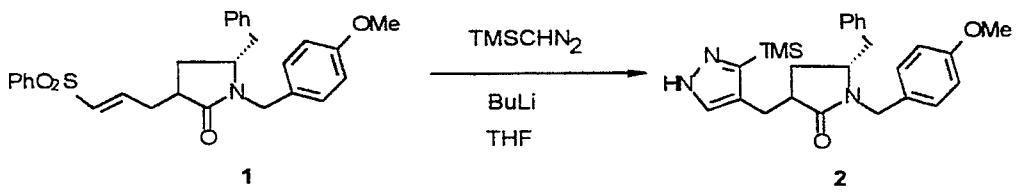


1 2

In an oven-dried 250 mL round-bottomed flask, N-chlorosuccinimide (2.5177 g, 18.9 mmol) was dissolved in 75 mL of CH_2Cl_2. The solution was cooled to 0 °C and thiophenol (1.90 mL, 18.5 mmol) was added dropwise via syringe causing an immediate formation of a yellow color and an exotherm. The orange solution of PhSCl was stirred for 30 minutes at room temperature and a

solution of the allyl lactam **1** (6.156 g, 18.4 mmol) was added dropwise dissipating the orange color. The light yellow solution was stirred for two hours and the solvent was removed in vacuo. CCl_4 was added to the yellow oil that remained and the undissolved succinimide was removed by filtration. The filtrate was evaporated in vacuo to afford the diastereomeric chlorosulfides as a yellow oil that was chromatographed (CH_2Cl_2) rapidly to remove low R_f impurities. The two highest R_f spots were the chlorosulfide diasteromers. The purified mixture of chlorosulfides was dissolved in CH_2Cl_2 and m-chloroperbenzoic acid (2.0 g, 11.6 mmol) was added with cooling from an ice-bath. The mixture was stirred for 10 minutes and filtered. The filtrate was evaporated in vacuo to afford a yellow oil (8.125 g, 86%) that produced two low R_f spots (CH_2Cl_2) using thin-layer chromatography for the two chlorosulfone diastereomers. The oil was redissolved in CH_2Cl_2 and DBU (2.7 mL, 18.1 mmol) was added dropwise at room temperature. The solution was heated for 15 minutes causing the solution to turn dark yellow. The solution was cooled and the solvent was evaporated in vacuo. The residue was chromatographed (CH_2Cl_2) to afford the pure vinyl sulfone **2** (4.805 g, 55%) as a colorless oil.

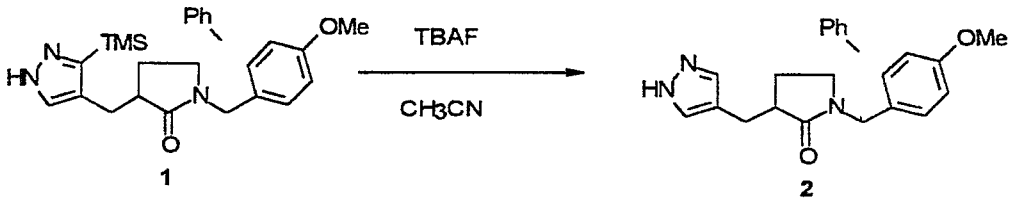
B.



1 **2**

In an oven-dried 25 mL round-bottomed flask, trimethylsilyl diazomethane (140 uL, 0.280 mmol) was dissolved in 5 mL of THF. The bright yellow solution was cooled to -78 °C and n-BuLi (320 uL, 480 mmol) was added. In a separate oven-dried 25 mL round-bottomed flask, the vinyl sulfone PMB lactam **1** (108 mg, 0.227 mmol) was dissolved in 5 mL of THF and added dropwise via syringe at -78 °C to the lithiate solution. The resulting solution was stirred for 1 hour at -78 °C and then two hours at 0 °C. The mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to afford a cloudy, colorless oil that was chromatographed (20% EtOAc/CH_2Cl_2) to produce the TMS pyrazole PMB lactam **2** (88.4 mg, 87%) as a clear, colorless oil.

C.

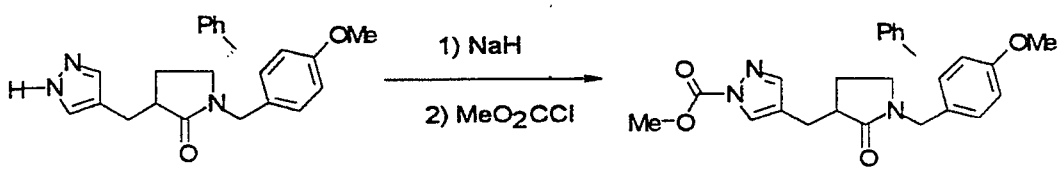


1 2

In an oven-dried 25 mL round-bottomed flask, the TMS pyrazole PMB lactam **1** (1.1345 g, 2.53 mmol) was dissolved in 110 mL of 91% CH_3CN/H_2O. Tetrabutylammonium fluoride (2.7 mL of a 1.0M solution in THF, 2.70 mmol) was added dropwise via syringe. The reaction was refluxed for 48 hours and cooled. The solvent was evaporated in vacuo and the residue was

dissolved in CH_2Cl_2. The organic solution was washed with 1N HCl solution, dried ($MgSO_4$), and evaporated in vacuo to afford a yellow oil that was chromatographed (20% EtOAc/CH_2Cl_2) to afford the pyrazole (688 mg, 72%) as a light yellow oil.

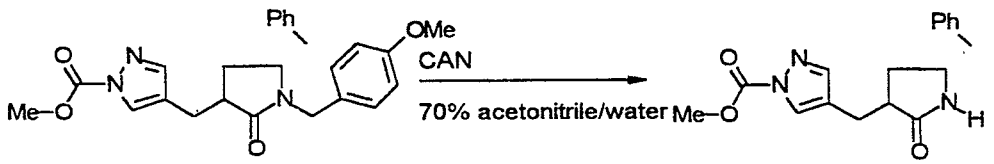
D.



1 2

In an oven-dried 100 mL round-bottomed flask, the pyrazole PMB lactam **1** (588 mg, 1.57 mmol) was dissolved in 25 mL of THF. NaH (50 mg of a 60% dispersion in mineral oil, 2.08 mmol) was added. Gas evolution was observed. Methyl chloroformate (140 uL, 1.81 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), and evaporated in vacuo to afford the pyrazole carbamate PMB lactam **2** (588 mg, 87%) as a light yellow oil.

E.

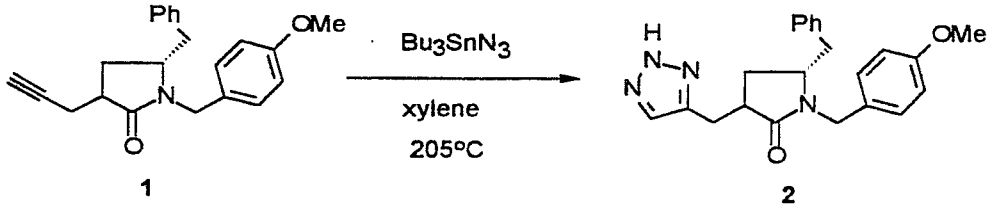


1 2

In an oven-dried 100 mL round-bottomed flask, the pyrazole carbamate PMB lactam **1** (577 mg, 1.33 mmol) was dissolved in 30 mL of 70% CH_3CN-H_2O. Ceric ammonium nitrate (2.5123 g, 4.58 mmol) was added. The orange solution was stirred at room temperature until the starting material was no longer evident by TLC (1 hr). The light yellow solution was poured into water and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to afford the pyrazole carbamate lactam **2** (228 mg, 55%) as a clear, colorless oil.

Example 41

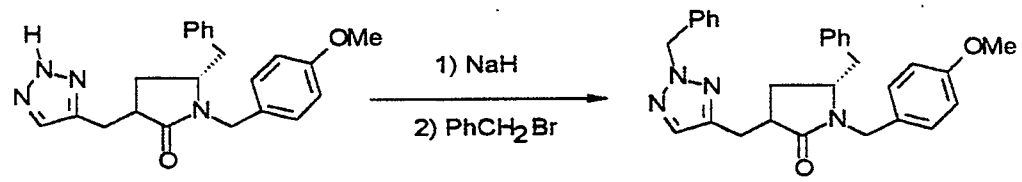
A.



1 2

In a heavy-walled screw-top test tube, the propargyl lactam **1** (1.111 g, 3.33 mmol) was dissolved in 7 mL of xylene. Tributyltin azide (1.965 g, 5.92 mmol) was added, the tube was sealed and heated to 205 °C overnight. The dark brown solution was cooled and directly chromatographed using a gradient from CH_2Cl_2 to 50% EtOAc/CH_2Cl_2 to afford the triazole PMB lactam **2** (827 mg, 66%) as a light yellow oil.

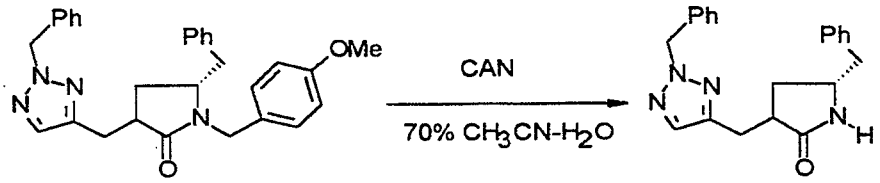
B.



1 2

In an oven-dried 100 mL round-bottomed flask, the triazole PMB lactam **1** (827 mg, 2.20 mmol) was dissolved in 40 mL of THF. NaH (124 mg of a 60% dispersion in mineral oil, 5.17 mmol) was added. Gas evolution was observed. Benzyl bromide (400 uL, 3.36 mmol) was added. The reaction was stirred at reflux until the starting material was not longer evident by thin-layer chromatography (50% EtOAc/CH_2Cl_2). The mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), evaporated in vacuo to afford a dark yellow residue that was chromatographed (20% EtOAc/CH_2Cl_2) to produce the benzyl triazole PMB lactam **2** (740 mg, 72%) as a light yellow oil.

C.

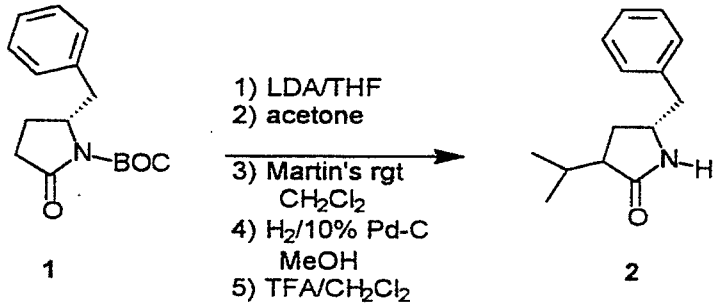


1 2

In an oven-dried 50 mL round-bottomed flask, the benzyl triazole PMB lactam **1** (740 mg, 1.59 mmol) was dissolved

in 22 mL of 70% CH_3CN-H_2O. Ceric ammonium nitrate (2.1 g, 3.83 mmol) was added. The orange solution was stirred at room temperature until the starting material was no longer evident by TLC (1 hr). The mixture was poured into water and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to afford the benzyl triazole lactam **2** (336 mg, 61%) as a clear, colorless oil.

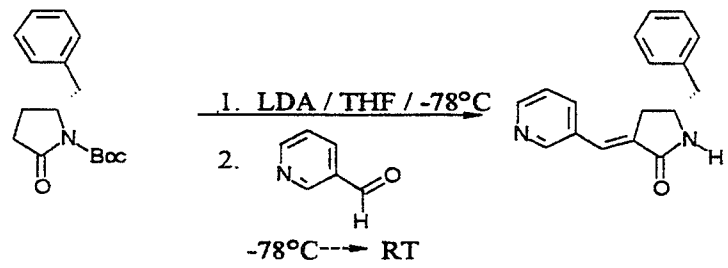
Example 42



BOC-lactam 1 (1.8 g, 6.6 mmol) was dissolved in THF (50 mL) and cooled to -78 °C. To this solution was added LDA (Aldrich, 1.5 M in cyclohexane, 5.3 mL, 7.9 mmol) via syringe over 10 minutes. After stirring for 60 min at -78 °C, acetone (4.9 mL, 66 mmol) was added via syringe over 1 minute. The reaction was stirred for an additional 40 minutes before being quenched with 1N HCl (15 mL). Ethyl acetate (100 mL) was added and the layers were partitioned. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to a yellow oil that slowly

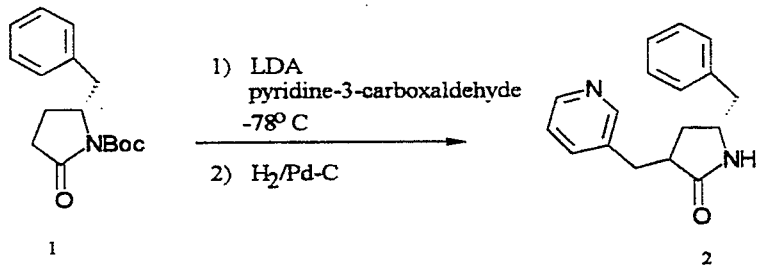
crystallized. The crude alcohol was dissolved in dichloromethane (50 mL) and Martin's sulfurane (Aldrich, 7.5 g, 11 mmol) was added in one portion. The reaction was stirred for 36 h at room temperature before being concentrated in vacuo. Flash chromatography over silica gel (3:1 hexane:ethyl acetate) provided the alkene as a mixture of isomers. The alkene, 10% Pd-C (1.0 g), and methanol (40 mL) were combined in a Parr bottle and pressurized to 50 psi of hydrogen gas. After 4 h of agitation, the reaction vessel was evacuated and filtered through a plug of Celite. The cake was washed with ethyl acetate (20 mL) and the combined filtrate was concentrated in vacuo to give the isopropyl BOC-lactam as a pale yellow oil. The lactam was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (10 mL) was added slowly. The reaction was stirred at room temperature for 24 h before being diluted with ethyl acetate (100 mL) and carefully neutralized with 10% sodium carbonate to pH 7. The layers were partitioned and the organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (3:1 ethyl acetate:hexane) gave the isopropyl lactam as a white powder. MS (ES+) = 240 (M+Na)

Example 43



A stirred, cooled (-78 °C) solution of 1.4 g (5.0 mmol) of pyrrolidinone in 35 mL of anhydrous tetrahydrofuran was treated in a dropwise fashion with 3.6 mL (7.2 mmoL) of lithium diisopropylamide. The resultant solution was stirred for 70 min, and subsequently treated with 0.57 mL (6.0 mmoL) of 3-pyridine carboxaldehyde. The homogenous solution was allowed to ambiently warm to RT, and stirring was continued overnight. The reaction mixture was diluted with 400 mL of dichloromethane, washed 1X with 150 mL of water, dried (magnesium sulfate), filtered, concentrated, and purified on silica gel using 3:1 ethyl acetate/hexanes as the eluent affording 0.6 g (46%) of the desired compound as a golden oil which solidified upon standing. ^{1}H NMR (d6-DMSO, 400MHz) 8.65 (s, 1H); 8.47 (m, 2H); 7.83 (d, J = 8.0 Hz, 1H); 7.41 (m, 1H); 7.23 (m, 5H); 7.03 (t, J = 2.7 Hz, 1H); 3.96 (m, 1H); 3.07 (m, 1H); 2.89 - 2.65 (series of m, 3H). M+H (265.2).

Example 44



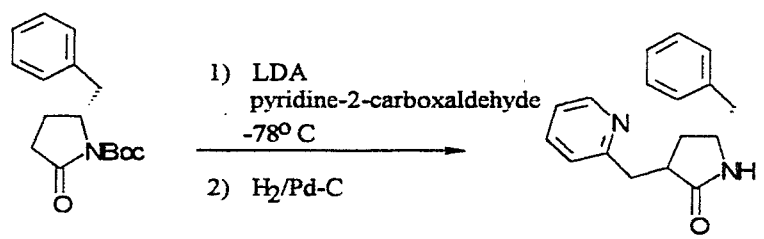
1 2

The first step of the sequence was performed as for **Example 43.** The olefin was carried forward as follows:

step 2

A vigorously stirred suspension of 330 mg (1.25 mmoL) of eneamide and 80 mg of 10% palladium on carbon (Degussa) in 12mL of anhydrous methanol was hydrogenated (Hydrogen balloon) for 1 h. The mixture was diluted with 100 mL of methanol, carefully filtered, concentrated, and purified on silica gel using ethyl acetate as the eluent affording 295 mg (89%) of an isomeric mixture of the desired compounds as a golden oil which solidified upon standing. 1H NMR (d6-DMSO, 400MHz) d 8.36 (s, 2H); 7.88 (s, 1H); 7.56 (d, J = 7.9 Hz, 1H); 7.27 - 7.12 (m, 7H); 3.66 (m, 1H); 2.96 - 2.37 (series of m, 7H). M+H (267.2); M+Na (289.2)

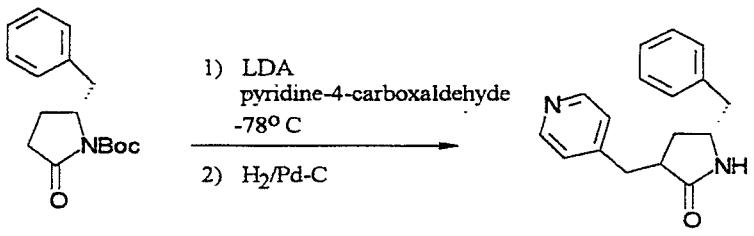
Example 45



1 2

The synthesis of the 2-pyridyl methylpyrrolidone was carried out as shown in **Example 44.**

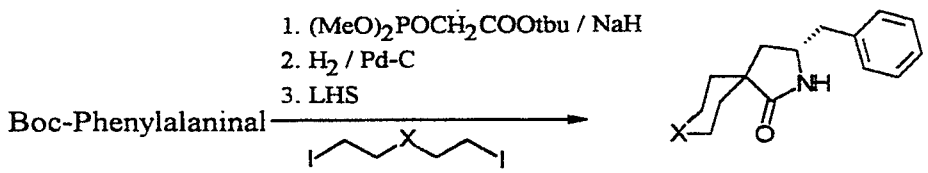
Example 46



1 2

The 4-pyridylmethylpyrrolidone was prepared following procedures outline for **Example 44.**

Example 47



X = N-Bn

A.

A solution of 5.06g (20 mmol, 1 equiv) of tert-Butyl-P,P-dimethylphosphonoacetate in 15 mL THF cooled to 0 °C was treated with 0.528g of NaH at 0 °C and then warmed up to room temperature for 30 min. Next, solution of 5.0g (20 mM, 1 equiv) of Boc-Phenylalaninal in 5 mL THF was added dropwise at 0°C and the reaction continued for 2 h. The crude product was diluted with ethyl acetate and partitioned with aqueous citric acid (2x), sodium bicarbonate (2x), organics collected and dried over magnesium sulfate. The product was then dissolved in 100 mL methanol, added 0.6g 10% Pd/C and hydrogenated at 25 psi overnight, and the desired compound purified on a silica column using 1/4 ethyl acetate/hexane. Yield 3.8g (51.4%).

^1H NMR ($CDCL_3$, 300 MHz) δ (broad signals and conformational averaging) 7.20 (m, 5H), 4.46 (m. 0.5H), 3.79 (m, 0.5H), 3.72 (s, 0.5H), 2.80 (m, 0.5H), 2.46 (m. 0.5H), 2.27 (m, 1H), 1.78 (m, 1H), 1.50 (m. 1H), {1.44, 1.42, 1.41, 1.38} (all s, total 18H). Low resolution MS *m/e* 372.2 ($M+Na^+$).

B.

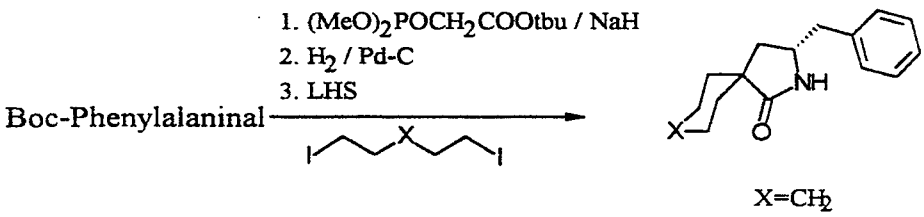
A solution of 4.63 g (13.25 mmol, 1 equiv) of the above ester in 200 mL of THF was treated with 40 mL (39.75 mmol, 3 equiv) of 1M lithium bis(trimethylsilyl) amide in THF at -78 °C. After 90 min at -78 °C, the solution was added 5.5g (13.25 mmol, 1 equiv) of N-benzyl-N-bis(iodoethane) in 10 mL of THF and the reaction continued for 6 hours during which it reached the room temperature. The reaction was quenched with 10% aqueous solution of citric acid and extracted to ethyl acetate, and the product treated with 1:1 (v/v) DCM/TFA (40 mL) for 40 min, after which solvents were removed and the crude purified to homogeneity by RP HPLC with total yield of 14.2%. The resulting TFA salt was then neutralized with triethylamine, extracted between ethyl acetate/water, organics collected and dried, thus yielding a free base form of the spiropyrrolidone product which is used in subsequent coupling to the epoxide. ^{1}H NMR (TFA salt, $CDCL_3$, 300 MHz) δ 7.30 (m, 10H), 5.85 (m, 1H), 4.16 (m, 2H), 3.86 (m, 1H), 3.68 (m, 1H), 3.36 (m, 3H), 2.88 (dd, 1H), 2.62 (dd, 1H), 1.7-2.2 (m, 6H). Low resolution MS *m/e* 335.2 ($M+H^+$)

Example 48

Spirocycle X=O was synthesized according to bisalkylation protocol of Example 47 above except that bis-O-(iodoethyl) ether was used in reaction step B (1.26g, 3,87 mmol, 1 equiv). ^{1}H NMR (d_6-DMSO, 300 MHz) δ 7.79 (s, 1H), 7.22 (m, 5H), 3.73 (m, 3H), 3.24 (m, 2H), 2.88 (dd, 1H, J=4.8, 13.4), 2.57 (dd, 1H, J=8.4, 13.4), 2.03 (m, 1H), 1.76 (m, 1H), 1.55 (m, 2H), 1.22

(m, 1H), 1.01 (m, 1H). Low resolution MS *m/e* 246.2 ($M+H^+$).

Example 49



Spirocycle X=CH_2

A.

A solution of 1.36g (3.88 mmol, 1 equiv) of the ester from **Example 47** step A in 5 mL of THF was cooled to -78 °C and treated with 9.32 mL (9.32 mmol, 2.4 equiv) of 1M lithium bis(trimethylsilyl) amide in THF. After 1 h at -78 °C, 0.992g (4.27 mmol, 1.1 equiv) of 1,5-iodochloropentane was added and the reaction allowed to progress at -15 °C for 1 h, quenched with 10% aqueous citric acid, and extracted to ethyl acetate, resulting in 1.60g of product. Low resolution MS *m/e* 476.2 ($M+Na^+$)

B.

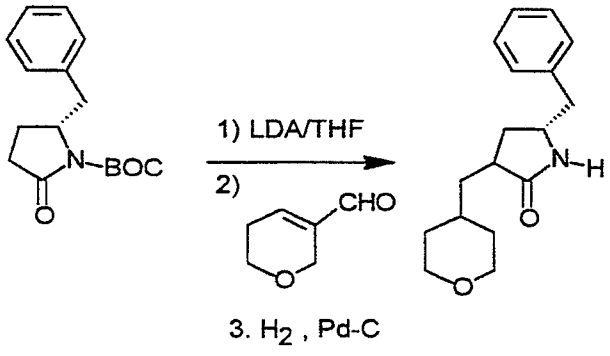
A solution of 1.6g (3.53 mmol, 1 equiv) of the above chloride in 30 mL acetone was treated with 5.29 g (35.3 mmol, 10 equiv) of NaI and refluxed overnight. Solvents were then removed and the residue partitioned between ethyl acetate/water. Organics were dried with magnesium

sulfate and purified on silica gel using 1/3 ethyl acetate/hexane resulting in 1.2 g of the desired iodide (62.4% yield after chromatography). ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.20 (m, 5H), 4.38 (m, 1H), 3.79 (m, 1H), 3.13 (t, 2H, J=6.9), 2.73 (m, 2H), 2.25 (m, 1H), 1.76 (m, 2H), 1.43 (s, 9H), 1.38 (s, 9H), 1.2-1.7 (m, 7H). Low resolution MS *m/e* 568 ($M+Na^+$), *m/e* 362.2 ($M+H^+$)

C.

A solution 1.15g (2.1 mM, 1 equiv) of the above product in 20 mL of anhydrous THF was cooled to -78 °C and treated with 3.2 mL (3 mmol, 1.5 equiv) of 1M lithium bis(trimethylsilyl) amide in THF. The reaction was then allowed to warm up to room temperature, solvents removed and the crude product purified on preparative HPLC. ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.32 (m. 4H), 7.19 (d, 12H), 3.88 (m, 1H), 2.82 (m, 2H), 2.24 (dd, 1H), 1.2-1.8 (m, 11H). Low resolution MS *m/e* 384.2 ($M+Na^+$), *m/e* 362.2 ($M+H^+$).

Example 50



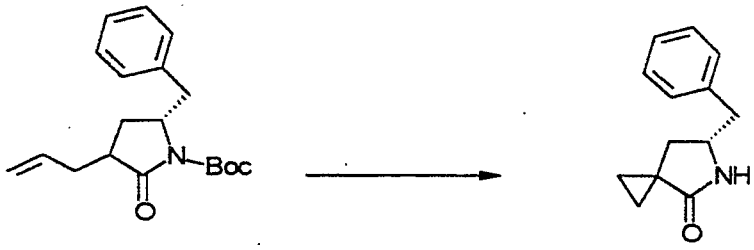
A.

The Boc-pyrrolidone (4.4 g, 16 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. To this solution was added LDA (Aldrich, 1.5 M in cyclohexane, 12.8 mL, 19 mmol) via syringe over 10 minutes. After stirring for 60 min at -78 °C, 3-formyl-5,6-dihydro-2H-pyran (US Patent 4,532,337) (1.8 g, 16 mmol) in THF (5 mL) was added via syringe over 1 minute. The reaction was then allowed to reach room temperature and stir for 20 h before being quenched with saturated ammonium chloride (15 mL). Ethyl acetate (50 mL) was added and the layers were partitioned. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (95:5 chloroform:methanol) to give dihydropyran lactam as a beige powder. MS (ES+) = 270 (M+1), 292 (M+Na)

B.

The dihydropyran obtained above (1.2 g, 4.4 mmol), 10% Pd-C (0.2 g), and methanol (35 mL) were combined in a Parr bottle and pressurized to 50 psi of hydrogen gas. After 3 h of agitation, the reaction vessel was evacuated and filtered through a plug of Celite. The cake was washed with methanol (20 mL) and the combined filtrate was concentrated in vacuo. Flash chromatography over silica gel (95:5 chloroform:methanol) gave the tetrahydropyran lactam 2 as a white powder. MS (ES+) = 274 (M+1), 296 (M+Na)

Example 51



A.

A solution of 2.6g (8.24 mmol, 1 equiv) of the allyl-pyrrolidone in 80 mL tetrahydrofuran and 25 mL water was cooled to 0 °C and treated with 5.29 g (24.7 mmol, 3 equiv) $NaIO_4$, followed by the addition of 838 mg of 2.5% solution of osmium tetroxide in 2-methyl-2-propanol. The reaction was continued for 2 h at room temperature, solvents removed and the residue partitioned between ethyl acetate and water. Ethyl acetate was then dried over $MgSO_4$, resulting in 3.0 g of the crude aldehyde.

^1H NMR ($CDCL_3$, 300 MHz) δ 9.75 (s, 1H), 7.22 (m, 5H), 4.32 (m, 1H), 3.05 (m, 2H), 2.82 (m, 3H), 2.53 (m, 1H), 2.22 (m, 1H), 1.58 (s, 9H). Low resolution MS *m/e* 356.1 ($M+Na^+$); *m/e* 689.3 ($2M+Na^+$).

B.

A solution of 2.88g of the above aldehyde in 10 mL methanol was cooled to 0 °C and sodium borohydride was added over 2 h, until all the starting material (Rf=0.55, Merck Kiselgel 60, 0.25 mm, 1:1 ethyl acetate/hexane) was consumed. The title compound had Rf=0.30 (same conditions). Solvents were then removed, and the residue was extracted between ethyl acetate and

10% aqueous citric acid. Organic fractions were washed with water and dried over magnesium sulfate. Purification on a silica column (1:1 ethyl acetate/hexane) afforded 1.5 g (57% yield) of the alcohol. Low resolution MS *m/e* 342.2 ($M+Na^+$); *m/e* 661.4 ($2M+Na^+$).

C.

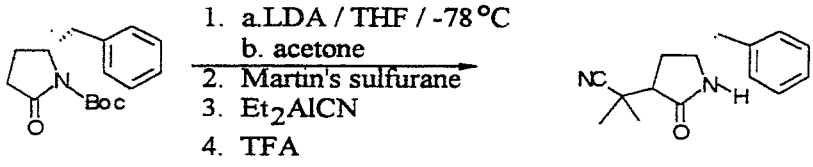
A solution of 0.46g (1.44 mmol, 1 equiv) of the above alcohol in 4 mL tetrahydrofuran was treated with 0.215 g (1.875 mmol, 1.3 equiv) of mesyl chloride and 0.242g (1.875 mmol, 1.3 equiv) of diisopropylethylamine. The reaction was allowed to proceed for 30 min at room temperature, solvents removed and the residue partitioned between ethyl acetate and water. Organics were dried with magnesium sulfate and purified on a silica column (1/1 ethyl acetate/hexane), yielding 0.50 g (87.3%) of the desired mesylate. R_f=0.57 (Merck Kiselgel 60, 0.25 mm, 1:1 ethyl acetate/hexane). ^1H NMR ($CDCL_3$, 300 MHz) δ 7.22 (m, 5H), 4.39 (m, 3H), 3.09 (dd, 1H, J=6.4, 13.2), 2.98 (s, 3H), 2.76 (dd, 1H, J=8.9, 13.2), 1.64 (m, 2H), 1.57 (s, 9H).

D.

A solution of 0.33g (0.831 mmol, 1 equiv) of the above mesylate in 3 mL DMF was cooled to 0 °C and treated with 26 mg (1.080 mmol, 1.3 equiv) of sodium hydride. After 3h at room temperature the reaction was quenched with aqueous citric acid and purified on silica gel using 1:3 ethyl acetate/hexane (v:v). The resulting product (0.18g, 72.0% yield) was then treated with 1:1 dichloromethane/ trifluoroacetic acid (5 ml) for 1/2h,

resulting in 0.12g (71.8%, based on mesylate) of the desired product. ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.23 (m, 5H), 7.04 (broad s, 1H), 3.99 (m, 1H), 2.85 (m, 2H), 2.26 (dd, 1H, J=8.1, 12.9), 1.92 (dd, 1H, J=5.0, 12.9), 1.10 (m, 2H), 0.72 (m, 2H). Low resolution MS *m/e* 342.2 ($M+Na^+$);

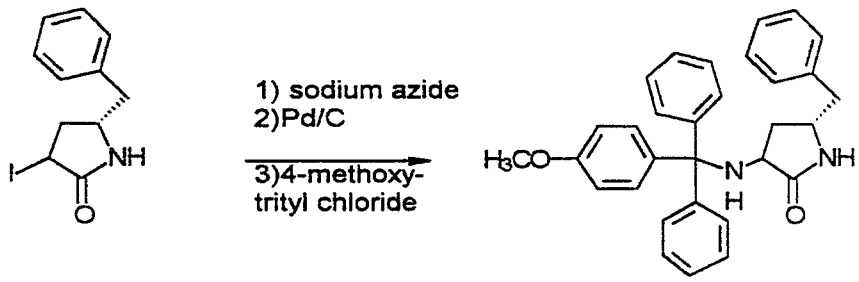
Example 52



A solution of 1.5g (5.4 mMol) of the pyrrolidinone in 25 mL of tetrahydrofuran was cooled to -78 °C and treated with 4.3 mL (6.5 mMol) of lithiumdiisopropyl amide (2M in THF). After stirring for 0.25h, acetone (2.8g (50 mMol) was added, the reaction mixture was kept at -78 °C for 2 h and then quenched with 1N hydrochloric acid. Extraction with ethyl acetate, drying over magnesium sulfate and removal of the solvent in vacuo afforded the crude product which was redissolved in 25 mL of dichloromethane and treated with 8g of Martin's sulfurane. After stirring for 12h at 25 °C, the mixture was participated between ethyl acetate and 1N hydrochloric acid. Drying over magnesium sulfate and removal of the solvent gave the desired alkene. 0.755 g of the crude alkene were dissolved in 15 mL of toluene and treated with 3 mL (3 mMol) of diethyl aluminumcyanide (1m in toluene) and the resulting mixture was stirred at 25 °C for 5 h.

The solvent was removed and the residue was chromatographed on silica gel (20% ethylacetate-hexanes) to give the desired nitrile (0.4g) as a colorless oil. Deprotection with trifluoroacetic acid-dichloromethane (1:1) for 3h at 25 °C followed by chromatography on silica gel gave the desired lactam (0.22g) as a white solid. M+H: 243

Example 53



A.

A solution of 3-iodo-5-benzyl-pyrrolidinone (2.67 g, 8.87 mmol) and sodium azide (0.69 g, 10.61 mmol) in dimethylformamide (20 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18h. The solvent was evaporated using a stream of nitrogen, and the residue was dissolved in ethyl acetate, washed with water and brine, and concentrated *in vacuo* to give a yellow solid. Chromatography on silica gel, eluting with hexane:ethyl acetate (4:1), gave 1.82 g of the product as a 1:1 mixture of diastereomers which was used without separation in the next reaction. MS: ES+, 239 (M+Na). The chromatography also gave 0.12 g of the trans isomer as a colorless oil and 0.43 g of the cis isomer as a colorless oil which crystallized

upon standing. TLC (hexane : ethyl acetate (1:1)) Rf trans isomer =0.6 and Rf cis isomer = 0.5.

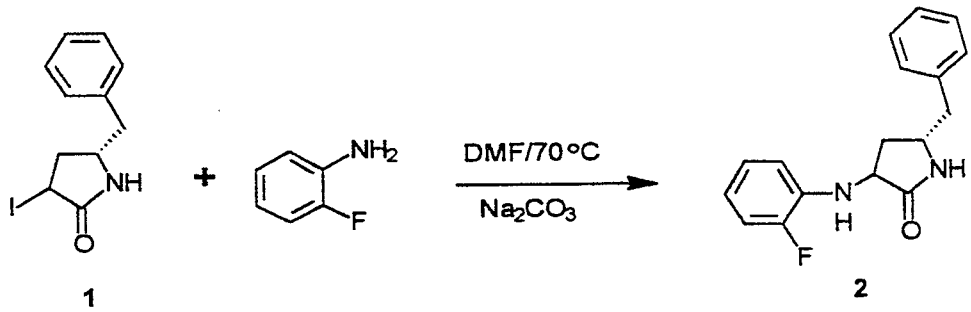
B.

A mixture of the above azide (0.575 g, 2.66 mmol) and 5% palladium on carbon (0.030 g) in methanol (20 mL) was stirred under 40 psi of hydrogen for 18h at ambient temperature. The mixture was filtered through a pad of Celite to remove the catalyst, followed by filtration through 5 g of silica gel, washing with chloroform:methanol (9:1). The filtrate was concentrated *in vacuo* to give 0.46 g (90%) of the product as a mixture of diastereomers. MS: ES+, 191 (M+1) and 213 (M+Na).

C.

A solution of the above amine (0.44 g, 2.3 mmol), 4-anisylchlorodiphenylmethane (0.71 g, 2.3 mmol) and triethylamine (0.5 mL, 3.5 mmol) in dichloromethane (20 mL) was stirred under a nitrogen atmosphere at ambient temperature for 18h. The solution was washed with water (2x50 mL) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (7:3) then with hexane:ethyl acetate (1:1), to give 0.41 g of the cis isomer as a yellow solid and 0.19 g of the trans isomer as a white solid. TLC (hexane : ethyl acetate (7:3)) Rf cis isomer =0.5 and Rf trans isomer = 0.4.

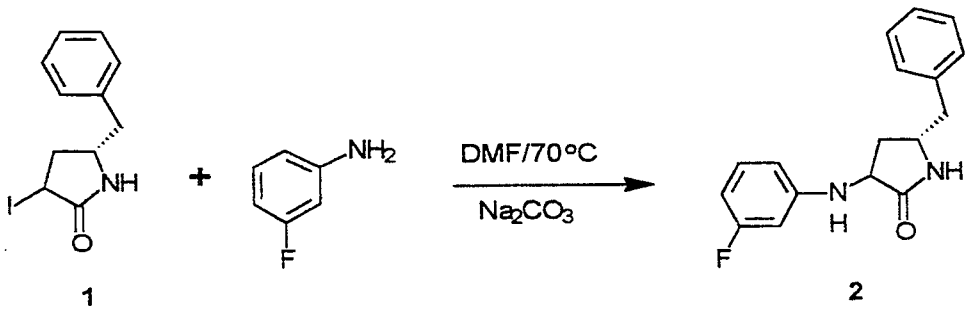
Example 54



1 2

Iodolactam 1 (prepared as described previously in Example 7) (0.55 g, 1.8 mmol) was dissolved in DMF (5 mL) and treated with 2-fluoroaniline (Aldrich, 0.20 g, 1.8 mmol) and solid sodium carbonate (0.39 g, 3.7 mmol). The reaction was then heated to 70 °C for 24 h before the solvent was removed in vacuo. Ethyl acetate (50 mL) and water (20 mL) were added and the layers were partitioned. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (1:1 hexane:ethyl acetate) gave the anilinolactam 2 as a pale yellow foam. MS (AP+) = 285 (M+1), 307 (M+Na)

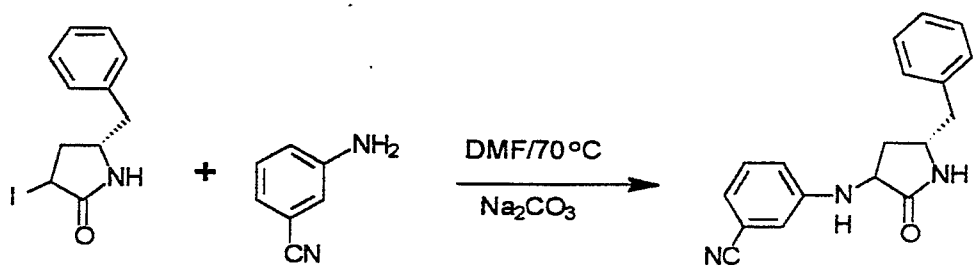
Example 55



1 2

Using the procedure described in Example 54, the anilinolactam was prepared, purified, and isolated as a beige foam. MS (AP+) = 285 (M+1), 307 (M+Na)

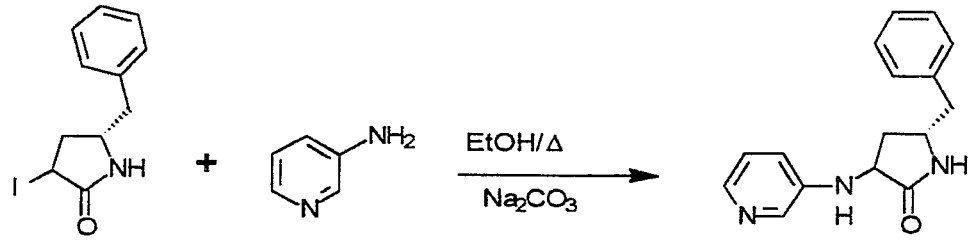
Example 56



1 2

Using the procedure described in Example 54, the anilinolactam was prepared, purified, and isolated as a beige foam. MS (AP+) = 292 (M+1), 314 (M+Na)

Example 57

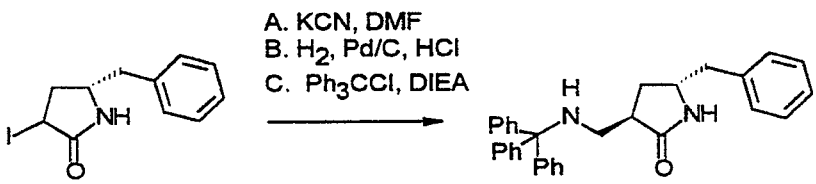


1 2

Iodolactam 1 (prepared as described previously in Example 7) (0.77 g, 2.6 mmol) was dissolved in absolute ethanol (10 mL) and treated with 3-aminopyridine (0.26 g, 2.8 mmol) and solid sodium carbonate (0.40 g, 3.8 mmol). The reaction was then heated at reflux for 24 h before the solvent was removed in vacuo. Chloroform (50

mL) and water (20 mL) were added and the layers were partitioned. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Preparatory silica gel TLC (95:5 chloroform:methanol) gave the pyridylaminolactam 2 as a red oil. MS (AP+) = 268 (M+1), 290 (M+Na)

Example 58



1. 2.

A.

To a solution of iodolactam 1 (13.43 g, 44.6 mmol, 1 eq) in dimethylformamide (60 mL) under nitrogen was added potassium cyanide (3.49 g, 1.2 eq). After stirring at ambient temperature for 24 h, the reaction mixture was evaporated *in vacuo* and the residue was partitioned between ethyl acetate, saturated aqueous brine and water. The layers were separated and the aqueous layer was back-extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash silica gel chromatography eluting with hexane : acetone (3:1). Fractions containing the product were combined, evaporated *in vacuo* to provide

5.89 g (66%) of cyanolactam as a mixture of diastereomers. MS (APCI): M+Na = 223.

B.

A solution of cyanolactam (5.78 g, 28.9 mmol) from step A in absolute ethanol (233 mL) under Nitrogen was combined with 10 wt.% Palladium on charcoal (2.33 g) and concentrated hydrochloric acid (9.31 mL, 4 eq.). The mixture was reduced under hydrogen gas at 50 psi for 16 h. The reaction was purged with nitrogen, filtered and evaporated *in vacuo*. The residue was combined with toluene (~ 100 mL) and concentrated *in vacuo* to a residue to remove residual water. The azeotropic removal with toluene was repeated four times leaving a residue which was dried under high vacuum to provide the crude amine as a gum (7.18 g, 103%). MS (ESI): M+1 = 205.

C.

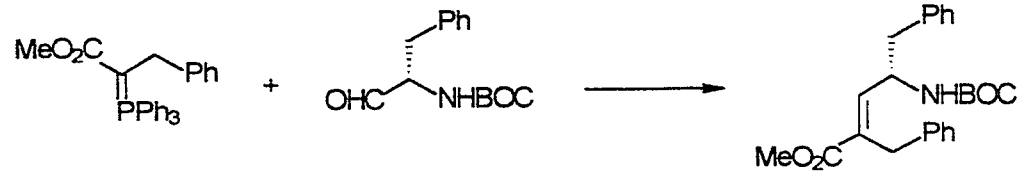
The crude amine (7.16 g, 29.8 mmol, 1 eq) from step B was combined under argon in dichloromethane (100 mL) with diisopropylethylamine (13 mL, 74.4 mmol, 2.5 eq) and triphenylmethylchoride (9.13 g, 32.7 mmol, 1.1 eq). After stirring at ambient temperature for 16 h, the reaction mixture was treated with 5% w/v aqueous potassium carbonate and transferred to a separatory funnel. After separating the layers, the aqueous layer was back-extracted with dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo* to proved a crude mixture of diastereomers. The mixture was

purified by flash silica gel chromatography eluting with ethyl acetate : hexane (3:7). Fractions containing the less polar diastereomer were combined and evaporated *in vacuo* to provide 3.52 g (26 %) of trityl protected amine as a crystalline solid. MS (APCI): M+Na = 469.

Example 59

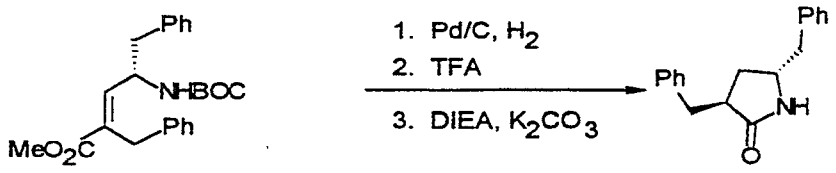
An alternate procedure for the synthesis of the benzyllactam:

A.



A mixture of methyl 2-(triphenylphosphoranylidene)-hydrocinnamate (13.20 g, 31.1 mmol, 1.15 eq) and N-tertbutoxycarobonyl-L-phenylalanal (6.76 g, 27.1 mmol, 1 eq) were combined in 200 mL chloroform and allowed to stir at ambient temperature over 64 h. The reaction was concentrated *in vacuo* and the residue was purified by flash silica gel chromatography eluting with 85:15 hexane : ethyl acetate. Fractions containing the product were combined and evaporated *in vacuo* to provide the olefin as a crystalline solid (9.38 g, 77%). MS (ESI): M + Na = 418.

B.



A solution of the olefin (9.30 g, 23.5 mmol, 1eq) from step A in absolute ethanol (250 mL) was combined under nitrogen with Palladium on carbon (10 wt%, 1.90 g) and reduced under a balloon of Hydrogen gas over 16 h. The reaction mixture was purged with nitrogen, diluted with dichloromethane, filtered, and evaporated *in vacuo* to low volume. The solution was diluted with dichloromethane and filtered through a pad of diatomaceous earth washing with dichloromethane. The filtrate was evaporated *in vacuo* and dried under vacuum to provide a 5:1 mixture of diastereomers of the BOC-amino ester as an oil (9.68 g, 104 %). MS (ESI): M + Na = 420.

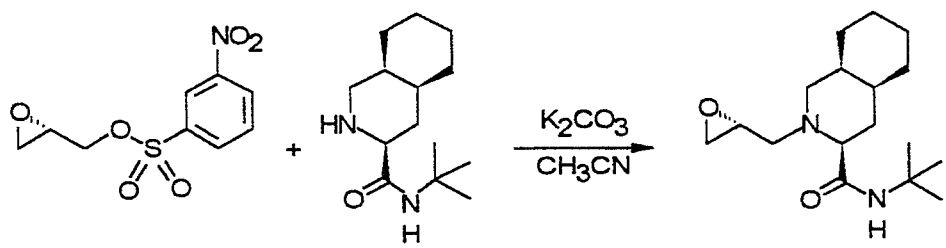
The oil was dissolved in dichloromethane (25 mL) and treated with trifluoroacetic acid (25 mL) under Argon. After stirring for 0.5 h at ambient temperature, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in methanol (50 mL) and treated with diisopropylethyl amine (17 mL) followed by anhydrous potassium carbonate (13.49 g, 98 mmol, 4 eq) and stirred for 16 h at ambient temperature under an Argon atmosphere. The mixture was evaporated *in vacuo* and the residue was partitioned between dichloromethane and water. The layers were separated and the aqueous layer

was back-extracted three times with dichloromethane. The combined organic layers were washed with aqueous hydrochloric acid (1N) and the layers were separated. The aqueous layer was back-extracted with dichloromethane and the combined organic layers were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to a residue. The crude product was purified by flash silica gel chromatography eluting with a gradient of 45-60 % ethyl acetate in hexane. Fractions containing the less polar diastereomer were combined and concentrated *in vacuo* to a solid and dried under high vacuum to provide the enantiopure lactam as a white crystalline solid (4.48 g, 72%). MS (ESI): M + Na = 288. H NMR (CDCl3): 1.90 (m, 1H); 2.01 (m, 1H); 2.67 (m, 4H); 3.16 (m, 1H); 3.65 (m, 1H); 5.70 (s, 1H); 7.18 (m, 10H).

Example 60

Synthesis of Compound 123

A.

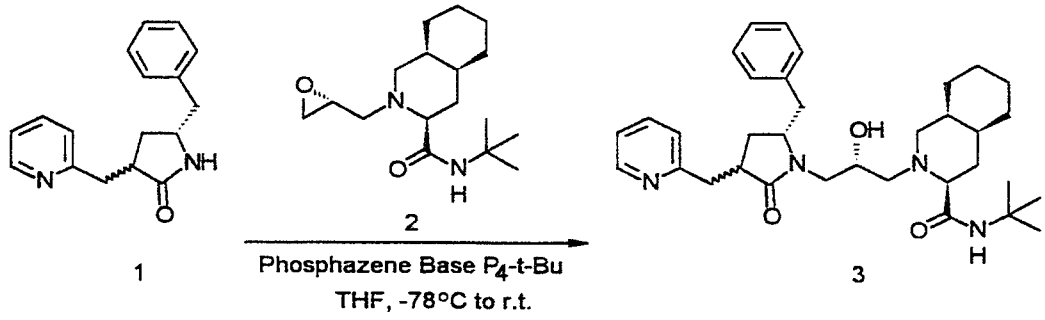


1 2 3

To a suspension of (2*S*)-(+)-glycidyl 3-nitrobenzenesulfonate 1 (Aldrich, 19.47 mmol) and

potassium carbonate (Baker, 38.93 mmol) in dry acetonitrile was added (*S*)-t-butyl decahydro-3-isoquinoline carboxamide 2 (NSC Technologies, 21.41 mmol) and the reaction stirred at ambient temperature overnight. The solvent was removed *in vacuo*, and the residue taken up in ethyl acetate/water, the organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 10% diethyl ether/dichloromethane to give 3.62 g of product 3; HPLC Rt = 9.2 min (100%), TLC R_f = 0.26 (10% diethyl ether/dichloromethane); ^{1}H NMR ($CDCl_3$) d 6.59 (br s, 1 H), 3.00 (d, 1 H), 2.97 (m, 1 H), 2.89 (dd, 1H), 2.73 (m, 1H), 2.65 (m, 1 H), 2.57 (m, 1 H), 2.22 (dd, 1H), 2.08 (dd, 1H), 1.81-1.70 (m, 4 H), 1.65-1.19 (m, 8 H), 1.38 (s, 9 H).

B.



2-pyridylmethyl lactam 1 (35 mg, 0.13 mmol) was dissolved in anhydrous THF (1 mL) and cooled to -78 °C. Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 130 uL, 0.13 mmol.) was added to give an

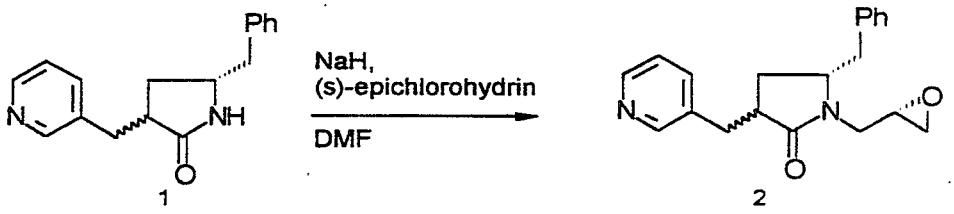
orangish brown anion. The anion solution was stirred at -78 °C for 35 minutes and was then cannulated under nitrogen over 30 seconds into a -78 °C solution of **2** (39 mg, 0.13 mmol) in 1mL of THF and was washed in with 0.5 mL of THF. The reaction was gradually warmed to room temperature over 4 hr, then stirred at room temperature for 3 days. The reaction was cooled to -78 °C, quenched with 0.5 mL of a saturated ammonium chloride solution, and concentrated *in vacuo* to remove the THF. The residue was partitioned between ethyl acetate and saturated bicarbonate solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with water, brine and dried (MgSO4) and filtered. Concentration *in vacuo* afforded 75 mg crude material which was purified via silica gel to give 18 mg(25%) of **3**. Maldi MS: M + H = 561.5 (MW = 560.79). TLC (EtOAc) Rf = 0.19 (major diast.) & 0.29 (minor diast.). TLC (5% MeOH/EtOAc) Rf = 0.28 (major diast.) & 0.36 (minor diast.). HPLC retention times were 11.24 min. (major) & 11.32 min. (minor).

^{1}H NMR ($CDCl_3$) d 8.52 (m, 1H), 7.61 (m, 1 H), 7.34-7.10 (m, 7H), 6.10-5.95 (m, 1H), 4.11 (m, 1H), 3.96-3.73 (m, 3H), 3.46-2.74 (m, 6H), 2.65-2.47 (m, 2H), 2.23 (m, 2H), 2.10-1.15(m, 15H), 1.37 (s,9H).

Example 61

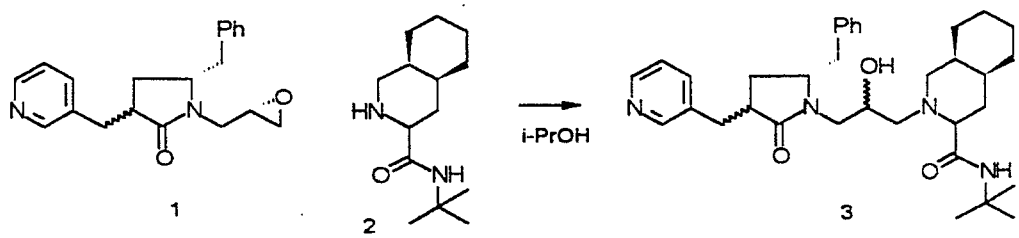
Synthesis of Compound 72

A.



3-pyridylmethyl lactam 1 (85 mg, 0.32 mmol) was dissolved in DMF (1.5 mL), cooled to 0 °C, and to this solution was added sodium hydride (0.48mmol) to give a yellow anion. The reaction mixture was stirred at 0 °C for 70 minutes after which (s)-epichlorohydrin (35 ul, 0.45 mmol) was added neat. The reaction was stirred at 0 °C for 5 minutes, then warmed to room temperature and stirred for 24 hours. The reaction was cooled to 0 °C and quenched with 0.5 mL of a saturated ammonium chloride solution. The reaction was partitioned between ethyl acetate and a saturated bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with water, brine and dried (MgSO4) and filtered. Concentration *in vacuo* afforded 49 mg of crude epoxide which was used without further purification.

B.



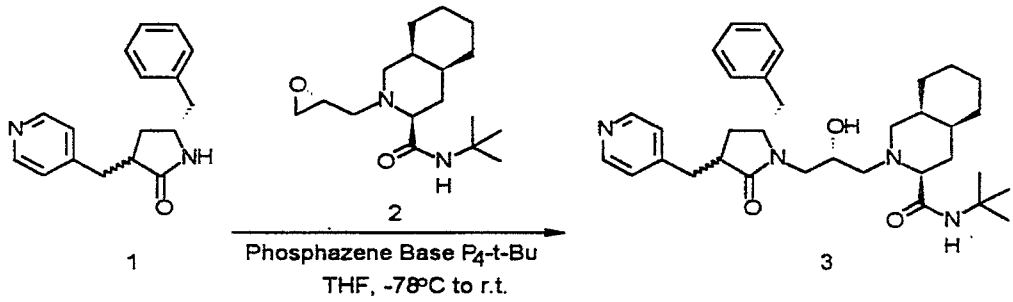
1 2 3

Crude lactam epoxide 1 (49 mg) and decahydroisoquinoline 2 (91 mg, 0.38 mmol) were heated to 65-70 °C in isopropanol. After 90 hours the reaction was cooled to 25 °C and stirred for 1 hour at room temperature. The reaction was then concentrated *in vacuo*, and purified by silica gel chromatography, eluting with 5 % MeOH : EtOAc, providing 30 mg (87% pure by HPLC) of desired product 3 as a mixture of 4 diastereomers. HPLC shows 2 split peaks 11.30 min. & 11.04 min.. TLC (5% MeOH/CH_2Cl_2) Rf = 0.27. TLC (10% MeOH/CH_2Cl_2) Rf = 0.45.

^{1}H NMR ($CDCl_3$) d 8.45-8.35 (m, 2H), 7.48 (m, 1 H), 7.35-7.09 (m, 6H), 6.63-5.94 (m, 1H), 3.98-3.63 (m, 3H), 3.42-2.73 (m, 5H), 2.70-2.11 (m, 5H), 2.07-1.20(m, 16H), 1.36 (s,9H).

Example 62

Synthesis of Compound 54



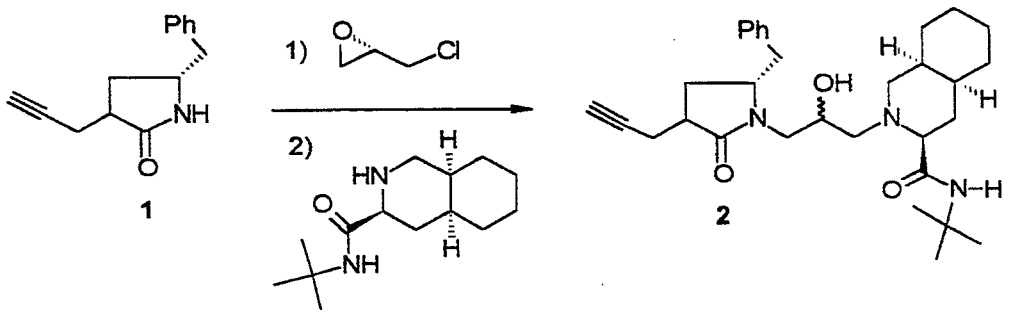
4-pyridylmethyl lactam **1** (33 mg, 0.12 mmol) was dissolved in anhydrous THF (1 mL) and cooled to -78 °C. Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 125 uL, 0.125 mmol) was added to give a brown anion. The anion solution was stirred at -78 °C for 35 minutes and was then cannulated under nitrogen over 30 seconds into a -78 °C solution of **2** (39 mg, 0.13 mmol) in 1mL of THF and was washed in with 0.5 mL of THF. The reaction was gradually warmed to room temperature over 4 hr, then stirred at room temperature for 3 days. The reaction was cooled to -78 °C, quenched with 0.5 mL of a saturated ammonium chloride solution, and concentrated *in vacuo* to remove the THF. The residue was then partitioned between ethyl acetate and saturated bicarbonate solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were then washed with water, brine and dried (MgSO4) and filtered. Concentration *in vacuo* afforded 83 mg crude material which was purified via silica gel

to give 11 mg(16%) of **3**. Maldi MS: M + H = 560.4. (MW = 560.79). TLC (EtOAc) Rf = 0.08 (major diast.) & 0.16 (minor diast.). TLC (5% MeOH/EtOAc) Rf = 0.18 (major diast.) & 0.26 (minor diast.). HPLC retention time was 11.05 min.

^{1}H NMR ($CDCl_3$) d 8.50 (m, 2H), 7.35-7.02 (m, 7H), 5.89 (m, 1H), 4.05-3.78 (m, 3H), 3.37-2.69 (m, 5H), 2.62-2.45 (m, 4H), 2.26 (m, 2H), 2.08-1.16(m, 15H), 1.38 (s,9H).

Example 63

Synthesis of Compound 130

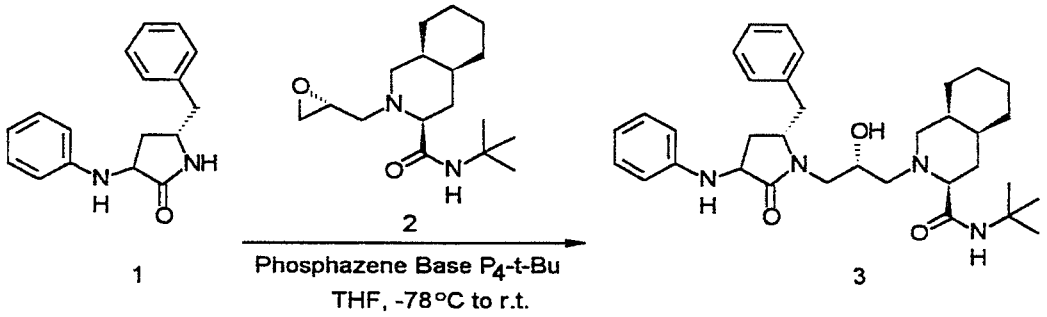


In an oven-dried 25 mL round-bottomed flask, alkyne lactam **1** (54.6 mg, 0.682 mmol) was dissolved in 5 mL of DMF. Sodium hydride (34.4 mg of a 60% dispersion in mineral oil, 0.860 mmol) was added with cooling using an ice-bath. Gas evolution was observed. (S)-Epichlorohydrin (60 uL, 0.765 mmol) was added. The mixture was stirred overnight at room temperature, then the decahydroisoquinoline amide (182 mg, 0.770 mmol) was added. The mixture was heated to 80 °C overnight. The mixture was cooled, poored into water, and

extracted with CH_2Cl_2. The organic extract was washed several times with water, dried ($MgSO_4$), and evaporated in vacuo to afford a yellow residue that was purified by preparative HPLC to afford the a diastereomeric mixture of alkyne DHIQ lactam **2** (120 mg, 34%) as a light yellow oil. HPLC: retention times of 13.57, 13.67, 13.87 minutes in a 5:1:1 ratio respectively. ^1H NMR : d 1.3-1.4 three singlets in a 2:1:1 ratio; 1.4-2.7 (several overlapping multiplets, 2.8-2.95 (multiplet), 3.0-3.7 (multiplet), 3.8-4.1 (multiplet), 5.95-6.05 (multiplet), 6.1, 6.18, 6.32, 6.4 (broad singlets in a 1:1:1:1 ratio), 6.2-6.3 (doublet of doublets), 7.15-7.35 (multiplet). MALDI-MS: peak at 506.3 ($M + H^+$).

Example 64

Synthesis of Compound 124

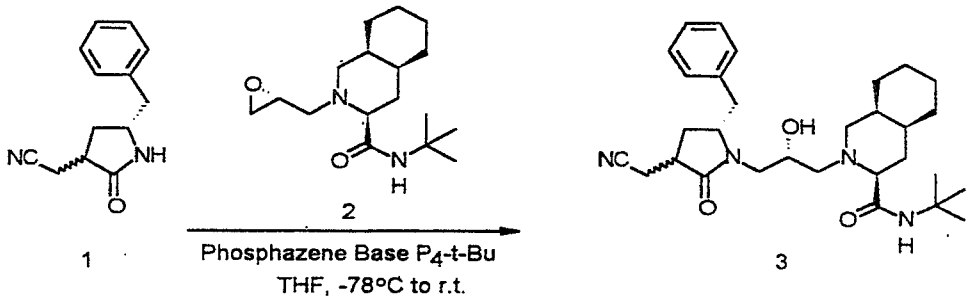


The lactam 1 (0.13 mmol) was dissolved in dry THF at -78 °C and to this solution was added Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 0.14 mmol). After stirring 15 minutes the anion solution was added via cannula to a solution of epoxide 2 (0.13 mmol)

dissolved in dry THF at -78 °C and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was taken up in dichloromethane and filtered through a plug of silica gel eluting with 8% MeOH in dichloromethane. Product containing fractions were concentrated *in vacuo* and the resultant residue further purified by preparative HPLC (column: Delta-Pak C_{18} 15mm 100Å 19x300 mm. Gradient: 20% to 100% acetonitrile in water with 0.1% TFA. Flow rate: 20 ml/min. Detection: 214 nm) to yield 3 mg of product 3 as a mixture of diastereomers; TLC R_f = 0.44 (8% MeOH/CH_2Cl_2); HPLC Rt = 14.8, 14.9 min (95%); MALDI-TOF MS *m/z* 561 (M^+); ^{1}H NMR ($CDCl_3$) d 7.35-7.10 (m, 7 H), 6.73 (m, 1 H), 6.58 (d, 2 H), 5.82 (br s, 1 H), 4.12-3.85 (m, 4 H), 3.51 (m, 1H), 3.30 (m, 1H), 2.92 (m, 1 H), 3.63-2.20 (m, 4 H), 2.05-1.12 (m, 18 H), 1.38 (s, 9 H).

Example 65

Synthesis of Compound 127

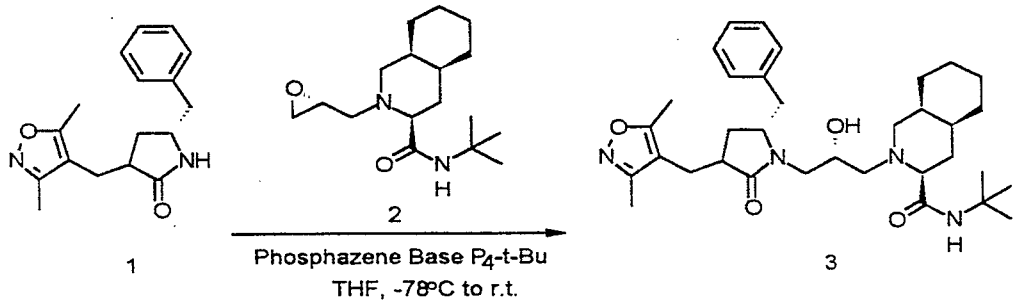


Cyanomethyl lactam 1 (82 mg, 0.38 mmol) was dissolved in anhydrous THF (2 mL) and cooled to -78 °C. Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 380 uL, 0.38 mmol) was added to give a yellow anion. The anion solution was stirred at -78 °C for 35 minutes and was then cannulated under nitrogen over 30 seconds into a -78 °C solution of **2** (112 mg, 0.38 mmol) in 2mL of THF and was washed in with 0.5 mL of THF. The reaction was gradually warmed to room temperature over 4 hr, then stirred at room temperature for 3 days. The reaction was cooled to -78 °C, quenched with 0.5 mL of a saturated ammonium chloride solution, and concentrated *in vacuo* to remove the THF. The residue was then partitioned between ethyl acetate and saturated bicarbonate solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with water, brine and dried (MgSO4) and filtered. Concentration *in vacuo* afforded 375 mg crude material which was purified via silica

gel (8 : 2, ethyl acetate: CH_2Cl_2, to give 118 mg(61%) of 3 that was < 80% pure. 58 mg was purified via prep. HPLC to give 10 mg of pure material as a 2: 1 mixture of diastereomers. HPLC retention times were 12.73 min. (67%) & 12.86 min. (33%). Maldi MS: M + H = 510.47 (MW = 508.71). TLC (EtOAc) Rf = 0.37 & 0.31.
^1H NMR ($CDCl_3$) d 7.38-7.13 (m, 5H), 6.09-5.82 (br s, 1H), 4.29-3.96 (m, 3H), 3.84 (m, 1H), 3.49-2.91 (m, 5H), 2.77-2.18 (m, 9H), 2.10-1.20(m, 11H), 1.39 (s,9H).

Example 66

Synthesis of Compound 131

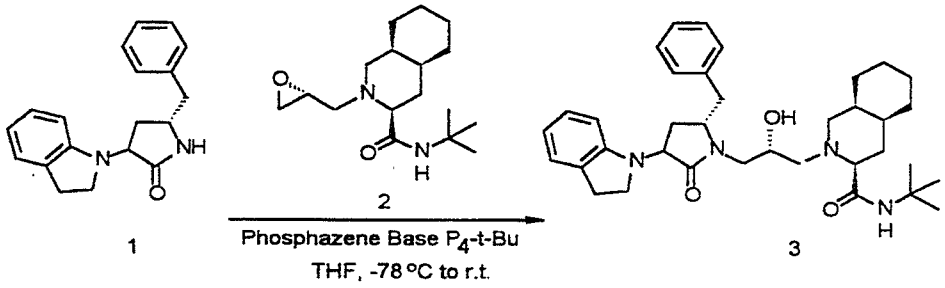


The lactam 1 (0.061 mmol) was dissolved in dry THF at -78 °C and to this solution was added Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 0.067 mmol). After stirring 15 minutes the anion solution was added via cannula to a solution of epoxide 2 (0.061 mmol) dissolved in dry THF at -78 °C and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine,

followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was purified by flash silica gel chromatography eluting with 3% MeOH in dichloromethane to give 2.1 mg of product 3 as a 1:1 mixture of diastereomers; TLC R_f = 0.14 (2:1 ethyl acetate/hexanes); HPLC Rt = 13.6, 13.8 min (68%); MALDI-TOF MS *m/z* 580 (M^+); ^{1}H NMR ($CDCl_3$) d 7.32-7.08 (m, 5 H), 5.86 (br s, 1 H), 4.08-3.73 (m, 4 H), 3.65-3.14 (m, 4H), 3.00-2.49 (m, 8H), 2.41-0.92 (m, 13 H), 2.27 (s, 1.5 H), 2.22 (s, 1.5 H), 2.16 (s, 1.5 H), 2.11 (s, 1.5 H), 1.46 (s, 9 H).

Example 67

Synthesis of Compound 126

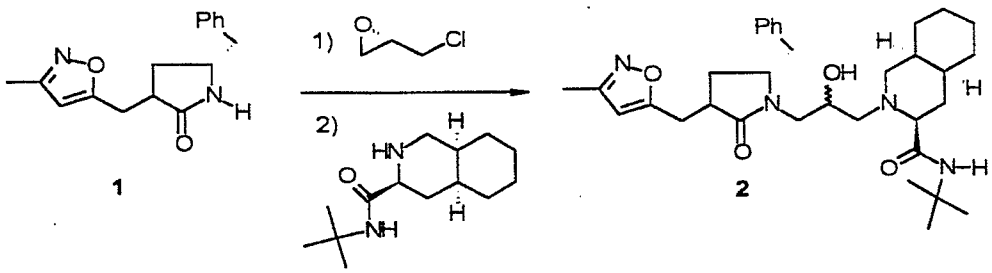


The lactam 1 (0.20 mmol) was dissolved in dry THF at -78 °C and to this solution was added Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 0.21 mmol). After stirring 15 minutes the anion solution was added via cannula to a solution of epoxide 2 (0.20 mmol) dissolved in dry THF at -78 °C and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted

with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was taken up in dichloromethane and filtered through a plug of silica gel eluting with 3% MeOH in dichloromethane. Product containing fractions were concentrated *in vacuo* and the resultant residue further purified by preparative HPLC (column: Delta-Pak C_{18} 15mm 100Å 19x300 mm. Gradient: 20% to 100% acetonitrile in water with 0.1% TFA. Flow rate: 20 ml/min. Detection: 214 nm) to yield 2.5 mg of product 3 as a mixture of diastereomers; TLC R_f = 0.21 (3% MeOH/CH_2Cl_2); HPLC Rt = 14.8 min (98%); MALDI-TOF MS *m/z* 588 (M^+).

Example 68

Synthesis of Compound 132

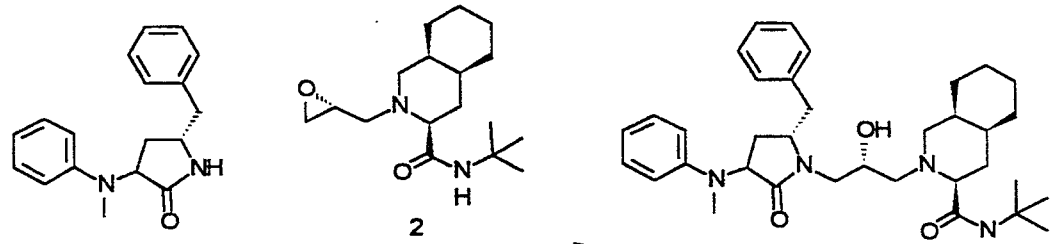


In an oven-dried 25 mL round-bottomed flask, isoxazole lactam **1** (54.6 mg, 0.201 mmol) was dissolved in 3 mL of THF. (S)-Epichlorohydrin (20 uL, 0.255 mmol) was added. P-4-tBu phosphazene base (210 uL, 0.210 mmol)

was added dropwise via syringe initially producing a dark orange-brown color that faded. The mixture was stirred for 30 minutes at room temperature and the mixture was poured into water and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in anhydrous CH_3CN and the decahydroisoquinoline amide (54.4 mg, 0.230 mmol) was added. The mixture was refluxed overnight. The solvent was evaporated and the residue was purified by preparative HPLC to afford the isoxazole DHIQ lactam **2** (38 mg, 34%) as a light yellow oil. HPLC: retention times of 12.28, 12.86, 13.68 minutes at 93% purity. ^1H NMR : d 1.3-1.4 three singlets in a 4:4:1 ratio; 1.4-2.7 (several overlapping multiplets, 1.4-2.3 (several overlapping multiplets), 2.45-3.35 (several overlapping multiplets), 3.35-4.1 (several multiplets), 4.3-4.4 (doublet), 5.8 (multiplet), 5.9, 6.0, and 6.3 (three broad singlets in a ratio of 4:4:1 ratio), 7.1-7.2 (multiplet), 7.2-7.4 (multiplet). MALDI-MS: calc'd: 564.9; found 565.5 ($M + H^+$).

Example 69

Synthesis of Compound 125



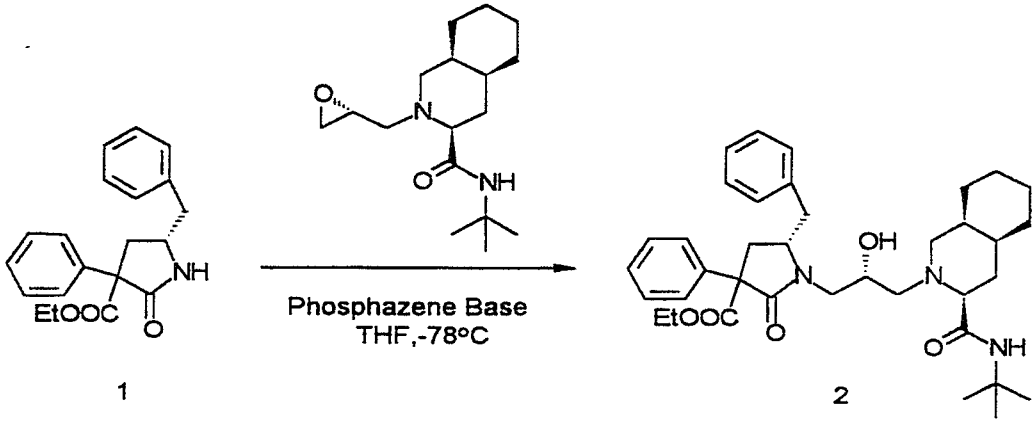
The lactam 1 (0.12 mmol) was dissolved in dry THF at -78 °C and to this solution was added Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 0.13 mmol). After stirring 15 minutes the anion solution was added via cannula to a solution of epoxide 2 (0.12 mmol) dissolved in dry THF at -78 °C and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was taken up in dichloromethane and filtered through a plug of silica gel eluting with 3% MeOH in dichloromethane. Product containing fractions were concentrated *in vacuo* and the resultant residue further purified by preparative HPLC (column: Delta-Pak C_{18} 15mm 100Å 19x300 mm. Gradient: 20% to 100% acetonitrile in water with 0.1% TFA. Flow rate: 20 ml/min. Detection: 214 nm) to yield 1.5 mg of product 3 as a

single diastereomer; TLC R_f = 0.27 (3% MeOH/CH_2Cl_2); HPLC Rt = 14.7 min (100%); MALDI-TOF MS *m/z* 576 (M^+); ^1H NMR ($CDCl_3$) d 7.40-7.15 (m, 7 H), 6.70 (m, 1 H), 6.55 (d, 2 H), 5.80 (br s, 1 H), 4.28 (m, 1 H), 4.05-3.90 (m, 2 H), 3.70-3.38 (m, 2H), 3.20 (m, 1H), 3.00-2.75 (m, 2 H), 2.70 (s, 3 H), 2.55 (m, 2H), 2.30 (m, 2H), 2.20-0.80 (m, 14 H), 1.35 (s, 9 H).

Example 70

Sunthesis of Compound 128

A.

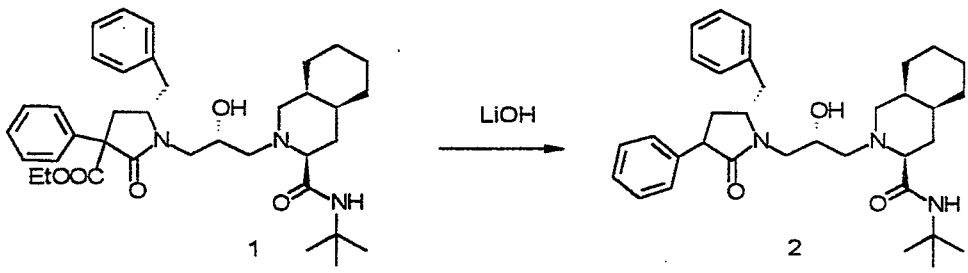


1 2

The lactam 1 (90 mg, 0.28 mmol) was dissolved in THF (3 mL) and cooled to -78 °C. This was followed by the addition of the phosphazene base (Fluka; 1M in hexane, 0.28 mL, 0.28 mmol). After stirring at -78 °C for one hour the epoxide was added as a solution in 1 mL THF. The reaction was then warmed to 25 °C and stirred for an additional 3 hours. The reaction was then quenched

by the addition of water and extracted by ethyl acetate. The organic portion was then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude oil was purified by silica gel chromatography, eluting with 1:1, ethyl acetate:hexanes, this provided the two major products (HPLC indicated two components for each isolate).

B.

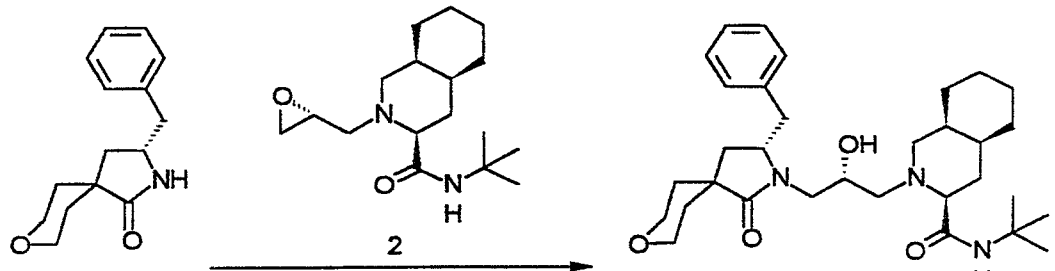


To the elaborated lactam 1 (40 mg) in 2:1, THF:H_2O (5 mL) was added LiOH (2 eq.). The reaction was then stirred at 40 °C for 16 hours. TLC indicated the formation of a new component. The reaction was diluted by ethyl acetate, after which the organic portion was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. to yield product 2 as a mixture of diastereomers.

^1H NMR ($CDCl_3$) : d 7.10-7.50 (m, 10 H), 5.90-6.15 (m, 1H), 3.90-4.40 (m, 2H), 3.20-3.70 (m, 3H), 2.80-3.10 (m, 2H), 2.60-2.70 (m, 2H), 2.20-2.60 (m, 3H), 1.60-2.10 (m, 9H), 1.40 (q, 15H), 1.20-1.40 (m, 8H).

Example 71

Synthesis of Compound 259



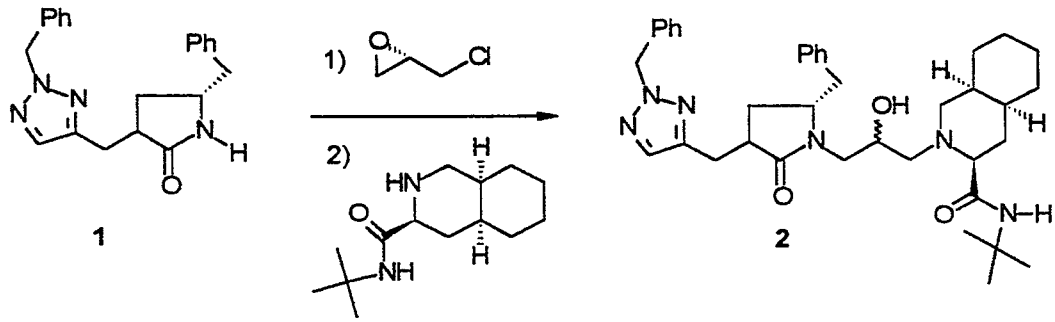
1 2 3

The lactam 1 (0.11 mmol) was dissolved in dry THF at -78 °C and to this solution was added Phosphazene Base P_4-t-Bu (Fluka, 1.0M in hexane, 0.12 mmol). After stirring 15 minutes the anion solution was added via cannula to a solution of epoxide 2 (0.11 mmol) dissolved in dry THF at -78 °C and the reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated aqueous NaHCO3 and brine, followed by drying (MgSO4), filtration and concentration *in vacuo*. The crude residue was taken up in dichloromethane and filtered through a plug of silica gel eluting with 5% MeOH in dichloromethane. Product containing fractions were concentrated *in vacuo* and the resultant residue further purified by preparative HPLC (column: Delta-Pak C_{18} 15mm 100Å 19x300 mm. Gradient: 20% to 100% acetonitrile in water with 0.1% TFA. Flow rate: 20 ml/min.

Detection: 214 nm) to yield 12 mg of product 3; TLC R_f = 0.50 (8% MeOH/CH_2Cl_2); HPLC Rt = 12.8 min (100%); MALDI-TOF MS *m/z* 541 (M^+); ^1H NMR ($CDCl_3$) d 7.35-7.16 (m, 5 H), 5.86 (br s, 1 H), 4.08-3.76 (m, 4 H), 3.49-3.22 (m, 4 H), 2.89 (br s, 1 H), 2.50 (m, 2 H), 2.25 (br s, 1H), 2.14-1.11 (m, 22 H), 1.38 (s, 9 H).

Example 72

Synthesis of Compound 260



In an oven-dried 25 mL round-bottomed flask, triazole lactam **1** (124 mg, 0.358 mmol) was dissolved in 5 mL of THF. (S)-Epichlorohydrin (50 uL, 0.639 mmol) was added. P-4-tBu phosphazene base (370 uL of 1.0M solution in hexane, 0.370 mmol) was added dropwise via syringe initially producing a dark orange-brown color that faded. The mixture was stirred for 30 minutes at room temperature and the decahydroisoquinoline amide (124 mg, 0.525 mmol) was added. The mixture was refluxed overnight. The solvent was evaporated and the residue was purified by preparative HPLC to afford the triazole DHIQ lactam (189.1 mg, 84%). HPLC: retention times of 12.94, 14.22 minutes at 99% purity.

^{1}H NMR : d1.3-1.4 two singlets in a 1:1 ratio; 1.4-3.1 (several overlapping multiplets, 1.4-2.3 (several overlapping multiplets), 2.45-3.35 (several overlapping multiplets), 3.2-4.2 (several multiplets), 5.4-5.6 (multiplet), 6.1 and 6.45 (two broad singlets in a 1:1 ratio), 5.9, 6.0, and 6.3 (three broad singlets in a ratio of 4:4:1 ratio), 7.1 (doublet), 7.2-7.5 (multiplet). MALDI-MS: calc'd (-DHIQ): 401.2; found 403.6 (M - DHIQ + $2H^+$).

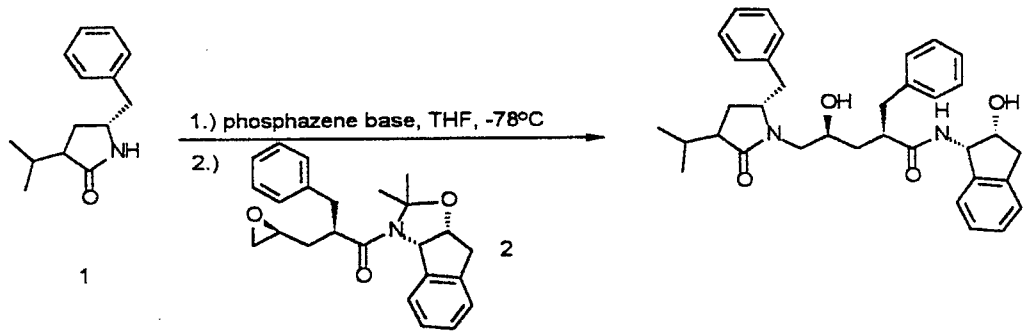
Example 73

Synthesis of Compound 129

In a heavy-walled screw-top test tube, the alkyne lactam **1** (83 mg, 0.164 mmol) was dissolved in 5 mL of xylene. Tributyltin azide (200 mg, 0.602 mmol) was added, the tube was sealed and heated to 205° C overnight. The dark brown solution was cooled and directly chromatographed using a gradient from CH_2Cl_2 to 50% EtOAc/MeOH to afford the triazole product **2** (14 mg, 2.5%) as a light yellow oil. HPLC: retention times of 12.01, 12.44, 13.01, 13.22 minutes in an 8:4:1:1 ratio at 99% purity. MALDI-MS: calc'd (-DHIQ): 550.4; found 552.9 (M + $2H^+$).

Example 74

Synthesis of Compound 227

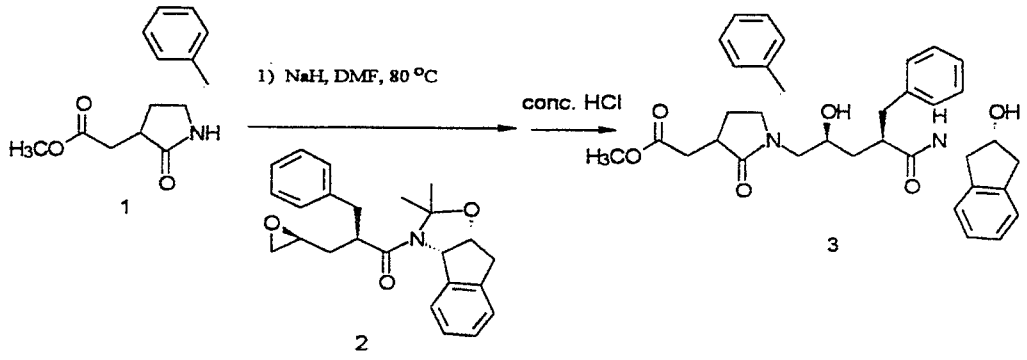


To a cooled solution (-78 °C) of lactam 1 (0.10g, 0.46mmol) in anhydrous THF (1.0mL) was added phosphazene base P4 t-butyl solution (1.0M in hexanes, 0.46mL,0.46mmol) with stirring. After a 15 min. stirring period, epoxide 2 (0.173g,0.46mmol) was added in one portion and the reaction was allowed to slowly warm to rt. After 0.5h at rt, 1.0M HCl (10.0mL) was added and the solution was diluted with ethyl acetate (60mL).. The ethyl acetate was washed with sat. $NaHCO_3$ (1 x 10mL), brine (1 x 10mL) dried ($MgSO_4$), filtered, and evaporated to give a brown foam. The crude acetonide (0.270g, 0.46mmol) was dissolved in isopropanol (10mL) and treated with conc. HCl (3.0mL) at rt. After 2.0h., the solution was adjusted to pH 11 with 3.0N NaOH and extracted with ethyl acetate (3 x75mL) . The ethyl acetate was dried($MgSO_4$) and evaporated to give the crude product which was purified by column chromatography: methylene chloride/methanol (98/2) to give the product as an off white solid (0.090g, 36%). MS: crude acetonide: M+Na = 617;

product: M+Na = 577 ^{1}H NMR ($CDCl_3$) 0.90(m, 6H); 1.15(m, 1H); 1.40(m, 1H); 1.50-1.80(m, 2H); 1.90(m,1H); 2.18(m, 2.25H); 2.30-2.50(m, 1H); 2.60(m, 0.75H); 2.80-3.10(m, 4H); 3.30(m, 2H); 3.60(m, 1.25H); 3.80(m, 1.75H); 3.95(m, 1H); 4.25(m, 1H); 4.40(m, 0.75H); 5.00(m, 0.25H); 5.25(m, 1H); 5.95(d, 0.25H); 6.10(d, 0.75H); 7.00-7.40(m, 14H)

Example 75

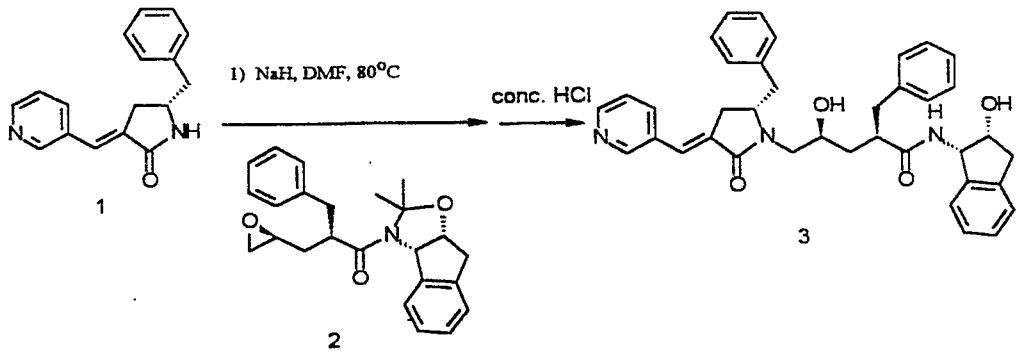
Synthesis of Compound 232



Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography: 60/40 hexane/ethyl acetate. MS: M+NA = 647. The product was purified by column chromatography: 98/2 CH_2Cl_2/MeOH. MS: M+H = 585 ^{1}H NMR ($CDCl_3$) 1.70(m, 2H); 1.80(m, 1H); 1.90(m, 1H); 2.10(m, 1H); 2.40-3.10(m, 10H); 3.60(s, 3H); 3.75(m, 1H); 3.90(m, 1H); 4.0(m, 1H); 4.30(m, 3H); 5.30(m, 1H); 6.10(d, 1H); 7.00-7.40(m, 14H).

Example 76

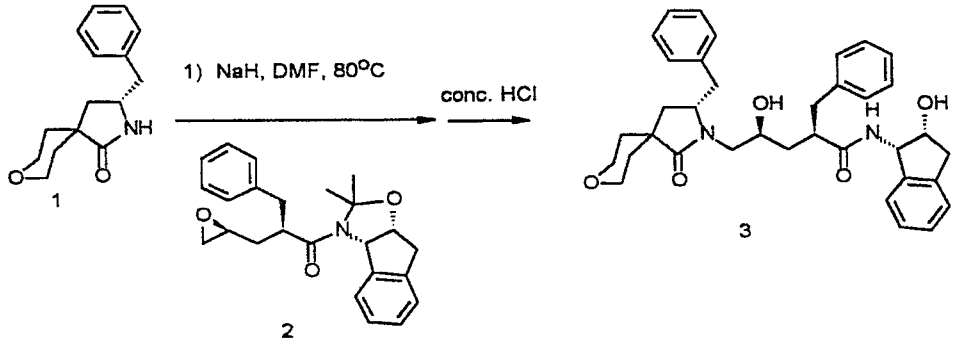
Synthesis of Compound 231



Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography: 98/2 CH_2Cl_2/MeOH. MS: M+H = 642. The product was purified by column chromatography: 96/4 CH_2Cl_2/MeOH. MS: M+H = 602 ^{1}H NMR ($CDCl_3$) 1.50-2.50(m, 6H); 2.50-3.40(m, 6H); 3.50-4.40(m, 7H); 5.25(m, 1H); 5.95(m, 1H); 7.00-7.60(m, 18H).

Example 77

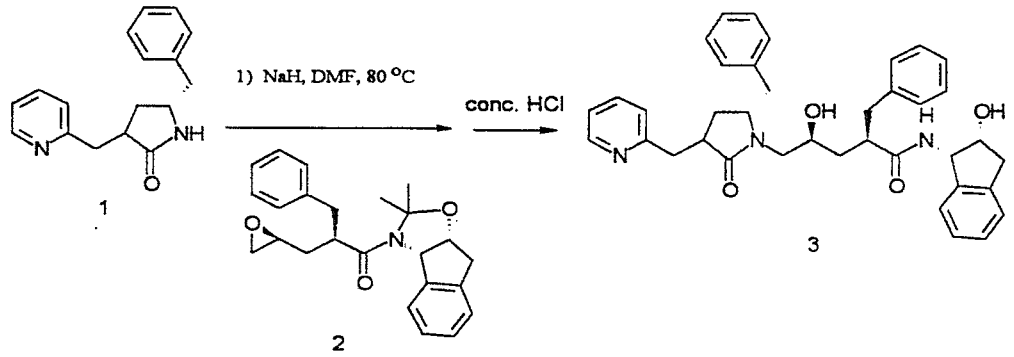
Synthesis of Compound 216



Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography: 50/50 hexane/ethyl acetate. MS: M+NA = 645. The product was purified by column chromatography: 96/4 CH_2Cl_2/MeOH. MS: M+NA = 605 ^{1}H NMR ($CDCl_3$) 1.10-1.40(m, 2H); 1.70(m, 2H); 1.80-2.10(m, 4H); 2.35(m, 0.5H); 2.50(m, 1H); 2.65(m,0.5H); 2.80-3.10(m, 4H); 3.20(m, 2H); 3.30-3.55(m, 3H); 3.70(m, 1H); 3.80-4.00(m, 4H); 4.25(m, 1H); 4.37(m, 1H); 5.27(m, 1H); 6.15(d, 1H); 7.10-7.40(m, 14H).

Example 78

Synthesis of Compound 221

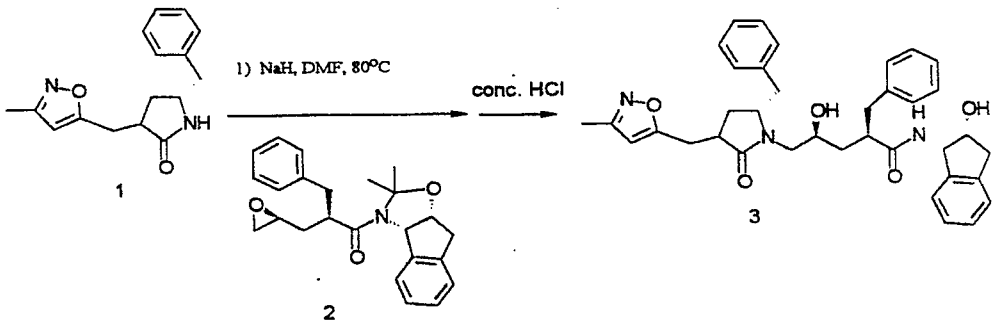


1 2 3

Prepared using the procedure outlined in **Example 24**. The acetonide was not purified by column chromatography. MS: (crude) M+H = 644. The product was purified by column chromatography: 96/4 CH_2Cl_2/MeOH. MS: M+H = 604 ^{1}H NMR ($CDCl_3$) 1.40-2.20(m, 6H); 2.30(m, 1H); 2.50-3.40(m, 9H); 3.75(m, 2H); 4.00(m,1H); 4.25(m, 1H); 5.30(m, 1H); 6.35(d, 0.5H); 6.50(d, 0.5H); 7.00-7.40(m, 14H); 7.50(m, 2H); 8.50(m, 2H).

Example 79

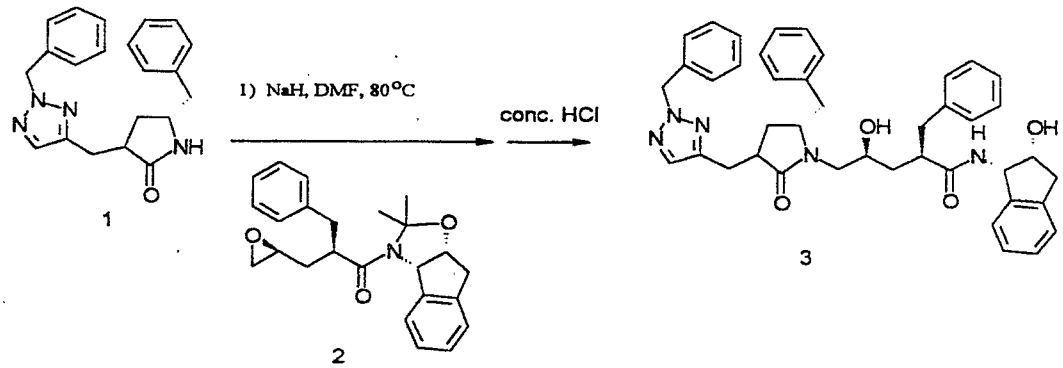
Synthesis of Compound 223



Prepared using the procedure outlined in **Example 24**. The acetonide was not purified by column chromatography. MS: (crude) M+NA = 670. The product was purified by column chromatography: 97/3 CH_2Cl_2/MeOH. MS: M+NA = 630 ^1H NMR ($CDCl_3$) 1.40(m, 1H); 1.30-1.80(m, 2H); 1.95(m, 1H); 2.10(m, 1H); 2.25(m, 2H); 2.30-3.40(m, 7H); 3.60-3.80(m, 2H); 3.85(m,1H); 4.00(m, 1H); 4.25(m, 1H); 4.45(m,1H); 5.30(m, 1H); 5.80(m,1H); 6.15(d, 1H); 7.10-7.40(m, 14H).

Example 80

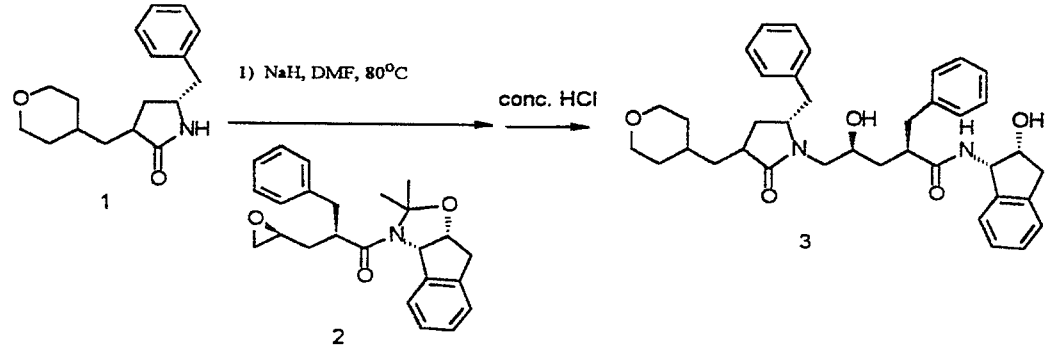
Synthesis of Compound 230



Prepared using the procedure outlined in **Example 24.** The acetonide was not purified by column chromatography. MS: (crude) M+NA = 746. The product was purified by column chromatography: 97/3 CH_2Cl_2/MeOH. MS: M+NA = 706.

Example 81

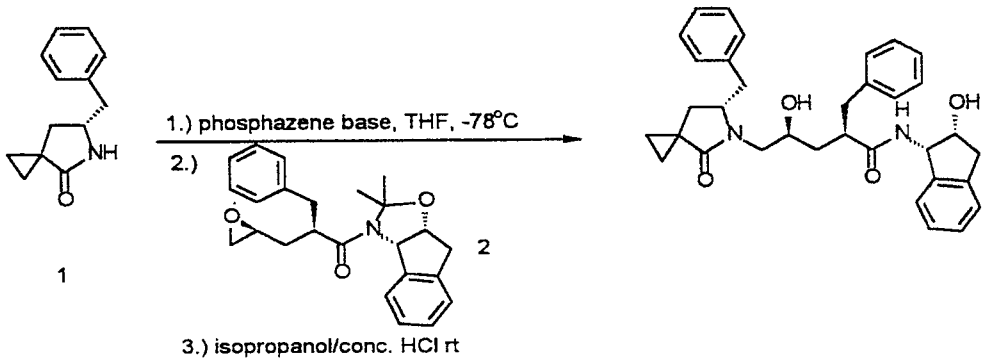
Synthesis of Compound 224



Prepared using the procedure outlined in **Example 24**. The acetonide was not purified by column chromatography. MS: (crude) M+NA = 673. The product was purified by column chromatography: 96/4 CH_2Cl_2/MeOH. MS: M+NA = 633 ^1H NMR ($CDCl_3$) 0.090-1.30(m, 4H); 1.40-1.80(m, 4H); 1.90-2.35(m, 3H); 2.45 (m, 1H); 2.65(m, 1H); 2.70-3.10(m, 6H); 3.25(m, 3H); 3.60-4.00(m, 6H); 4.25(m, 1H); 4.35(m, 0.5H); 4.75(m, 0.5H); 5.25(m, 1H); 6.20(m, 1H); 7.10-7.40(m, 14H).

Example 82

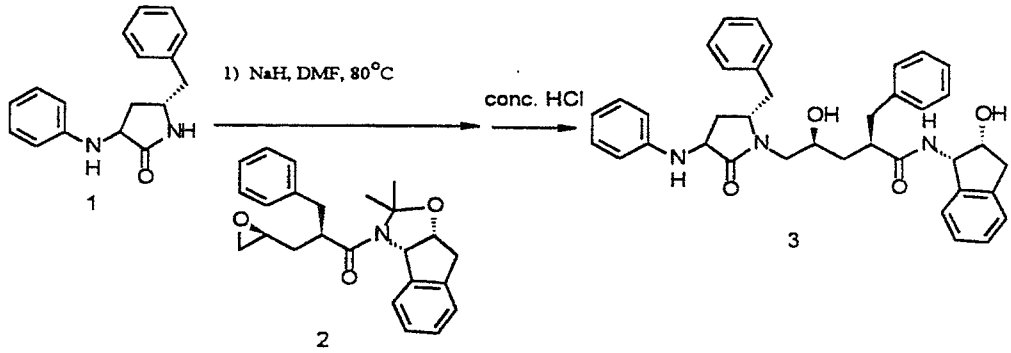
Synthesis of Compound 225



Prepared using the procedure outlined in **Example 74**. The acetonide was not purified by column chromatography. MS: (crude) 2M+NA = 1179. The product was purified by column chromatography: 80/20 ethyl acetate/hexane. MS: M+H = 539 ^1H NMR ($CDCl_3$) 0. 55 (m, 1H); 0.659m, 1H); 0.95(m, 1H); 1.05(m, 1H); 1.75(m, 2H); 1.95(m, 1H); 2.20 (dd, 1H); 2.65(dd, 1H); 2.70-3.10(m, 6H); 3.20(d, 1H); 3.65(dd, 1H); 3.95m, 2H); 4.25(t, 1H); 5.25(m, 1H); 5.95(d, 1H); 7.10-7.40(m, 14H).

Example 83

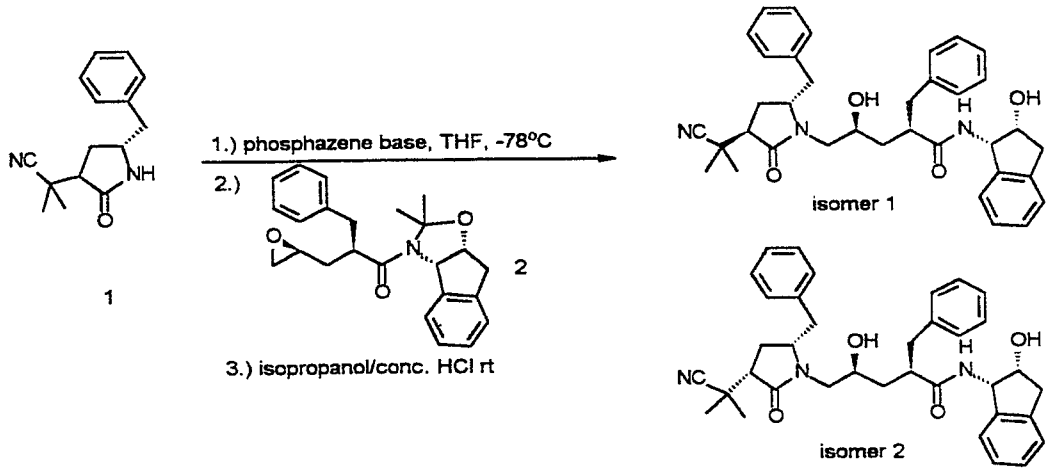
Synthesis of Compound 226



Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography:60/40 hexane/ethyl acetate. MS: M+NA = 666. The product was purified by column chromatography: 40/60 hexane/ethyl acetate. MS: M+H = 604 ^{1}H NMR 1. 55 (m, 0.5H); 1.70m, 0.5H); 1.95(m, 1H); 2.50 (m, 1H); 2.70-3.10(m, 7.5H); 3.15(dd, 1H); 3.30(m, 1H); 3.40(m, 1H); 3.75(m, 1H); 3.80-4.10(m, 2H); 4.25(m, 2.5H); 4.45(m, 0.5H); 5.25(m, 1H); 6.15(m, 1H); 6.45(d, 1H); 6.55(q, 1H); 6.70(q, 1H); 7.10-7.40(m, 16H).

Example 84

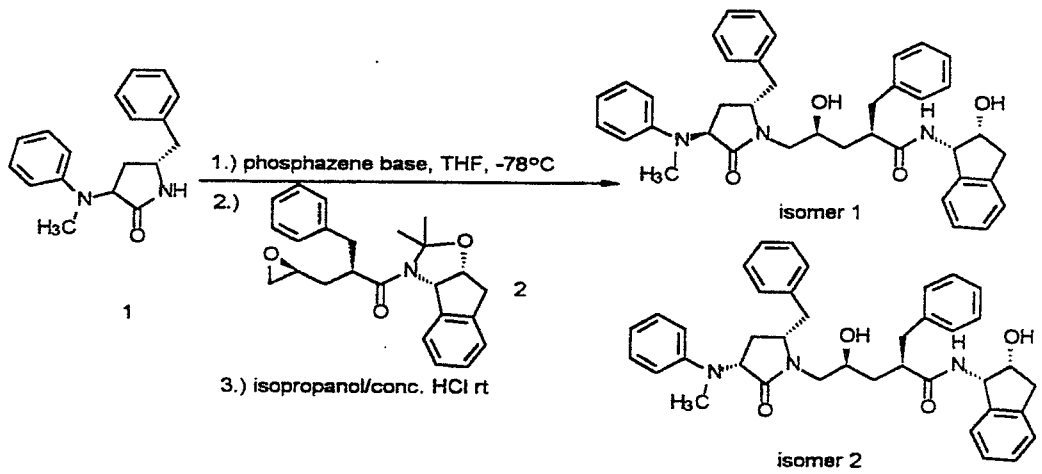
Synthesis of Compound 229



Prepared using the procedure outlined in **Example 74** The acetonide was purified by column chromatography and the diasteriomers were isolated separately. MS: (isomer 1) M+NA = 642; (isomer 2) M+NA = 642. The individual diastereomers were deprotected and purified by column chromatography: 98/2 CH_2Cl_2/MeOH to give isomer 1 and isomer 2. MS: (isomer 1) M+NA = 602; (isomer 2) M+NA = 602. ^1H NMR ($CDCl_3$) isomer 1: 1.05 (d, 1H); 1.35(s, 3H); 1.45 (s, 3H); 1.75(m, 1H); 1.90-2.20(m, 3H); 2.65(m, 1H); 2.70-3.10(m, 8H); 3.70(m, 1H); 3.95(m, 2H); 4.20(m, 1H); 4.35(m, 1H); 5.25(m, 1H); 6.05(d, 1H); 7.10-7.40(m, 14H). ^1H NMR ($CDCl_3$) isomer 2: 1.10 (d, 1H); 1.40(s, 3H); 1.50 (s, 3H); 1.75(m, 1H); 1.95(m, 1H); 2.15(m, 1H); 2.50(m, 2H); 2.80-3.10(m, 6H); 3.35(m, 2H); 3.65(m, 1H); 3.80(m, 1H); 4.00(m, 2H); 4.25(m, 1H); 5.25(m, 1H); 5.95(d, 1H); 7.10-7.40(m, 14H).

Example 85

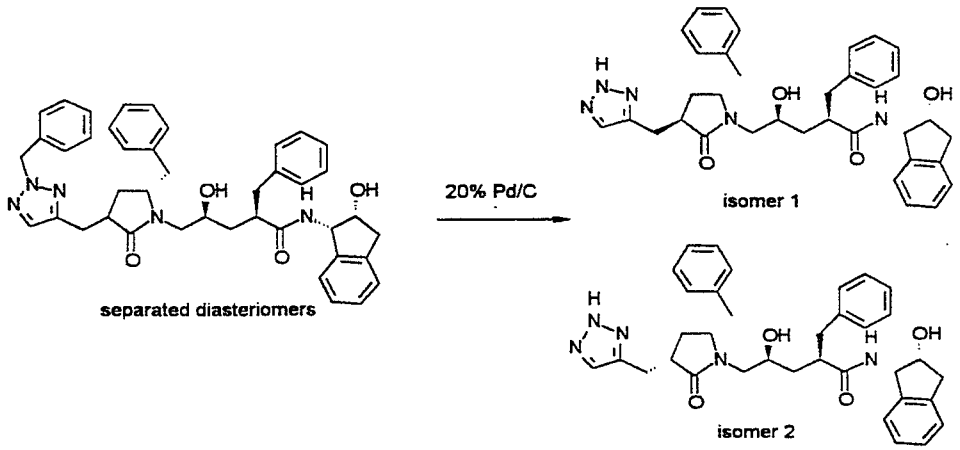
Synthesis of Compound 261



Prepared using the procedure outlined in **Example 74**. The acetonide was purified by column chromatography: 60/40 hexane/ethyl acetate and the diasteriomers were isolated separately. MS: (isomer 1) M+H = 658; (isomer 2) M+H = 658. The individual diastereomers were deprotected and purified by column chromatography: 40/60 hexane/ethyl acetate to give isomer 1 and isomer 2. MS: (isomer 1) M+H = 618; (isomer 2) M+NA = 640. ^1H NMR ($CDCl_3$) isomer 1: 1.75(m, 1H); 1.90-2.20(m, 3H); 2.70(s, 3H); 2.75-3.15(m, 6H); 3.75(m, 1H); 4.00(m, 3H); 4.25(m, 1H); 4.65(m, 1H); 5.25(m, 1H); 6.05(d, 1H); 6.55(dd, 2H); 6.70(m, 1H); 7.00-7.40(m, 16H). ^1H NMR ($CDCl_3$) isomer 2: 1.70(m, 2H); 1.95(m, 1H); 2.25(m, 1H); 2.55(m, 1H); 2.70(s, 3H); 2.80-3.10(m, 8H); 3.35(dd, 1H); 3.40(dd, 1H); 3.75(m, 1H); 3.80(m, 1H); 4.05(m, 1H); 4.25(m, 1H); 4.55(t, 1H); 5.30(m, 1H); 6.05(d, 1H); 6.70(m, 2H); 7.10-7.40(m, 17H).

Example 86

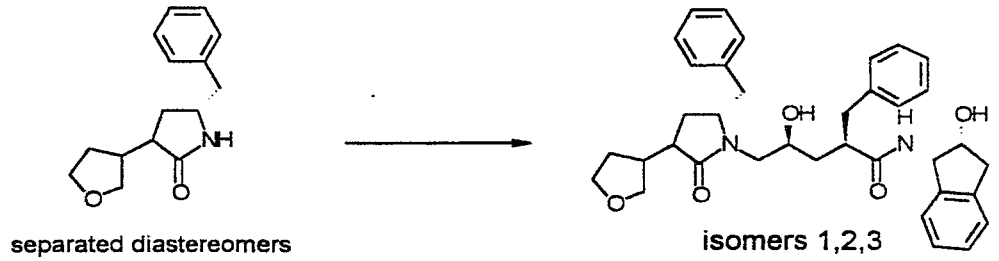
Synthesis of Compound 228



The benzyl triazole from **Example 80** was purified (and diastereomers isolated) by column chromatography: 97/3 CH_2Cl_2/MeOH. MS: M+NA = 706. The individual benzyl protected diastereomers were dissolved in MeOH and combined with 20% Pd/C (cat.). Each solution was hydrogenated under pressure(50 psi) at rt for 5 days and the resulting crude product was purified by column chromatography 96/4 CH_2Cl_2/MeOH to give isomers 1 and 2. MS: (isomer 1) M+H = 594; (isomer 2) M+NA = 616. ^1H NMR ($CDCl_3$) isomer 1: 1.60(m, 1H); 1.80(m, 2H); 2.40(s, 1H); 2.60-3.15(m, 10H); 3.65(m, 1H); 3.80(m, 1H); 4.00(m, 1H); 4.20(m, 1H); 5.25(m, 1H); 6.90(m, 1H); 7.00-7.40(m, 14H). ^1H NMR ($CDCl_3$) isomer 2: 1.30(m, 1H); 1.75(m, 1H); 1.95(m, 2H); 2.35(m, 1H); 2.50(m, 1H); 2.80-3.10(m, 8H); 3.25(d, 1H); 3.65(m, 1H); 3.80(m, 1H); 4.05(m, 1H); 4.30(m, 1H); 4.50(m, 1H); 5.25(m, 1H); 6.75(m, 1H); 7.10-7.40(m, 14H).

Example 87

Synthesis of Compound 219



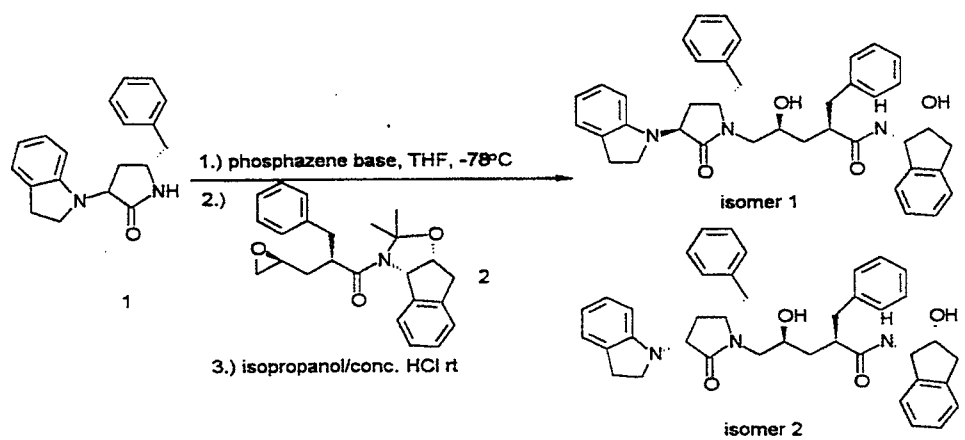
Isomer 1: Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography 30/70 hexane/ethyl acetate MS: M+NA = 645. The product was purified by column chromatography: 30/70 hexane/ethyl acetate MS: M+NA = 605 ^{1}H NMR ($CDCl_3$) 1.45(m, 1H); 1.70(m, 1H); 1.80-2.05(m, 4H); 2.25 (q, 1H); 2.35(q, 1H); 2.65(m, 1H); 2.75-3.10(m, 8H); 3.60(m, 3H); 3.75(m,1H); 3.85(m, 1H); 3.95(m, 2H); 4.25(m, 1H); 5.25(m, 1H); 6.05(m, 1H); 7.10-7.40(m, 14H).

Isomers 2,3:(Chiral center within THF ring has opposite configuration to that of isomer 1 above). Prepared using the procedure outlined in **Example 74**. The acetonide was purified (diastereomers isolated) by column chromatography 30/70 hexane/ethyl acetate MS: M+NA = 645. The individual diastereomers were purified by column chromatography: 30/70 hexane/ethyl acetate MS: (isomer 2) M+NA = 605 (isomer 3) M+NA = 605 ^{1}H NMR ($CDCl_3$) (isomer 2) 1.45(m, 2H); 1.90(m, 2H); 2.10(m, 1H); 2.30 (m, 1H); 2.35(m, 1H); 2.45(m, 1H); 2.75-3.10(m, 6H); 3.25(m, 2H); 3.65(m, 3H); 3.75(m,3H); 3.95(m, 2H); 4.25(m, 2H); 5.25(m, 1H); 6.10(m, 1H);

7.10-7.40(m, 14H). ^{1}H NMR ($CDCl_3$) (isomer 3) 1.15(m, 1H); 1.80(m, 1H); 1.95(m, 2H); 2.10(m, 1H); 2.25 (m, 1H); 2.40(m, 1H); 2.60(m, 1H); 2.75-3.10(m, 8H); 3.40(m, 1H); 3.60-4.00(m, 6H); 4.25(m, 1H); 5.25(m, 1H); 6.05(m, 1H); 7.10-7.40(m, 14H).

Example 88

Synthesis of Compound 233

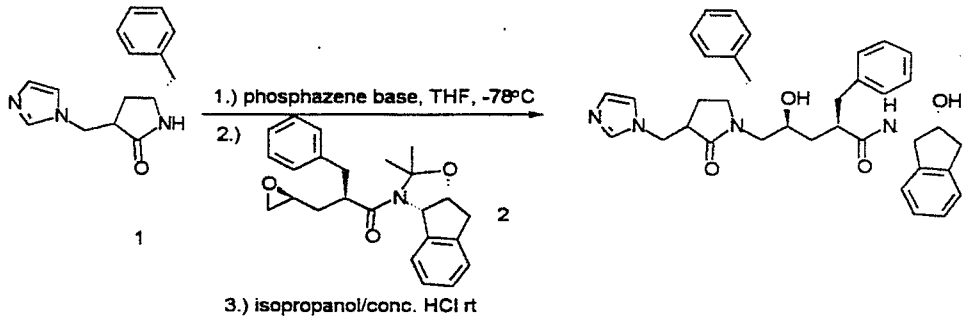


Prepared using the procedure outlined in **Example 74**. The acetonide was purified (diastereomers isolated) by column chromatography 45/55 hexane/ethyl acetate MS: M+NA = 692. The individual diastereomers were purified by column chromatography: 35/65 hexane/ethyl acetate MS: (isomer 1) M+H = 630 (isomer 2) M+H = 630 ^{1}H NMR ($CDCl_3$) (isomer 1) 1.75(m, 1H); 1.95(m, 1H); 2.10(m, 2H); 2.75-3.10(m, 8H); 3.15(d, 2H); 3.30(m, 2H); 3.80(m,2H); 4.00(m, 2H); 4.25(m, 1H); 5.25(m, 1H); 6.00(m, 1H); 6.20(d, 1H); 6.60(t, 1H); 6.95-7.40(m, 18H). ^{1}H NMR ($CDCl_3$) (isomer 2) 1.75(m, 1H); 1.95(m, 2H); 2.15(m, 1H); 2.55 (m, 1H); 2.75-3.10(m, 8H); 3.20-

3.50(m, 4H); 3.75 (m, 1H); 3.85(m,1H)4.00(m, 1H); 4,25(m, 1H); 4.35(m, 1H); 5.25(m, 1H); 6.10(m, 1H); 6.30(m, 1H); 6.56(t, 1H);7.10-7.40(m, 18 H).

Example 89

Synthesis of Compound 234

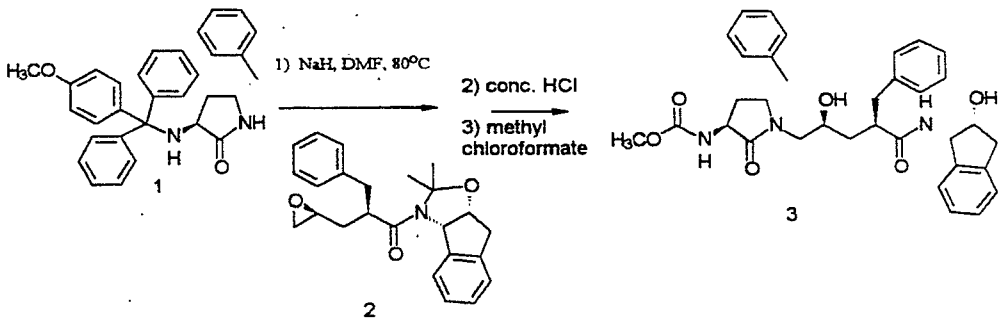


Prepared using the procedure outlined in **Example 74**. The acetonide was purified by column chromatography: 97/3 CH_2Cl_2/MeOH. MS: M+H = 633. The product was not purified. MS: M+H = 593.

Example 90

Synthesis of Compound 235

A.



A mixture of the trans isomer of the lactam above (0.125 g, 0.27 mmol) and 60% sodium hydride (0.010 g, 0.25 mmol) in dimethylformamide (4 mL) was stirred under a nitrogen atmosphere for 30 min. The epoxide (0.113 g, 0.30 mmol) was added and the mixture was heated at 60 °C for 4h. The mixture was re-charged with 60% sodium hydride (0.015 g, 0.37 mmol) heated at 60 °C for an additional 1.5h, and stirred at ambient temperature for 18h. The mixture was diluted with dichloromethane, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (7:3) then with hexane:ethyl acetate (1:1) to give 0.11g (48%) of product as a brown oil. MS: AP+, 862 (M+Na) and AP-, 874 (M+Cl).

B.

A solution of the acetonide (0.11g, 0.13 mmol) in 2-propanol (7 mL) and concentrated hydrochloric acid (3

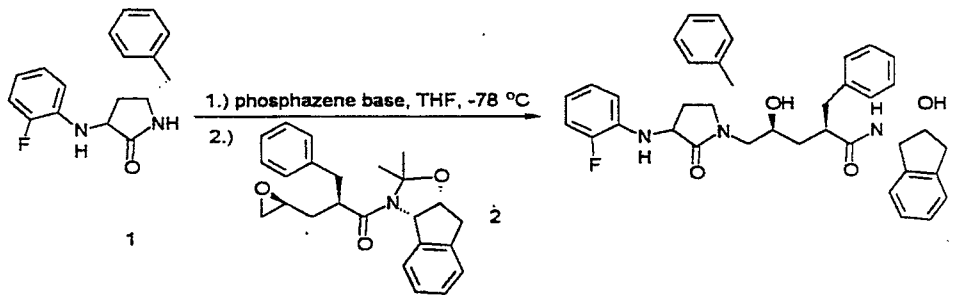
mL) was stirred at ambient temperature for 3h, neutralized with 2N sodium hydroxide, and extracted with diethyl ether. The extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 0.040 g (58%) yield of the crude product, which was used without further purification. MS: ES+, 550 (M+Na) and ES-, 562 (M+Cl).

C.

A solution of the amine (0.14 g, 0.27 mmol), methylchloroformate (0.023 mL, 0.30 mmol) and Et_3N (0.05 mL, 0.36 mmol) in dichloromethane (2 mL) was stirrred at ambient temperature under a nitrogen atmosphere for 18h. The volatiles were removed *in vacuo*, and the residue was purified by reverse phase preparative HPLC to give a tan oil. Lyophilization gave 0.012 g (8%) of the product as a white solid. MS: ES+, 608 (M+Na). ^1H NMR ($CDCl_3$) 1.71 (m, 1H); 1.96 (m, 1H); 2.11 (m, 1H); 2.26 (m,1H); 2.71-3.05 (m, 8H); 3.50 (s, 3H); 3.65 (m, 1H); 3.82 (m, 1H); 4.00-4.39 (m, 5H); 5.28 (m, 1H); 5.43 (s, 1H); 6.40 (d,1H); 7.08-7.33 (m, 14H).

Example 91

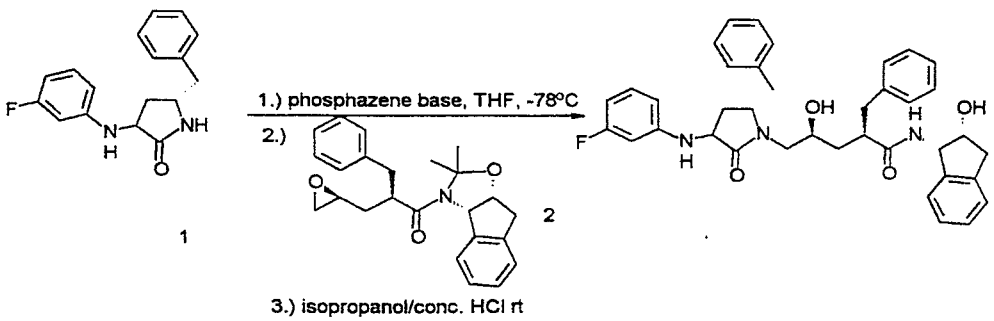
Synthesis of Compound 239



Prepared as described in **Example 74** with the exception that water, rather than 1.0 N HCl was used to quench the reaction. MS (AP-) of the acetonide = 660 (M-1). MS (AP+) of the product = 644 (M+Na). ^{1}HNMR of the product ($CDCl_3$): d 1.68 (m, 3H), 2.07 (m, 3H), 2.54 (m, 2H), 2.92 (m, 6H), 3.43 (m, 1H), 3.78 (m, 1H), 4.00 (m, 2H), 4.50 (m, 1H), 5.34 (m, 1H), 6.10 (m, 1H), 6.70 (m, 1H), 7.24 (m, 18H)

Example 92

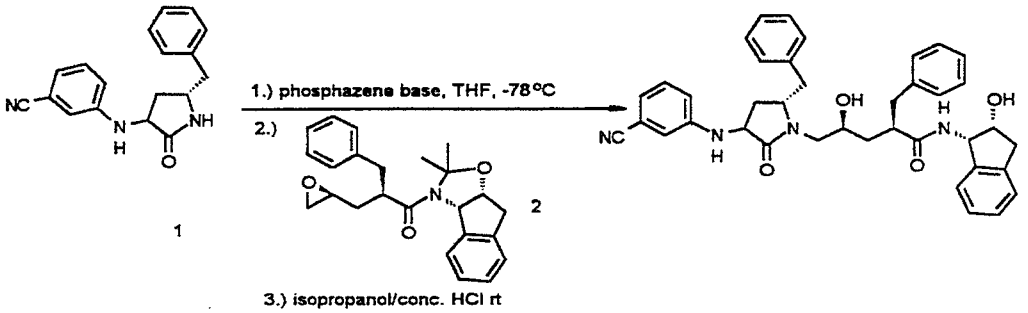
Synthesis of Compound 238



Prepared as described in **Example 74** with the exception that water, rather than 1.0 N HCl was used to quench the reaction. MS (AP+) of the acetonide = 684 (M+Na). MS (AP+) of the product = 644 (M+Na). ^{1}HNMR of the product ($CDCl_3$): d 1.62 (m, 3H), 2.00 (m, 3H), 2.50 (m, 2H), 2.80 (m, 6H), 3.30 (m, 2H), 4.00 (m, 2H), 4.34 (m, 1H), 5.33 (m, 1H), 6.14 (m, 1H), 6.30 (m, 1H), 7.24 (m, 18H)

Example 93

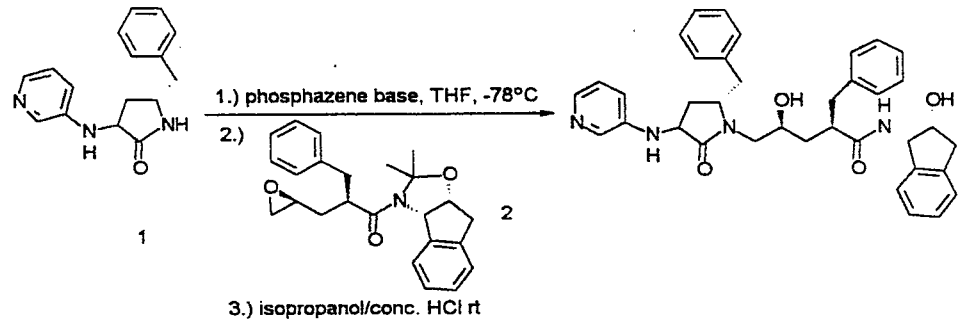
Synthesis of Compound 240



Prepared as described in **Example 74** with the exception that water, rather than 1.0 N HCl was used to quench the reaction. MS (AP+) of the acetonide = 691 (M+Na). MS (AP+) of the product = 651 (M+Na). ^{1}HNMR of the product ($CDCl_3$): d 1.66 (m, 3H), 2.08 (m, 3H), 2.59 (m, 2H), 2.95 (m, 6H), 3.40 (m, 1H), 3.85 (m, 1H), 4.14 (m, 2H), 4.27 (m, 1H), 5.32 (m, 1H), 6.22 (m, 1H), 6.73 (m, 1H), 7.25 (m, 18H).

Example 94

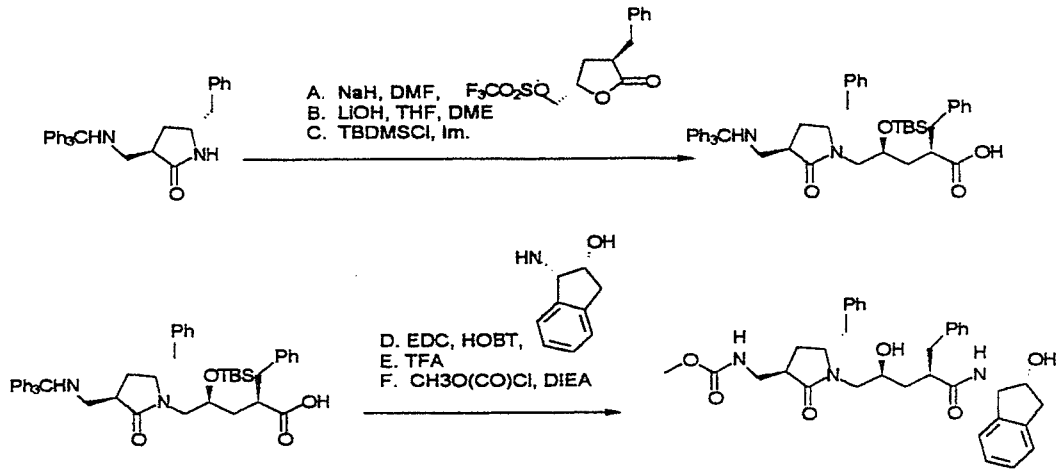
Synthesis of Compound 241



Prepared as described in **Example 74** with the exception that water, rather than 1.0 N HCl was used to quench the reaction. MS (AP+) of the acetonide = 645 (M+1). MS (AP+) of the product = 627 (M+Na). 1HNMR of the product (CDCl3): d 1.70 (m, 3H), 2.00 (m, 3H), 2.58 (m, 2H), 2.97 (m, 6H), 3.40 (m, 1H), 3.85 (m, 1H), 4.10 (m, 2H), 4.32 (m, 1H), 5.33 (m, 1H), 6.30 (m, 1H), 6.80 (m, 1H), 7.25 (m, 17H), 8.01 (m, 1H).

Example 95

Synthesis of Compound 208



A.

The lactam (1.20 g, 2.69 mmol, 1 eq) was dissolved in anhydrous dimethylformamide (8 mL) under Argon and cooled with an isopropanol dry ice bath to -40 °C. A solution of sodium bis(trimethylsilyl)amide (1.0M in THF, 2.69 mL, 2.69 mmol, 1 eq) was added dropwise via syringe and the reaction was stirred for 15 min. maintaining the bath temp between -40 - -50 °C. Dihydro-5(S)-[[[(trifluoromethyl)sulfonyl]oxy]methyl]-3(R)-(phenylmethyl)-3(2*H*)-furanone (J. Med. Chem., 1994, Vol. 37, No. 21, 3443-51; 1.00 g, 2.96 mmol, 1.1 eq) was added as a solid and the reaction was stirred vigorously for 10 min. and then quenched with several drops of glacial acetic acid. The reaction mixture was evaporated *in vacuo* to a residue and partitioned between ethyl acetate, saturated aqueous brine, and water. After separating the layers, the aqueous layer

was back-extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo* and purified by flash silica gel chromatography eluting with ethyl acetate : hexane (3:7). Fractions containing the alkylated lactam were combined, evaporated *in vacuo* to provide 0.883 g (52 %) of product as a foam. MS (ESI): M+Na = 657.

B.

The butyrolactone (1.202 g, 1.89 mmol, 1 eq) from step A was dissolved at ambient temperature in dimethoxyethane (20 mL) and cooled with an ice water bath. Aqueous lithium hydroxide (1.0 N, 4.75 mL, 4.75 mmol, 2.5 eq) was added via pipette and the mixture was stirred for 0.5 h. The reaction was warmed to ambient temperature and stirred for an additional 1 h. Aqueous citric acid (10% w/v) was added to reach an acidic pH and the mixture was evaporated in vacuo. The residue was partitioned between ethyl acetate : diethyl ether (4:1) and aqueous citric acid (10% w/v). After separating the layers, the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were washed with water, saturated aqueous brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo* and dried under high vacuum to provide the acid (1.32 g, 106%) as a foam. MS (APCI): M - 1 = 651.

C.

The acid (1.28 g, 1.97 mmol, 1 eq) from step B in 5 mL anhydrous dimethylformamide under Argon was combined

with imidizole (1.472 g, 21.6 mmol, 11 eq) followed by tertbutyldimethylsilyl chloride (2.96 g, 19.7 mmol, 10 eq) and stirred at ambient temperature for 16 h. The reaction was quench by addition of methanol (15 mL) and stirred for an additional 45 min. Aqueous lithium hydroxide (1.0 N, 2.0 mL, 1 eq) was added and the mixture was evaporated *in vacuo*. The residue was partitioned between ethyl acetate and aqueous sodium hydrogen sulfate (1.0 N). After separating the layers, the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo* and dried under high vacuum to provide the silyl protected acid (1.46 g, 97%) as a foam. MS (APCI): M - 1 = 766.

D.

The silyl protected acid (1.32 g, 1.72 mmol, 1 eq) from step C in anhydrous dimethylformamide (7 mL) under Argon was treated consecutively with diisopropylethyl amine (0.316 mL, 1.81 mmol, 1.05 eq), 1-hydroxybenzotriazole (0.244 g, 1.81 mmol, 1.05 eq), (1S,2R)-(-)-1-amino-2-indanol (0.283 g, 1.90 mmol, 1.1 eq), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.347 g, 1.81 mmol, 1.05 eq). After stirring at ambient temperature for 3 h, the reaction mixture was evaporated *in vacuo*, and partitioned between ethyl acetate, saturated aqueous brine, and water. After separating the layers, the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous

brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo* and purified by flash silica gel chromatography eluting with ethyl acetate : hexane (3:7). Fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide the protected amide (1.06 g, 69%) as a foam. MS (ESI): M+Na = 920.

E.

The protected amide (1.035 g, 1.15 mmol, 1 eq) from step D was dissolved in trifluoroacetic acid (15 mL) and stirred under Argon for 15 min. The reaction was evaporated *in vacuo* and trituratated with diethyl ether/hexane. After decanting the mother liquor, the residual solid was dried under high vacuum to provide a partially deprotected product. The crude material was dissolved again in trifluoroacetic acid (15 mL) and stirred for 20 min. under Argon. The reaction mixture was evaporated *in vacuo* to a residue and triturated with hexane/diethyl ether. The slurry was filtered, washed with hexane and dried under high vacuum to provide the deprotected amine (0.607 g, 83%) as a trifluoroacetic acid salt. MS (ESI): M+1 = 542.

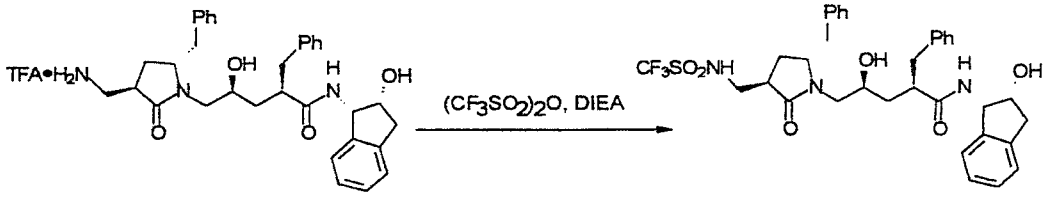
F.

The amine (0.025 g, 0.038 mmol, 1 eq) from step E was combined with diisopropylethylamine (0.0146 mL, 0.038 mmol, 2.2 eq) in dichloromethane (1.5 mL) under Argon. The solution was treated with methylchloroformate (0.0028 mL, 0.0362 mmol, 0.95 eq). After stirring for approximately 10 min., the reaction mixture was applied

directly to a 20x20 cm (500 uM, silica gel GF) preparative thin layer chromatography plate and eluted with 95:5 dichloromethane : methanol. The product band was removed from the plate and the product was washed from the silica gel with 85:15 dichloromethane : methanol (10 mL). The solution was evaporated *in vacuo*, triturated with hexane, evaporated *in vacuo*, and dried under high vacuum to provide the carbamate as a white solid (0.0164 g, 72 %). The product was lyophilized from acetonitrile : water (1:1). MS (APCI): M + Na = 622. H NMR (CDCl3 + NaOD): 1.66 (m, 1H); 1.90 (m, 3H); 2.29 (m, 1H); 2.64 (m, 1H); 2.92 (m, 7H); 3.18 (m, 1H); 3.40 (m, 1H); 3.56 (s, 3H); 3.66 (m, 1H); 3.85 (m, 1H); 3.98 (m, 1H); 4.26 (m, 1H); 5.27 (m, 1H), 6.07 (d, 1H, J=7.8); 7.14 (m, 6H); 7.28 (m, 8H).

Example 96

Synthesis of Compound 236

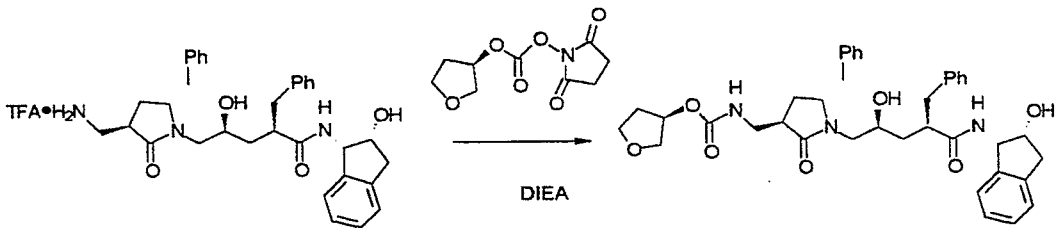


The aminomethyl pyrolidinone (0.025 g, 0.038 mmol, 1 eq) was combined with diisopropylethylamine (0.0146 mL, 0.038 mmol, 2.2 eq) in dichloromethane (1.5 mL) and cooled to -78 °C with a dry ice acetone bath. The solution was treated with trifluoromethane sulfonic anhydride (0.0064 mL, 0.038 mmol, 1 eq) in dichloromethane (0.5 mL). The reaction mixture was

then allowed to warm to room temperature and applied directly to a 20x20 cm (500 uM, silica gel GF) preparative thin layer chromatography plate and eluted with 95:5 dichloromethane : methanol. The product band was removed from the plate and the product was washed from the silica gel with 85:15 dichloromethane : methanol (10 mL). The solution was evaporated *in vacuo* to a residue and lyophilized from acetonitrile : water (1:1) to provide the desired product as a white lyophile (0.008 g, 31 %). MS (APCI): M + Na = 696. H NMR (CDCl3 + NaOD): 1.64 (m, 1H); 1.98 (m, 3H); 2.22 (m, 1H); 2.72 (m, 1H); 2.91 (m, 8H); 3.47 (m, 1H); 3.78 (m, 1H); 3.97 (m, 1H); 4.09 (m, 1H); 4.31 (m, 1H); 5.23 (m, 1H); 6.17 (d, 1H, J=8.7); 7.21 (m, 14H).

Example 97

Synthesis of Compound 211

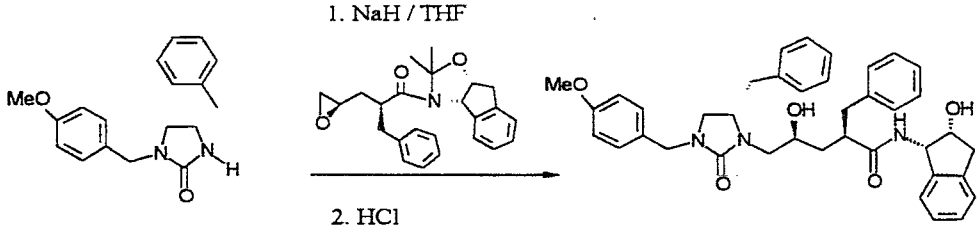


The aminomethyl pyrolidinone (0.030 g, 0.046 mmol, 1 eq) was combined with diisopropylethylamine (0.0175 mL, 0.10 mmol, 2.2 eq) and 3-(R)-hydroxy-tetrahydrofuran-N-hydroxysuccinimide carbonate (WO93-US8458, 0.016 g, 0.046 mmol, 1 eq) in dichloromethane (1.5 mL) and allowed to stir for 16 h at ambient temperature. The dichloromethane was removed *in vacuo* and replaced with acetonitrile (2 mL). The mixture was heated at reflux

for 20 min. and then cooled and evaporated *in vacuo*. The residue was dissolved in dichloromethane (~0.5 mL), applied directly to a 20x20 cm (500 uM, silica gel GF) preparative thin layer chromatography plate and eluted with 9:1 dichloromethane : methanol. The product band was removed from the plate and the product was washed from the silica gel with 85:15 dichloromethane : methanol (10 mL). The solution was evaporated *in vacuo* to a residue and lyophilized from acetonitrile : water (1:1) to provide the desired product as a white lyophile (0.022 g, 73 %). MS (ESI): M + Na = 678. H NMR (CDCl3 + NaOD): 1.65 (m, 1H); 1.93 (m, 5H); 2.32 (m, 1H); 2.65 (m, 1H); 2.90 (m, 7H); 3.22 (m, 1H); 3.37 (m, 1H); 3.54 (m, 2H); 3.79 (m, 4H); 3.97 (m, 1H); 4.22 (m, 1H); 5.11 (m, 1H); 5.27 (m, 1H); 6.34 (d, 1H, J=8.9); 7.22 (m, 14H).

Example 98

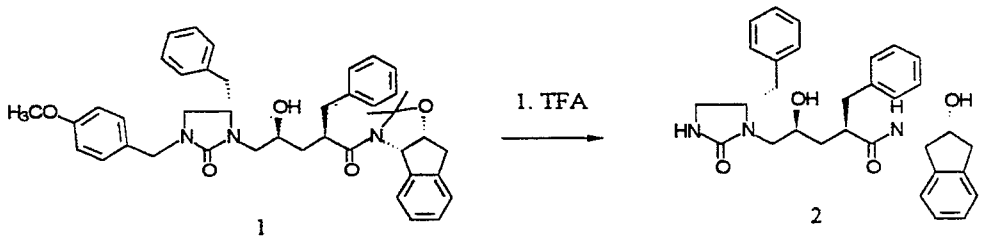
Synthesis of Compound 215



The starting cyclic urea was obtained following procedures outlined in **Examples 11 and 12**. Coupling with the epoxide followed the protocol detailed in **Example 24**.

Example 99

Synthesis of Compound 242

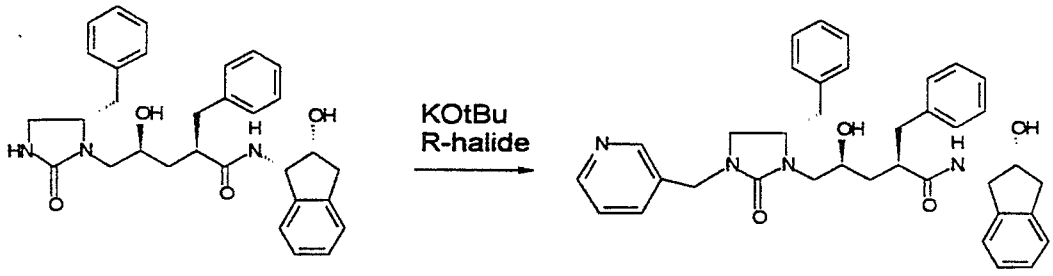


1 2

0.3g of the protected intermediate obtained in **Example 98** was treated with 10 mL of TFA over 5 h at room temperature. The reaction was quenched by removing the TFA, and the resulting crude treated with excess of sodium carbonate in methanol/water for 10 minutes. The solvents were removed, product extracted between ethyl acetate/water, organics combined, dried with magnesium sulfate, removed *in vacuo*, and purified by preparative HPLC, resulting in 0.15g (76.7%) of product 2. ^{1}H NMR (CDCl3, 300 MHz) δ 8.10 (1H, d, J=8.4), 7.24 (10H, m), 7.05 (5H, m), 5.28 (m, 1H), 4.10 (1H, t, J=4.2), 3.97 (1H, t, J=4.9), 3.53 (1H, m), 3.39 (2H, m), 2.95 (5H, m), 2.69 (m, 2H), 2.54 (1H, dd), 2.17 (1H, m), 1.92 (1H, m), 1.78 (m, 1H). Low resolution MS *m/e* 514.1 ($M+H^+$), *m/e* 536.2 ($M+Na^+$).

Example 100

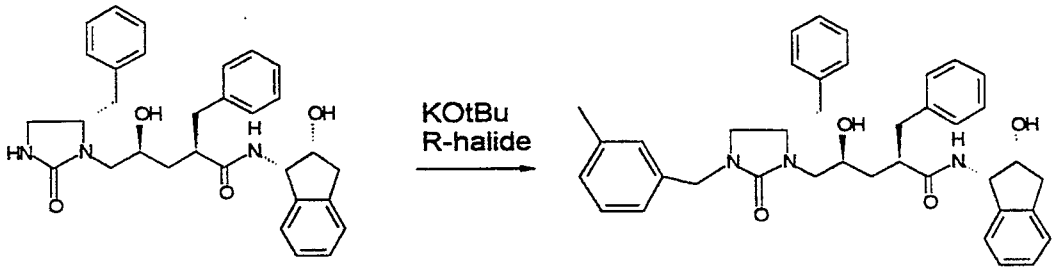
Synthesis of Compound 243



A solution of 20 mg (0.039 mmol) of the urea obtained Example 99 in 1 mL DMF was treated with potassium t-butoxide (26.3 mg, 0.234 mmol, 6 equiv) and equilibrated at room temperature for 10 min. Next, 6.3 mg of 3-picolyl chloride in 1 mL DMF was added and the reaction quenched after 20 min. Solvent were then removed and the residue purified on preparative RP HPLC resulting in 14.2 mg (60.20%) of the product. ^1H NMR (d6-acetone, 400 MHz) δ 8.57 (d, 1H, J=5.3), 8.42 (s, 1H), 8.01 (d, 1H, J=8.0), 7.80 (t, 1H, J=5.9), 7.20 (m, 14H), 6.92 (d, 1H, J=8.8), 5.23 (m, 1H), 4.29 (d, 1H, J=16.2), 4.29 (m, 1H), 4.11 (d, 1H, J=16.2), 3.98 (m, 2H), 3.48 (dd, 1H), 3.18 (m, 2H), 3.00 (m, 4H), 2.75 (m, 3H), 1.93 (m, 1H), 1.88 (m, 1H), 1.66 (m, 1H). Low resolution MS *m/e* 605.4 ($M+H^+$), *m/e* 627.4 ($M+Na^+$).

Example 101

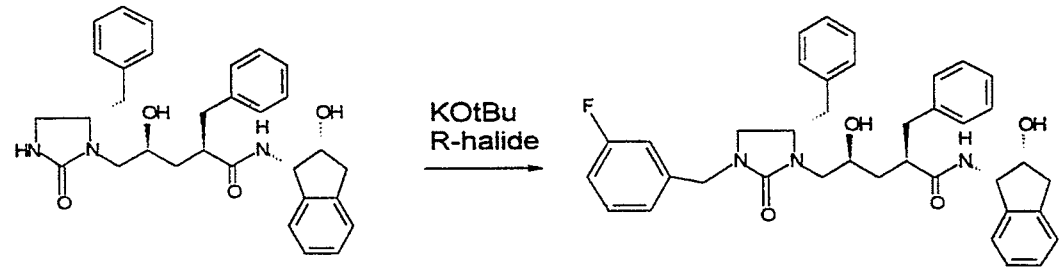
Synthesis of Compound 244



This compound was synthesized using the protocol outlined for **Example 100** starting from 51 mg (0.1 mM) of cyclic urea and 3-methylbenzyl bromide (18.5 mg, 0.1 mmol, 1 equiv), resulting in 6.2 mg of the product after preparative HPLC purification. ^{1}H NMR (d6-DMSO, 300 MHz) δ 7.68 (1H, d, J=8.5), 7.24 (19H, m), 5.18 (1H, m), 4.26 (1H, m), 4.16 (1H, d, J=15.7), 4.01 (1H, d, J=15.7), 3.79 (2H, m), 3.33 (1H, m), 3.05 (6H, m), 2.78 (m, 2H), 2.62 (2H, m), 2.24 (s, 3H), 1.80 (1H, m), 1.38 (1H, m). Low resolution MS *m/e* 618.2 ($M+H^+$).

Example 102

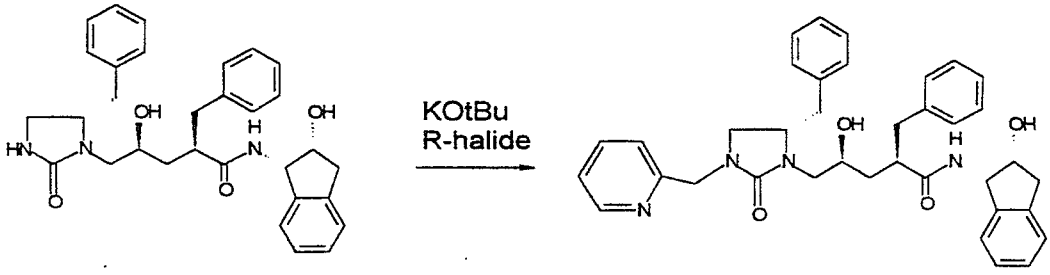
Synthesis of Compound 245



This compound was synthesized using the protocol outlined for **Example 100** starting from 51 mg (0.1 mM) of cyclic urea and 3-fluorobenzyl bromide (18.9 mg, 0.1 mmol, 1 equiv), resulting in 7.6 mg of the product after preparative HPLC purification. ^{1}H NMR (d6-DMSO, 300 MHz) δ 7.71 (1H, d, J=8.5), 7.24 (19H, m), 5.18 (1H, m), 4.28 (1H, m), 4.19 (1H, d, J=15.7), 4.03 (1H, d, J=15.7), 3.82 (2H, m), 3.33 (1H, dd), 3.05 (6H, m), 2.80 (m, 2H), 2.59 (2H, m), 1.79 (1H, m), 1.38 (1H, m). Low resolution MS *m/e* 622.1 ($M+H^+$).

Example 103

Synthesis of Compound 262

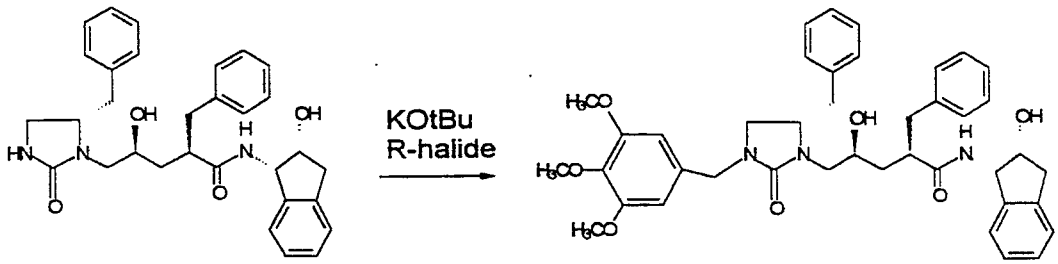


Obtained following the protocol outlined for **Example 100** using 2-picolyl chloride.

LC/MS-MH^+ 605.

Example 104

Synthesis of Compound 213

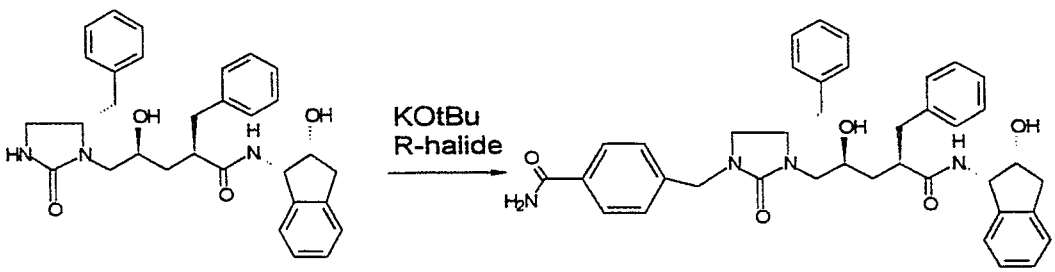


Obtained following the protocol outlined for **Example 100** using 3,4,5-trimethoxybenzyl chloride.

^{1}H NMR (DMSO)d_6 1.35 (t,1H),1.78 (t,1H), 2.45 (m,2H), 2.62 (m,2H), (s,6H), 3.8 (m,2H), 4.1 (q,2H), 4.28 (t,2H), 5.18 (m,2H), 6.45 (s,2H), 6.93-7.38 (m,16H) 7.68 (d,2H), LC/MS-MH^+ 694.

Example 105

Synthesis of Compound 246



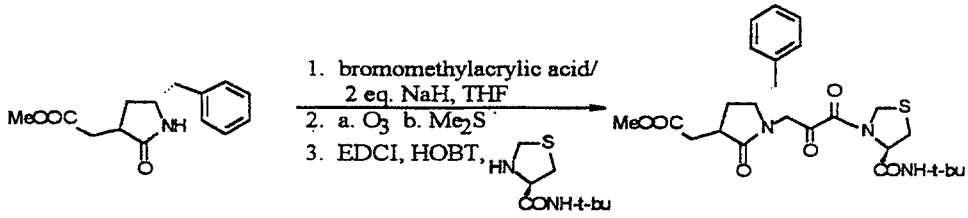
Obtained following the protocol outlined for **Example 100** using 4-amidobenzyl chloride.

^{1}H NMR (DMSOd_6) 1.35 (t,1H),1.78 (t,1H),2.45 (m,2H),2.62 (m, (s,6H), 3.8 (m,2H), 4.1(q,2H), 4.28

(t,2H), 5.18 (m,2H), 6.45 (s,2H), 6.93-7.38 (m,16H) 7.68 (d,2H), LC/MS-MH^+ 694.

Example 106

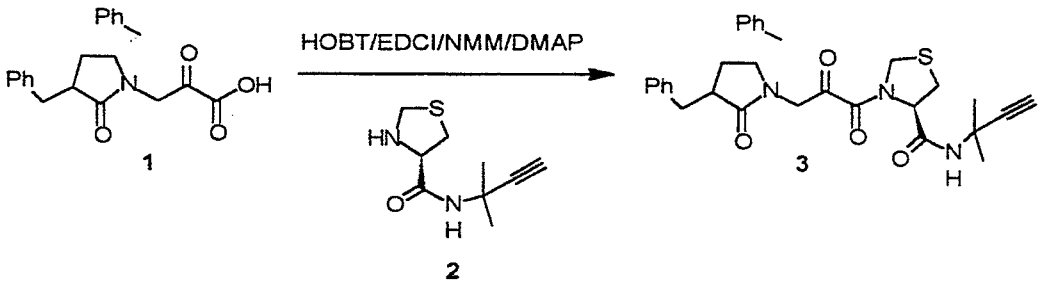
Synthesis of Compound 257



Following the procedure outlined in **Example 21** the desired ketoamide was obtained as a white fluffy solid after purification on reversed phase HPLC. M+H: 504 ^{1}H NMR: 1.38 and 1.48 (9H,s), 1.8-3.0(ca 7H,m), 3.72 and 3.73 (3H,s), 3.5(1H,m), 3.8(1H,m), 4.0(2H,m), 4.2-4.8(3H,m) 7.2-7.4(5H,m). Note: Complex NMR signals due to rotational isomers, diastereomers and ketone-hydrate equillibria.

Example 107

Synthesis of Compound 258

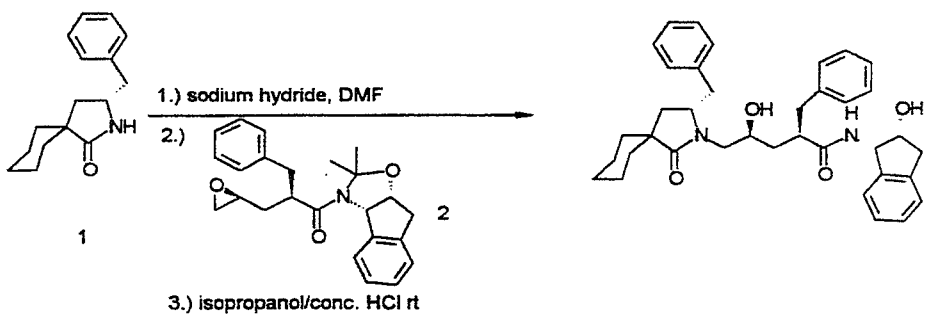


The procedure was followed as described in **Example 21** except that instead of thioproline-t-butylamide being coupled to the ketoacid 1, thioproline-dimethyl propargylamide 2 was used. This compound was made by treating a 0 °C solution of N-BOC-4-thio-L-proline (Sigma, 2.0 g, 8.6 mmol) in THF (40 mL) with diisopropylethylamine (4.5 mL, 26 mmol) followed by dropwise addition of isobutyl chloroformate (1.1 mL, 8.6 mmol) via syringe. The reaction was stirred for 30 minutes at 0 °C before the dropwise addition of 90% 1,1-dimethylpropargylamine (Aldrich, 1.0 mL, 8.6 mmol). After stirring for 17 h at room temperature, the reaction was concentrated in vacuo. Ethyl acetate (70 mL) and water (35 mL) were added to the residue and the layers were partitioned. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was then dissolved in dichloromethane (20 mL) and treated slowly with trifluoroacetic acid (20 mL). The reaction was stirred for 24 h before being diluted with ethyl acetate (70 mL) and carefully neutralized with 10% sodium carbonate to pH 7. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (1:1 hexane:ethyl acetate) gave amide 2 as a white foam. MS (ES+) = 199 (M+1). Coupling of ketoacid 1 (300 mg, 0.854 mmol) with amide 2 (170 mg, 0.854 mmol) gave ketoamide 3 (84 mg, 0.211 mmol, 25%) after preparatory silica gel TLC (3:1 ethyl acetate:hexane). MS (AP+) = 532 (M+1), 554 (M+Na); ^{1}HNMR ($CDCl_3$): d 1.66 (s, 3H), 1.69 (s, 3H), 1.94 (m, 2H), 2.37 (d, 1H), 2.51 (m, 3H), 2.92 (m, 1H), 3.21 (m,

2H), 3.52 (m, 1H), 3.83 (m, 1H), 4.22 (m, 2H), 4.44 (m, 1H), 4.81 (m, 1H), 5.00 (m, 1H), 6.57 (d, 1H), 7.1 (m, 4H), 7.22 (m, 6H).

Example 108

Synthesis of Compound 263

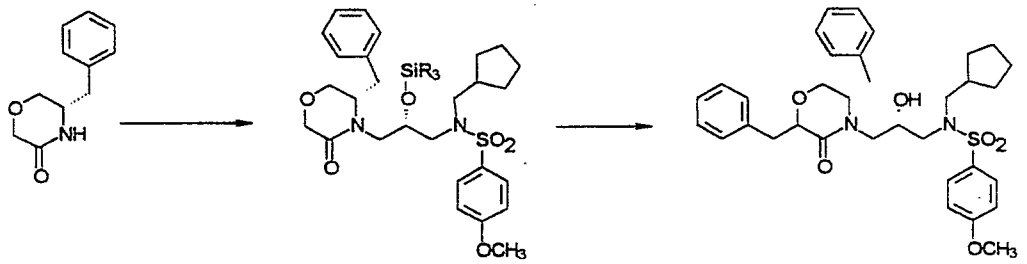


Prepared using the procedure outlined in **Example 24**. The acetonide was purified by column chromatography: 65/35 hexane/ethyl acetate. MS: M+Na = 643. The product was purified by column chromatography: 40/60 hexane/ethyl acetate. MS: M+Na = 603 ^{1}H NMR ($CDCl_3$) 1.05(m, 1H); 1.10-1.40(m, 6H); 1.50-1.75(m, 4H); 1.80-2.00(m, 2H); 2.45(m, 1H); 2.80-3.10(m, 4H); 3.20(m, 2H); 3.30(m, 1H); 3.45(s, 1H); 3.65(m, 1H); 3.80(m, 1H); 3.90(m, 1H); 4.25(m, 1H); 4.60(m, 1H); 5.27(m, 1H); 6.00(d, 1H); 7.10-7.40(m, 14H).

Example 109

Synthesis of Compound 206

A.



A solution of 22.3g (0.147 mol, 1 equiv) of S(-)-2-Amino-3-phenyl-1-propanol in 30 mL THF, cooled to 0 °C, was treated with 25.5 mL (0.147 mol, 1 equiv) of DIEA, followed by addition of 11.7 mL (0.147 mmol, 1 equiv) of chloroacetyl chloride. After 1 hr at room temperature, 18.0g (0.16 mol) of potassium -*tert*-butoxide was added at 0 °C, the reaction warmed up to room temperature and allowed to proceed for 15 min. Solvents were then removed and the crude residue partitioned between ethyl acetate/water, organics dried over $MgSO_4$ resulting in 23.8g (85%) of the desired product. ^1H NMR ($CDCL_3$, 300 MHz) δ 7.20 (m, 5H), 6.67 (s, 1H), 4.15 (m, 2H), 3.75 (m, 1H), 3.86 (dd, 1H, J=11.6, 3.7), 3.55 (dd, 1H, J=11.6, 6.3), 2.82 (m, 2H). Low resolution MS *m/e* 192.1 ($M+H^+$)

B.

A solution of 0.477g (2.5 mmol, 1 equiv) of the morpholinone above in 1 mL of anhydrous DMF was treated with 12 mg (0.5 mmol, 0.2 equiv) of sodium hydride

(95%) at 0°C. The reaction was continued at room temperature for 10 min, and then cooled down to 0°C, followed by addition of 0.813g (2.5 mmol, 1 equiv) of epoxide in 1 mL DMF. The reaction was then carried out at 50°C for 5 h. Following ethyl acetate/water extraction, the organics were combined and dried resulting in 1.18 g of crude product, used further without purification. Low resolution MS *m/e* 539.0 ($M+Na^+$).

C.

A solution of 1.18g (2.287 mol, 1 equiv) of the above crude in 4 mL anhydrous THF was treated with 0.44g (3.43 mol, 1.5 equiv) of DIEA, followed by 0.907g (3.43 mmol, 1.5 equiv) of TBDMS triflate. After 1 h at room temperature, the product was purified on silica gel (R_f=0.26, 1:3 ethyl acetate/hexane), yielding 0.85g of the TBDMS ether (59.0%). ^1H NMR ($CDCL_3$, 300 MHz) δ 7.50 (d, 2H, J=8.9), 7.24 (m, 5H), 6.97 (d, 2H, J=8.9), 4.40 (m, 1H), 4.21 (d, 1H, J=6.3), 4.17 (d, 1H, J=6.3), 3.82 (s, 3H), 3.65 (m, 2H), 3.54 (m, 1H), 3.35 (m, 1H), 3.17 (m, 1H), 3.00 (m, 4H), 2.77 (m, 1H), 2.21 (m, 1H), 1.79 (m, 1H), 1.57 (m, 5H), 1.24 (m, 1H), 1.03 (m, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H). Low resolution MS *m/e* 653.1 ($M+Na^+$), *m/e* 631.1 ($M+H^+$).

D.

A solution of 0.12g (0.19 mmol, 1 equiv) of the precursor above in 1.5 mL THF was cooled to -78°C and added 0.25 mL (0.25 mmol, 1.3 equiv) lithium bis(trimethylsilyl)amide (1M solution in THF). After 20 min, 0.029 mL (0.248 mmol, 1.3 equiv) of benzyl bromide

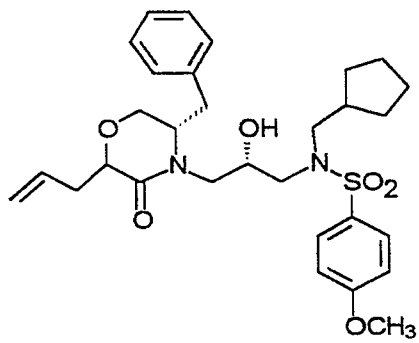
was added and reaction allowed to proceed at room temperature for additional 1 h. Purification on silica gel (mixture of diastereomers, R_f=0.46, 0.51 in 1:3 ethyl acetate/hexane) provided 44 mg (32.2%) of the TBDMS-protected product. Low resolution MS *m/e* 1464.6 ($2M+Na^+$), *m/e* 721.1 ($M+H^+$).

E.

A solution of 40 mg of the silylated product above in 0.3 mL THF was treated with 0.3 mL of 1M TBAF in THF for 25 min at room temperature and purified on a silica column, resulting in 30 mg of the final product. R_f=0.38 and 0.34 (2/5/0.3 ethyl acetate: hexane: methanol). ^1H NMR ($CDCL_3$, 300 MHz) shows both diastereomers and integrates as expected. Low resolution MS *m/e* 629.3 ($M+Na^+$).

Example 110

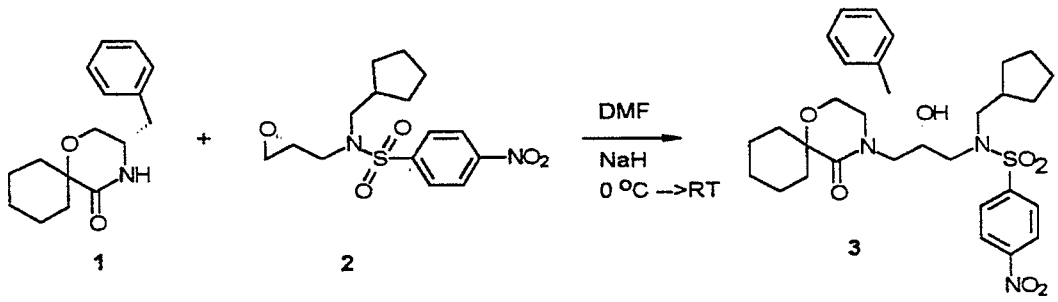
Synthesis of Compound 205



A solution of 0.12g (0.19 mmol, 1 equiv) of the compound prepared in **Example 109C** was dissolved in 1.5 mL THF and was treated with 0.30 mL (0.30 mmol, 1.5 equiv) of lithium bis(trimethylsilyl)amide (1M solution in THF) at -78 °C. After 20 min, 0.023 mL (0.266 mmol, 1.4 equiv) of allyl bromide was added, reaction allowed to warm up to the room temperature and carried out for additional 1 h. The reaction was then quenched with aqueous ammonium chloride and both diastereomers separated on a silica gel. The (lower) R_f=0.50 diastereomer (1:3 ethyl acetate/hexane) was then treated with 10-fold excess of TBAF (1M in THF) for 25 min at room temperature, followed by another silica purification, which provided 14 mg of the desired allylated product. ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.73 (d, 2H, J=9.0), 7.24 (m, 5H), 6.99, (d, 1H, J=8.9), 5.84 (m, 1H), 5.12 (m, 2H), 4.27 (m, 1H), 4.10 (m, 1H), 3.86 (s, 3H), 3.84 (m, 3H), 3.58 (m, 1H), 2.8-3.3 (m, 7H), 2.62 (m, 2H), 2.09 (m, 1H), 1.60 (m, 6H), 1.24 (m, 2H). Low resolution MS *m/e* 579.3 ($M+Na^+$), *m/e* 1135.4 ($2M+Na^+$).

Example 111

Synthesis of Compound 207



A solution of 0.092g of the morpholinone described in **Example 20** (0.35 mmol, 1equiv) in 1.5 mL anhydrous DMF was cooled to 0 °C and added 9.6 mg (0.4 mmol, 1 equiv) of NaH. After 1/2h 0.13g (0.32 mmol) of the epoxide 2 was added and reaction carried out at room temperature for 10 h, quenched with 1N HCl_{aq}, and purified on preparative RP HPLC. Yield 70 mg (36.5%). Low resolution MS *m/e* 622.1 ($M+Na^+$), *m/e* 1221.1 ($2M+Na^+$)

Example 112

Using the methods described by Pennington et al. and Partaledis et al. (supra), we obtained inhibition constants for the following compounds of this invention:

Compound	K_i (nM)
1	160
2*	180
3*	1,800
5*	>10,000

6*	>10,000
7	9
8*	5
9*	90
10	>10,000
11	>10,000
12	>10,000
13	225
14	16
15	550
16	56
17	115
18	15
19	3,000
20	1.5
21	>20,000
22	600
23	70
24	350
25	83
26	58
27	3,000
28	1,400
30	>15,000
31	390
32	160
33	1,100
34	950
35	130
36	>20,000
37	>20,000
38	17

39	600
40	>20,000
41	>20,000
42	330
43	>10,000
44	120
45	30
46	>10,000
47	20
50*	100
51*	90
52*	1,100
54*	12
55*	30
56*	280
57*	400
58*	5,800
59*	>8,000
60*	170
61*	>1,000
62*	120
63*	200
64*	>5,000
65*	2,900
66*	1,300
67*	3,900
68*	>10,000
69*	>10,000
70*	790
71*	2,500
72*	85
73*	190

74*	1,200
76*	250
77*	560
78*	10
79*	>3,000
80*	3
82*	15
83*	0.50
85*	2,600
87*	15
88*	270
90*	220
91*	12
92* (isomer 1)	3.0
92* (isomer 2)	300
93*	420
95*	10
96*	4
98*	>10,000
102*	1,200
105*	>10,000
109*	250
111*	>10,000
112*	8,600
113*	>10,000
114*	>1,000
115*	>10,000
123* (isomer 1)	300
123* (isomer 2)	13
124* (isomer 1)	800
124* (isomer 2)	1900
125* (isomer 1)	400

125* (isomer 2)	1000
126*	86
127*	92
128*	96
129*	400
130*	100
131* (isomer 1)	42
131* (isomer 2)	52
132*	60
133* (isomer 1)	24
133* (isomer 2)	120
208*	100
209*	2,200
210*	100
211*	5,600
212*	5,900
213*	3,100
214*	240
215*	10,000
216*	1,000
217*	>10,000
218*	700
219* (isomer 1)	20
219* (isomer 2)	54
219* (isomer 3)	330
220*	7
221*	50
223*	18
224*	90
225*	370
226*	29
227*	100

228*		16
229*		28
232*		500
233*	(isomer 1)	23
233*	(isomer 2)	1200
235*		270
236*		3.6

* Inhibition constant measured at pH 6.0.

Example 113

Using the MT4 cell assay method (supra), we measured the antiviral activity for the following compounds of this invention:

Compound		IC_{50} (μM)
26		16
45		9
54		1.0
83		0.32
92	(isomer 1)	0.21
95		2
96		0.40
123	(isomer 1)	0.90
123	(isomer 2)	0.74
127		0.85
130		1.0
131	(isomer 1)	2.4
131	(isomer 2)	2.9
132		0.75

	214	2.15
	219 (isomer 1)	0.4
	219 (isomer 2)	1.7
	219 (isomer 3)	6.0
	220	0.10
	223	0.68
	224	2.0
	225	2.0
	226	3.5
	227	2.75
	228	0.48
	229	0.79
	232	2.47
	233 (isomer 1)	3.7
	233 (isomer 2)	1.6
	236	5.0

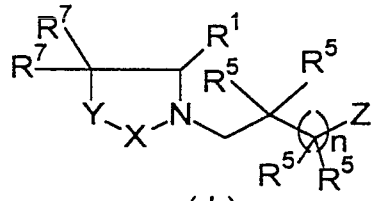
The above data show that each of the tested compounds inhibits HIV aspartyl protease.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

PCT/US97/01610
Vertex Pharmaceuticals Inc., et al
Our Ref.: B 2555 PCT

We Claim:

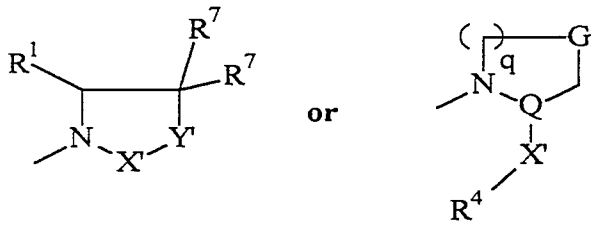
1. A compound according to formula I:



(I)

wherein:

each Z is



wherein any Z is optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and -$S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; wherein any member of R^1 is optionally substituted by one or more R^2;

each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and when two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom form a ring system; wherein any member of R^2 is optionally substituted by one or more R^3;

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)$-X-R^9, $N(R^9)$-X-OR^9, $N(R^9)$-X-$N(R^9)_2$, SR^9, X-R^9, O-X-$N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; X-R^9; $C(O)N(R^9)_2$; R^6; -C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; wherein any member of R^4 is optionally substituted by one or more groups independently selected from R^9 or R^3;

each R^5 is independently selected from the group consisting of H, OH, O and R^1;

each R^6 is independently selected from the group consisting of C6-C10 aryl, C3-C8 carbocyclyl and C3-C11 heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, -OR^9, -R^9, -$N(R^9)(R^9)$, -$N(R^9)$-X-R^9, SR^9, -X-R^9, -O-X-$N(R^9)_2$, -R^9-OR^9, -CN, -CO_2R^9, -X-$N(R^9)(R^9)$, halogen, -NO_2, and -CF_3;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C6-C10 aryl, C3-C8 carbocyclyl, and

C3-C11 heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C6-C10 aryl, C3-C8 carbocyclyl, C3-C11 heterocyclyl, C1-C10 alkyl substituted C6-C10 aryl , C1-C10 alkyl substituted C3-C8 carbocyclyl and C1-C10 alkyl substituted heterocyclyl; wherein any member of R^9 is optionally fused with R^8 and wherein any member of R^8 is optionally substituted by one or more groups independently selected from $-OR^8$, $-N(R^8)_2$, -CN, $-NO_2$, $-X-R^8$, $-X-N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)-XN(R^8)_2$, or halogen;

each Q is independently selected from the group consisting of CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, -O-, -S-, -S(O)- and $-S(O)_2-$;

each n is independently 1 or 2;

each r is independently 0, 1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

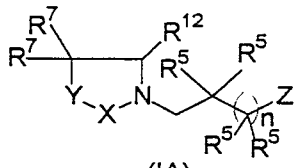
each G is independently selected from the group consisting of -NH-, $-NR^2-$, -O-, -S-, -S(O)-, $S(O)_2$, $-C(O)-$, and $-C(R^2)_2-$.

2. The compound according to claim 1, wherein:

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, and $-N(R^2)-CH_2-$; and

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, SR^9, $X-R^9$, $O-X-N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6.

3. The compound according to claim 1 having the structure of formula IA:



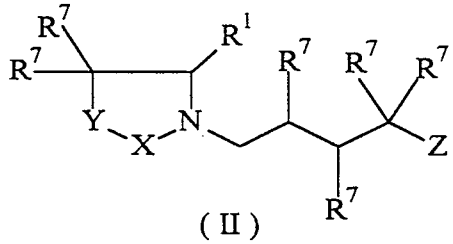
(IA)

wherein:

each R^{12} is independently selected from the group consisting of R^6; C_1-C_6 alkyl optionally substituted with R^6; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; wherein any member of R^{12} is optionally substituted by one or more R^2.

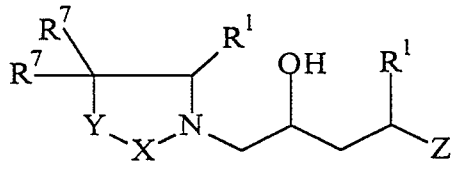
4. The compound according to claim 1, wherein n is 1.

5. The compound according to claim 1 having the structure of formula II:



(II)

6. The compound according to claim 1 having the structure of formula III:



(III)

7. The compound according to claim 1, wherein:

X is $-C(O)-$ or $-S(O)_2-$; and

Y is $-(C(R^2)_2)_p-M-$.

8. The compound according to claim 1, wherein:

X is $-C(O)-$ or $-S(O)_2-$; and

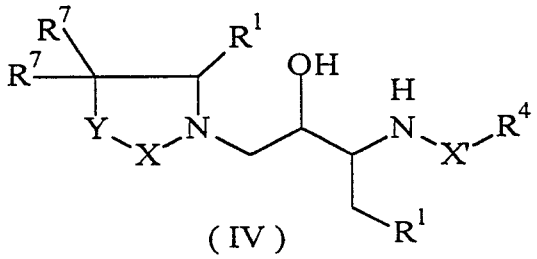
Y is $(-C(R^2)_2-)_p$.

9. The compound according to claim 1, wherein:

X is $-C(O)-$, $-C(O)C(O)-$ or $-S(O)_2-$; and

Y is $-N(R^2)-$ or $-N(R^2)-CH_2-$.

10. A compound according to formula IV:



(IV)

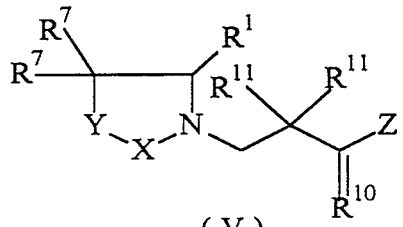
wherein:

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-; and

each R^1, R^2, R^7, R^4, p and M is independently as defined in claim 1.

11. A compound according to formula V:



(V)

wherein:

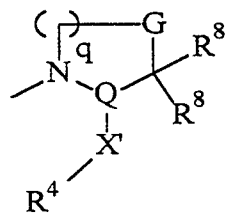
X is -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-;

R^{10} is O or H$_2$;

each R^{11} is independently H, OH or O, wherein both R^{11} are not simultaneously hydrogen;

Z is a structure of formula VI:



(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 substituents independently selected from R^2; and
each R^1, R^2, R^7, R^4, R^8, p, q, G, M, Q and X' is independently as defined in claim 1.

12. The compound according to claim 11, wherein R^{10} and R^{11} are O.

13. The compound according to claim 12, wherein:
q is 1;
G is S; and
X' is -C(O)-.

14. The compound according to claim 13, wherein R^4 is t-butylamino.

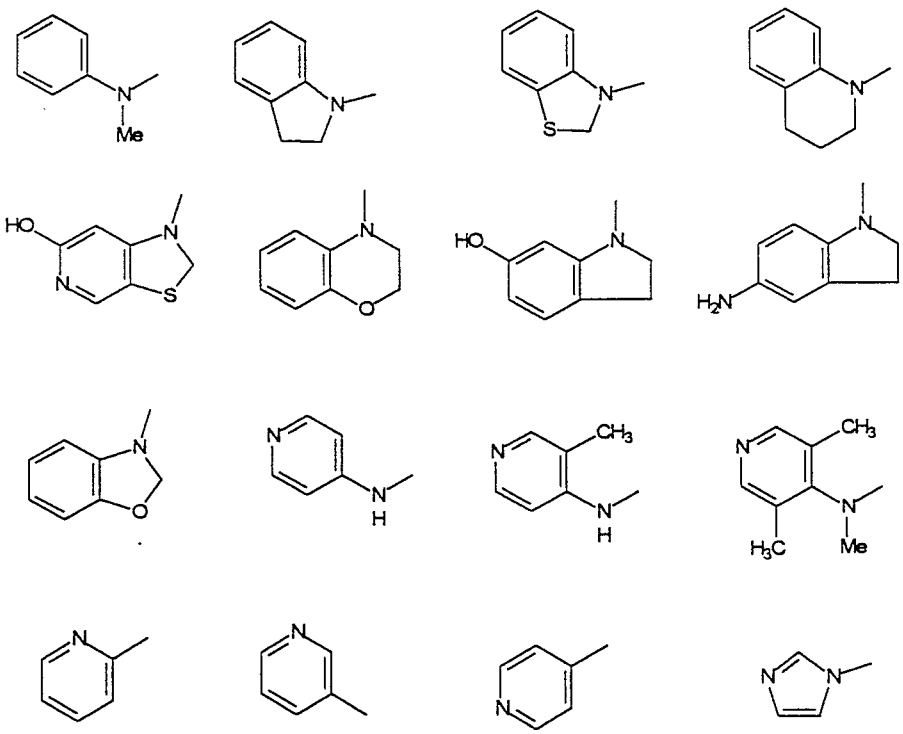
15. The compound according to claim 12, wherein:
X is -C(O)-;
Y is $-(C(R^2)_2)_p-$; and
R^7 is H.

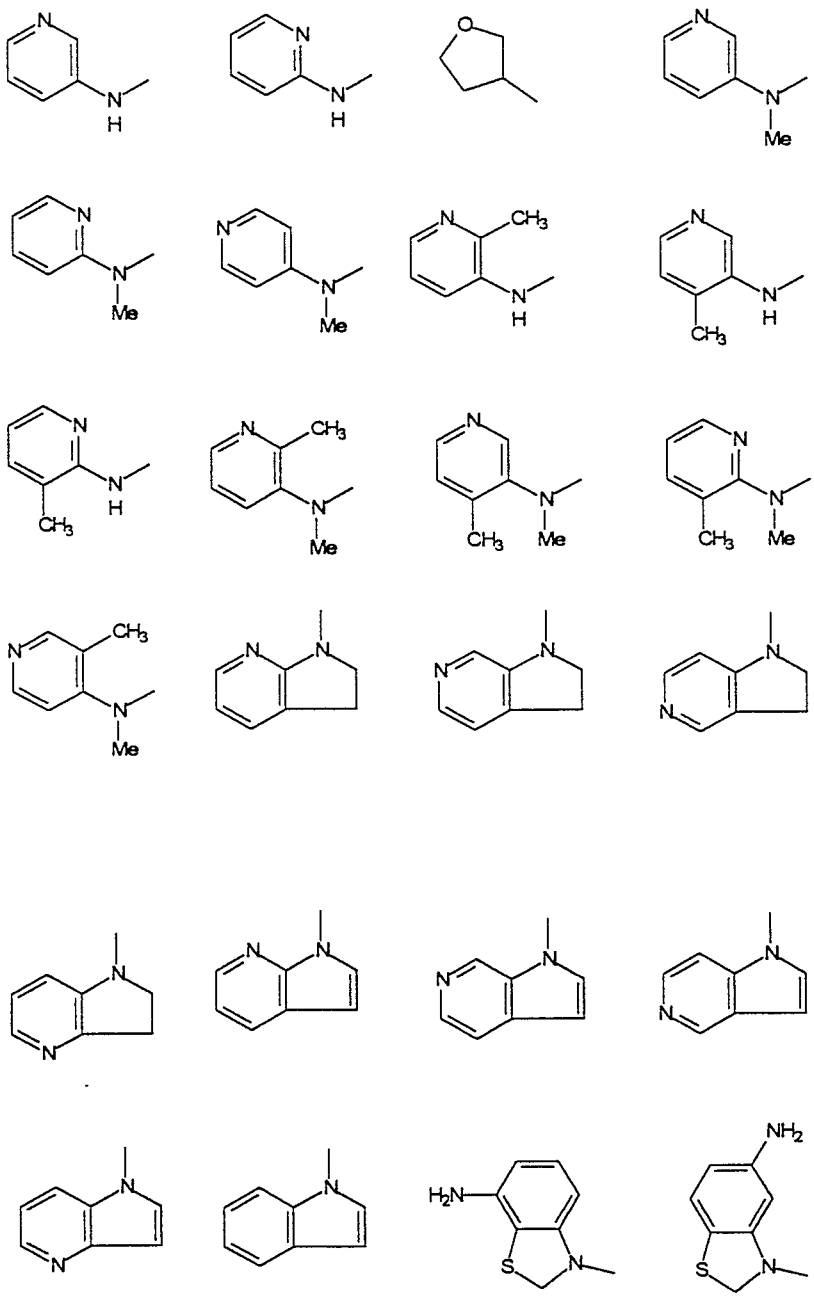
16. The compound according to claim 11, wherein:
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH.

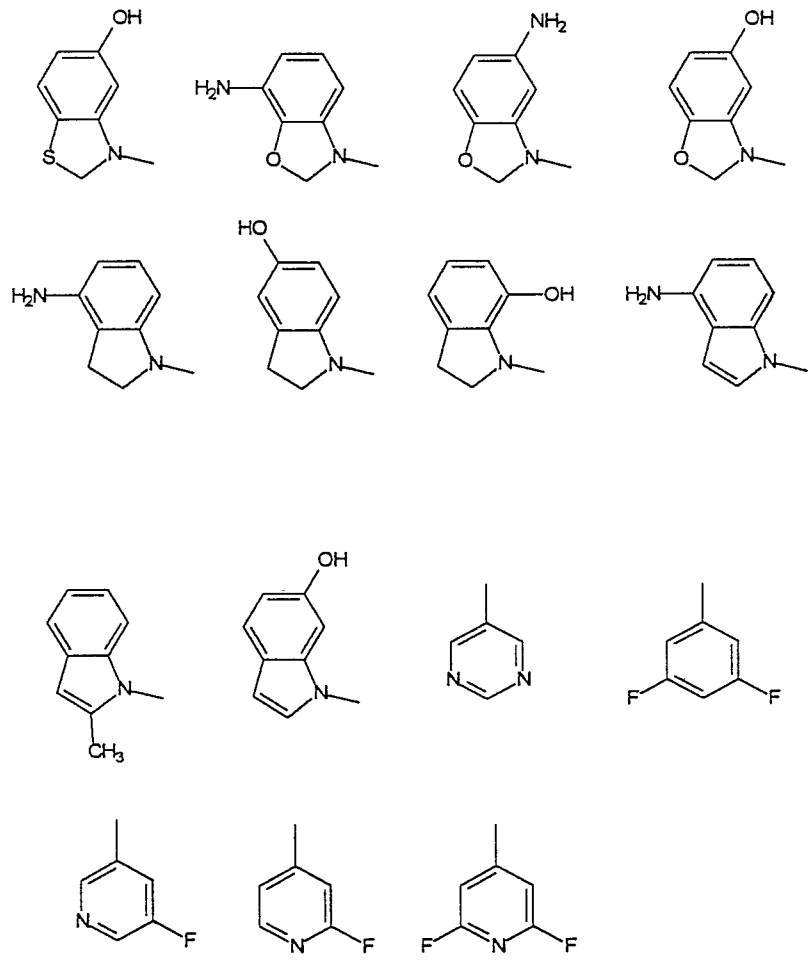
17. The compound according to claim 16, wherein R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3.

18. The compound according to claim 17, wherein R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

19. The compound according to claim 18, wherein at least one R^2 within the definition of Y is selected from the group consisting of:







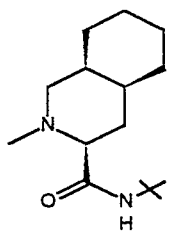
20. The compound according to claim 17, wherein at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

21. The compound according to claim 17, wherein at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3.

22. The compound according to claim 21, wherein at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

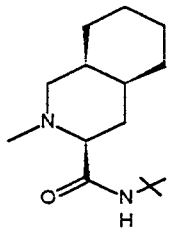
23. The compound according to claim 21, wherein R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

24. The compound according to any one of claims 17-23, wherein R^1 is benzyl; and Z is



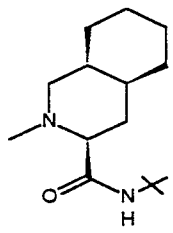
25. The compound according to any one of claims 17-23, wherein R^1 is benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, $-CN$, halogen, $-NO_2$, and $-CF_3$.

26. The compound according to claim 25, wherein Z is

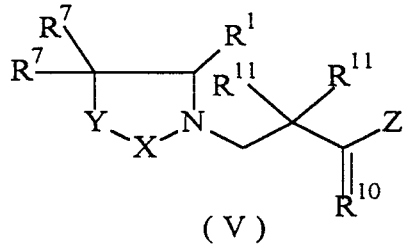


27. The compound according to claim 25, wherein R^1 is benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2.

28. The compound according to claim 27, wherein Z is



29. A compound according to formula V, wherein:



(V)

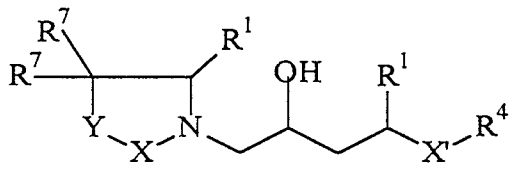
each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and
each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined in claim 1.

30. The compound according to claim 29, wherein R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3.

31. The compound according to claim 11, wherein:
X and X' is $-C(O)-$;
Y is $-N(R^2)-$;
R^7 is H;
R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH.

32. The compound according to claim 11, wherein:
X and X' is $-C(O)-$;
Y is $-(C(R^2)_2)-M-$;
M is O;
R^7 is H;
R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH.

33. The compound according to claim 1, having the structure of formula XII:



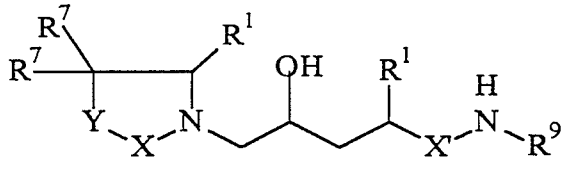
(XII)

wherein:

X and X' are independently -C(O)- or $-S(O)_2-$.

34. The compound according to claim 37, wherein R^4 is 1-amino-2-hydroxyindanyl.

35. The compound according to claim 1, having the structure of formula XIII:



(XIII)

wherein:

X and X' are independently -C(O)- or $-S(O)_2-$.

36. The compound according to claim 39, wherein:

X' is -C(O)-

Y is $-(C(R^2)_2)-$ or $-N(R^2)-$; and

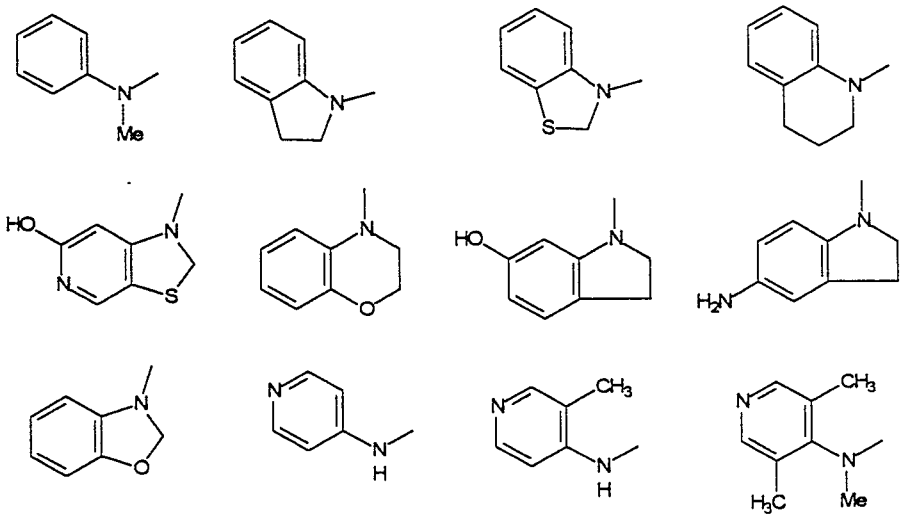
R^7 is H.

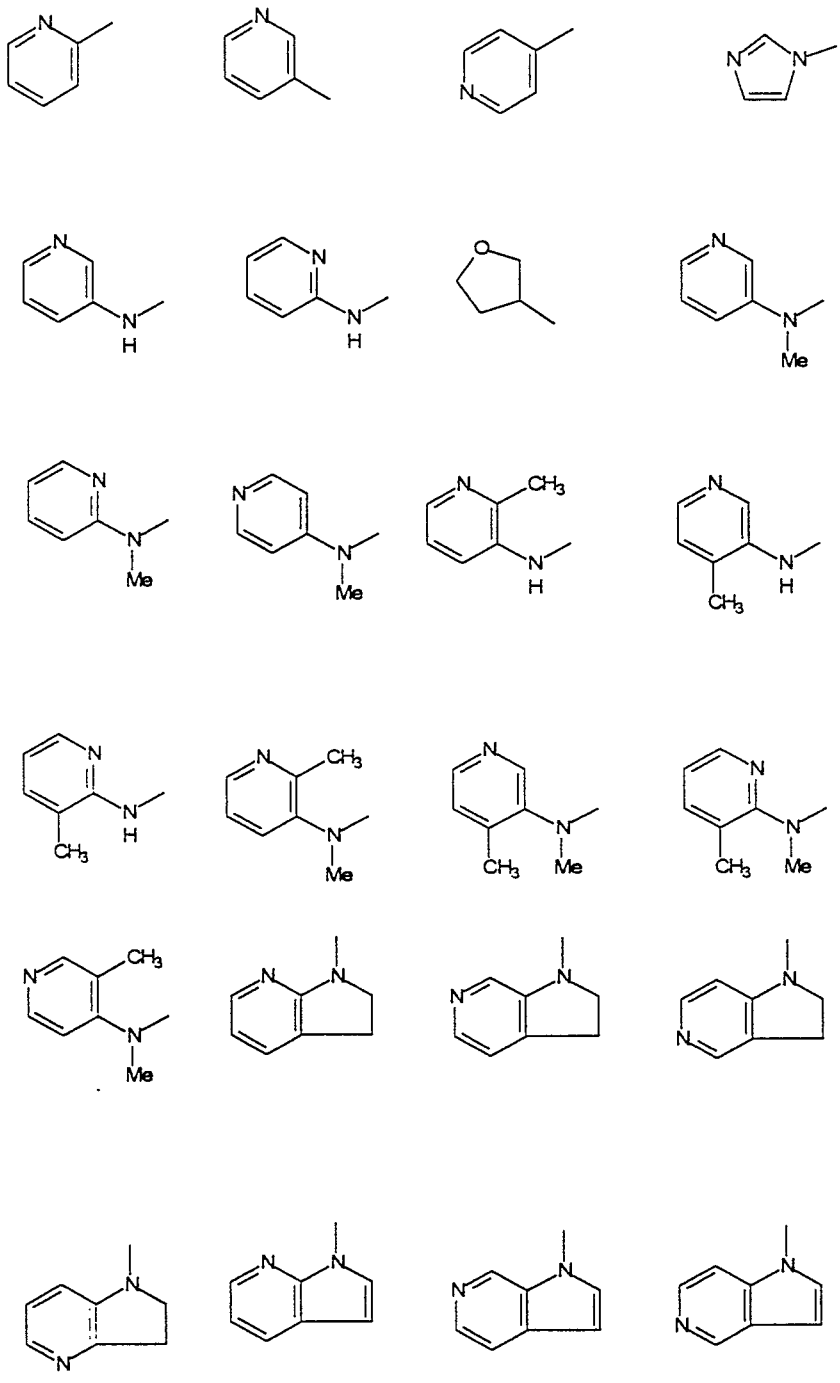
37. The compound according to claim 40, wherein:
X is -C(O)-; and
Y is $-(C(R^2)_2)-$.

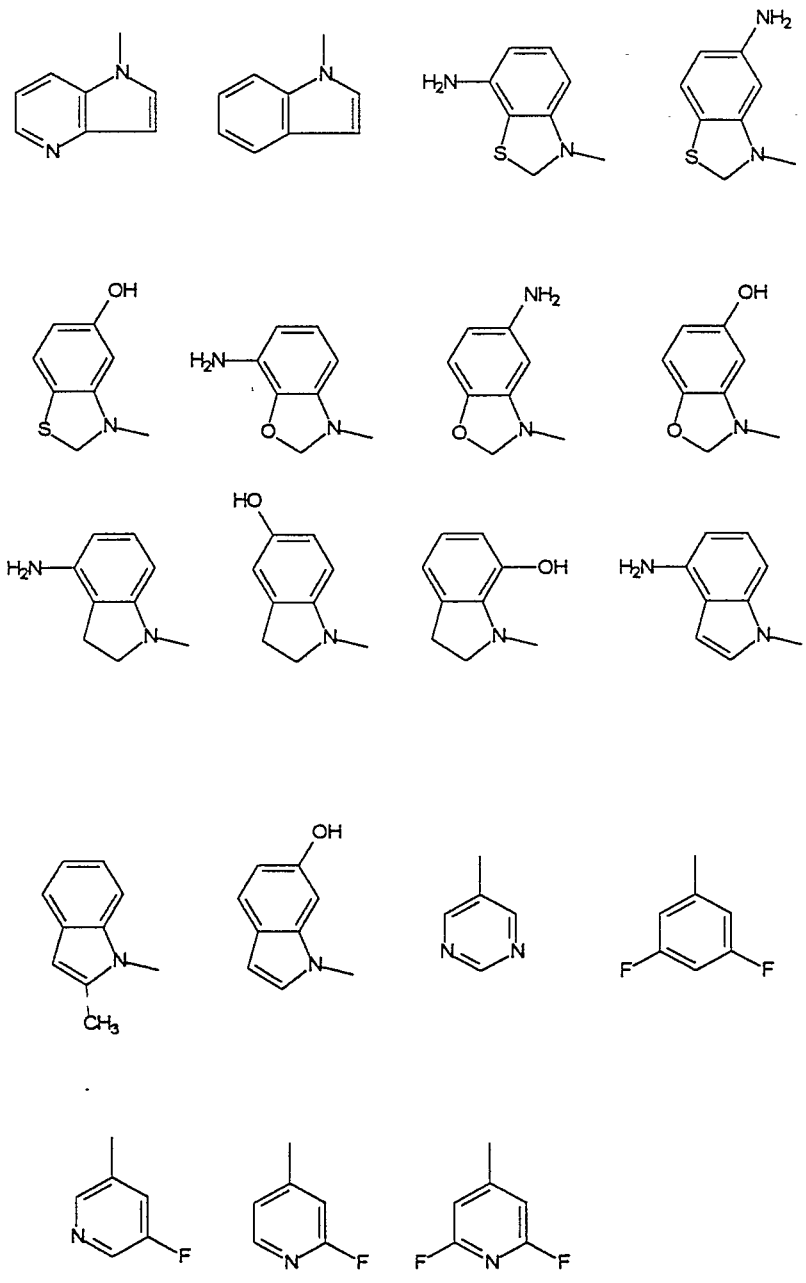
38. The compound according to claim 41, wherein R^2 within the definition of Y is selected from hydrogen, R^3, or C_1-C_6 alkyl optionally substituted with R^3.

39. The compound according to claim 42, wherein R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with 1-3 groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

40. The compound according to claim 43, wherein at least one R^2 within the definition of Y is selected from the group consisting of:







41. The compound according to claim 42, wherein at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$,

$-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

42. The compound according to claim 42, wherein at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3.

43. The compound according to claim 46, wherein at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$.

44. The compound according to claim 46, wherein R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$.

45. The compound according to any one of claims 42-48, wherein:

each R^1 is benzyl; and

each R^9 not within the definition of Y is 2-hydroxyindanyl.

46. The compound according to any one of claims 42-48, wherein each R^1 is independently selected from benzyl optionally substituted with 1-3 substituents

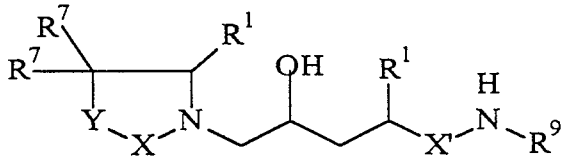
selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$.

47. The compound according to claim 50, wherein each R^9 not within the definition of Y is 2-hydroxyindanyl.

48. The compound according to claim 50, wherein each R1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2.

49. The compound according to claim 52, wherein each R^9 not within the definition of Y is 2-hydroxyindanyl.

50. A compound according to formula XIII, wherein:



(XIII)

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$,

$-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and
each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined in claim 1.

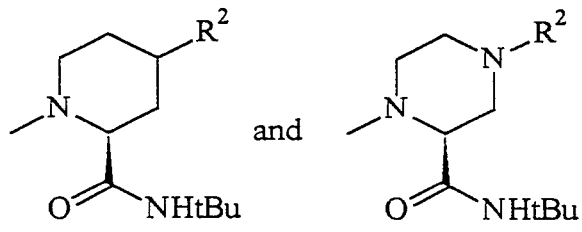
51. The compound according to claim 54, wherein R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3.

52. The compound according to claim 40, wherein:
X is $-C(O)-$; and
Y is $-N(R^2)-$.

53. The compound according to claim 40, wherein:
X is $-SO_2-$; and
Y is $-(C(R^2)_2)-$.

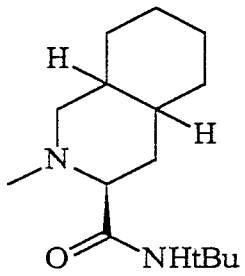
54. The compound according to claim 40, wherein
X is $-SO_2-$; and
Y is $-N(R^2)-$.

55. The compound according to claim 11, wherein:
R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH; and
Z is selected from the group consisting of:

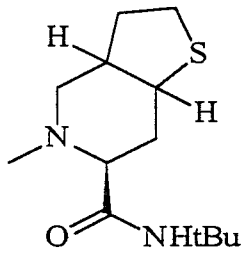


and R^2 is as defined in claim 1.

56. The compound according to claim 11, wherein Z is selected from the group consisting of

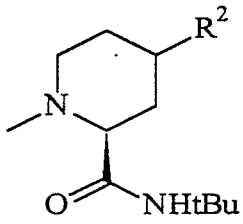


and

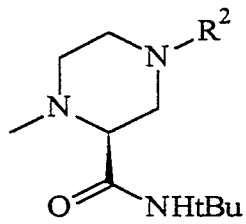


R^{10} is H_2; and
one R^{11} is H and one R^{11} is OH.

57. The compound according to any one of claims 16-32, wherein Z is selected from the group consisting of:

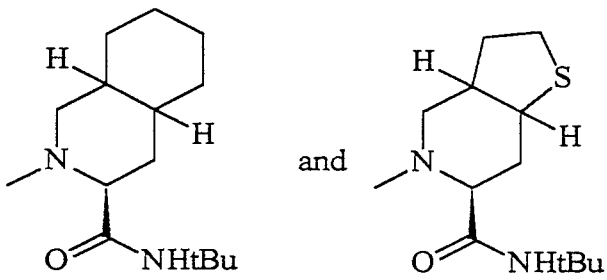


and

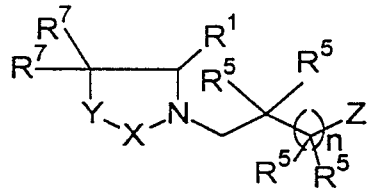


and R^2 is as defined in claim 1.

58. The compound according to any one of claims 16-32, wherein Z is selected from the group consisting of:

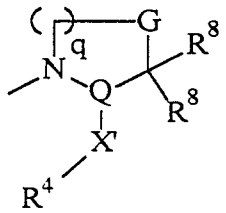


59. A compound according to formula I, wherein:



(I)

Z is selected from the group consisting of $-X'R^4$, $-N(R^1)-X'-R^4$, $-N(R^1)-N(R^1)-X'-R^4$, and formula VI;

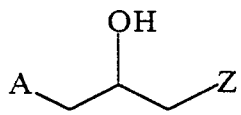


(VI)

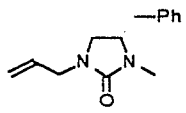
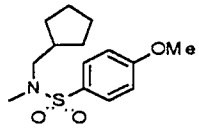
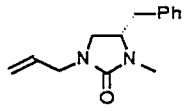
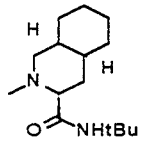
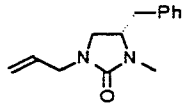
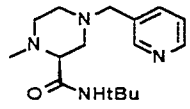
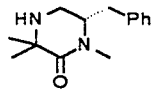
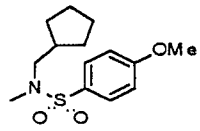
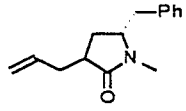
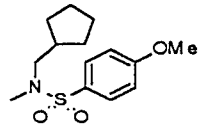
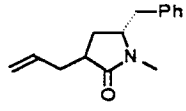
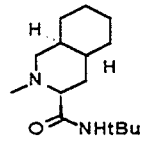
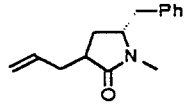
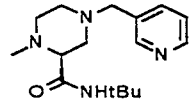
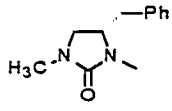
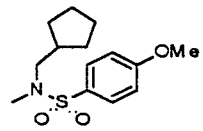
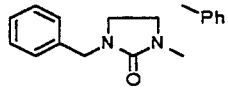
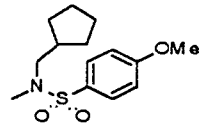
wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 members independently selected from R^2; and
each X, X', Y, Y' R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, Q, M, n, r, p, q and G is independently as defined in claim 1.

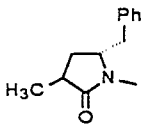
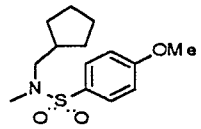
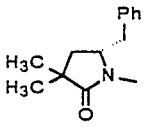
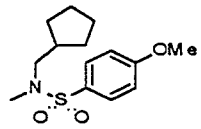
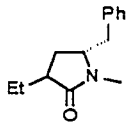
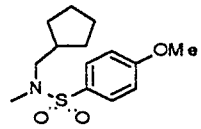
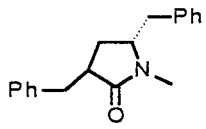
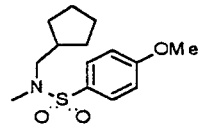
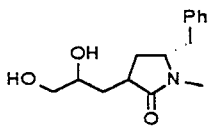
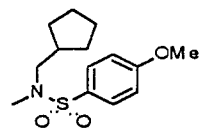
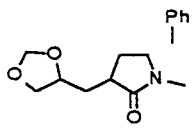
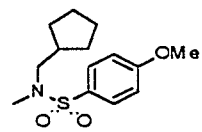
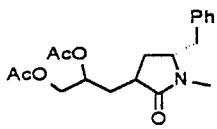
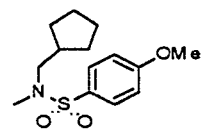
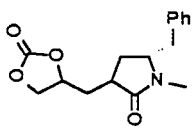
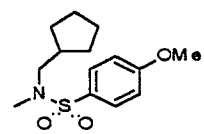
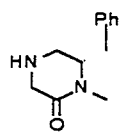
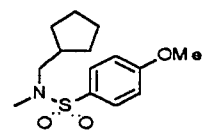
60. A compound selected from the group consisting of compound numbers: 1, 2, 3, 4, 7, 8, 9, 13, 14, 16, 17, 18, 20, 23, 24, 25, 26, 32, 35, 38, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 62, 63, 72, 75, 76, 78, 80, 82, 83, 91, 92, 94, 95, 96, 101, 102, 109, 121, 122, 123, 124, 126, 127, 128, 129, 131, 132, 133, 134, 135, 137, 138, 140, 141, 145, 146, 147, 149, 150, 155, 156, 160, 161, 162, 164, 165, 170, 171, 175, 176, 177, 179, 180, 185, 186, 190, 191, 192, 194, 195, 200, 201, 208, 219, 220, 228 and 264, as shown below in Tables A, B, C, and D:

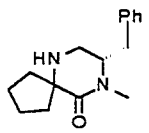
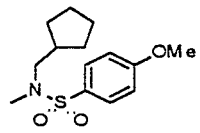
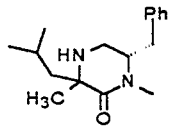
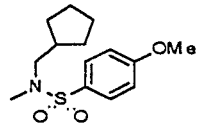
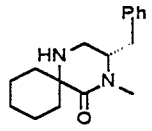
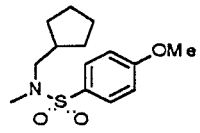
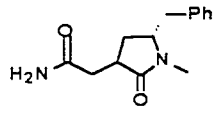
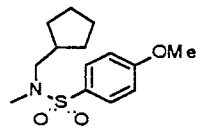
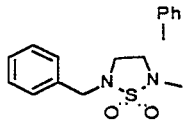
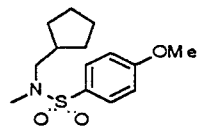
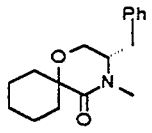
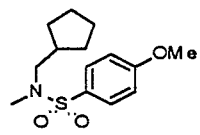
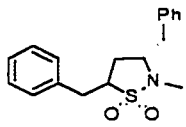
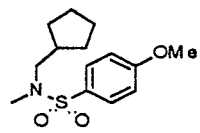
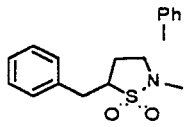
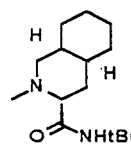
TABLE A

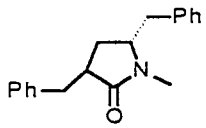
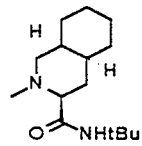
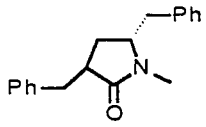
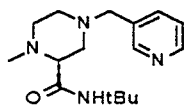
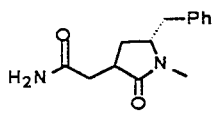
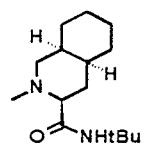
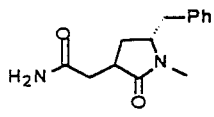
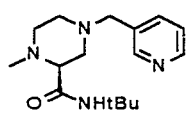
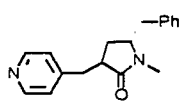
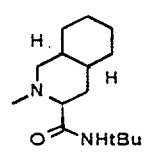
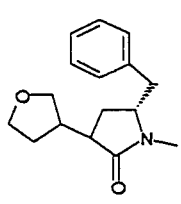
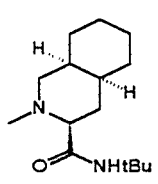
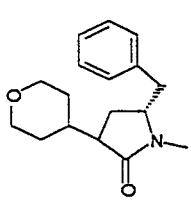
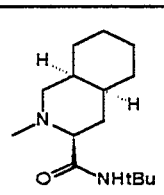


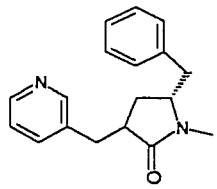
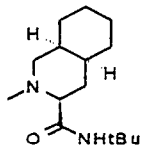
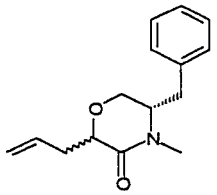
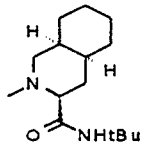
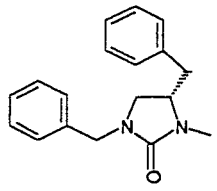
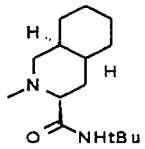
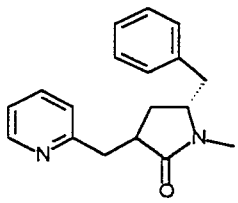
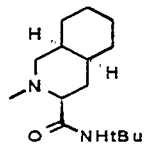
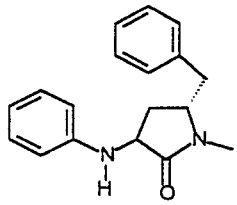
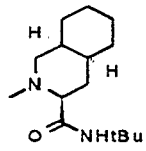
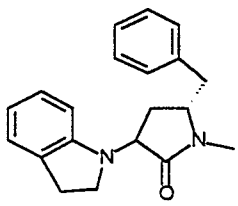
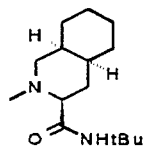
Cmpd. No.	A	Z

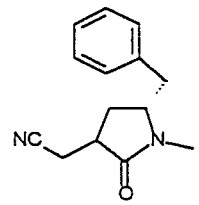
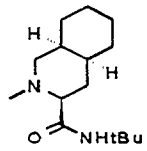
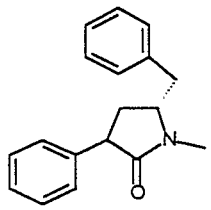
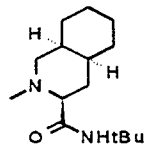
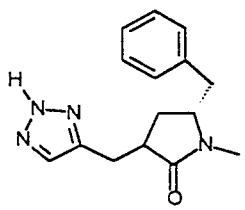
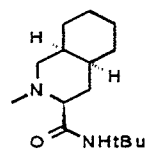
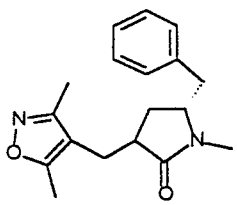
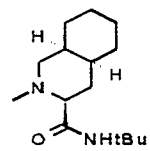
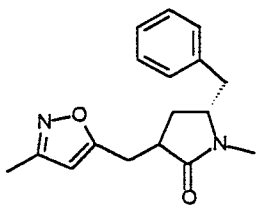
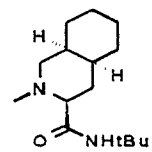
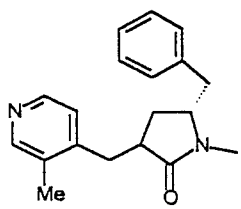
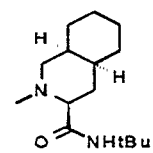
1		
2		
3		
4		
7		
8		
9		
13		
14		

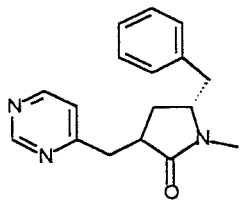
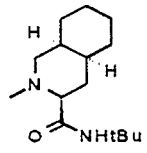
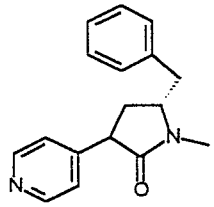
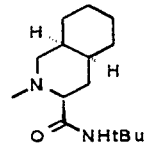
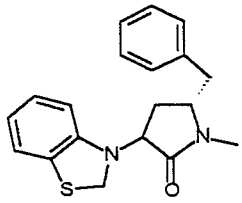
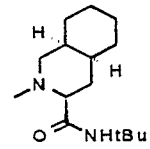
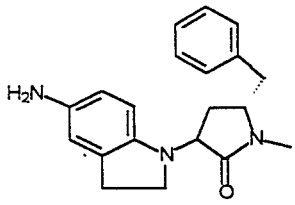
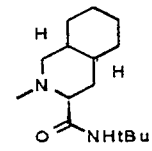
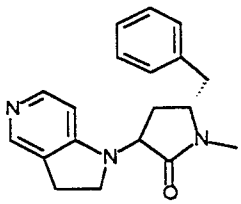
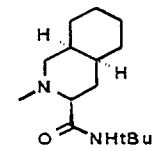
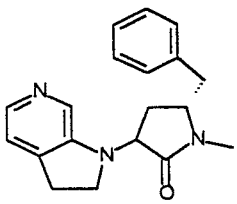
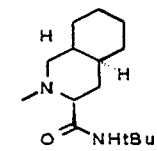
16		
17		
18		
20		
23		
24		
25		
26		
27		

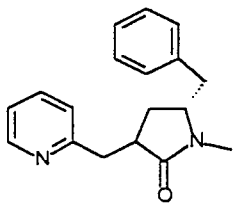
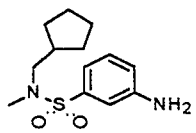
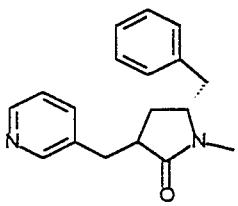
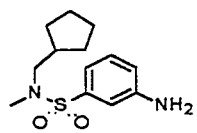
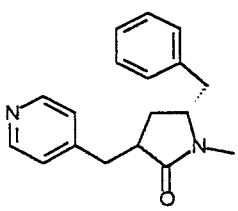
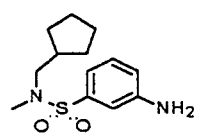
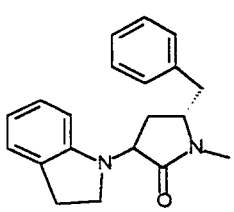
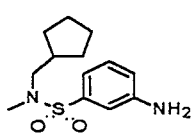
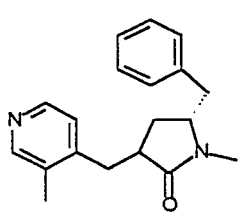
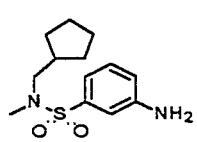
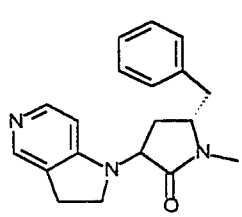
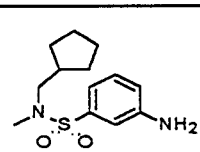
32		
35		
38		
45		
46		
47		
48		
49		

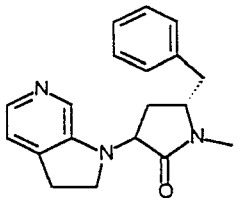
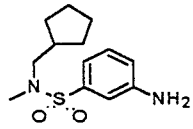
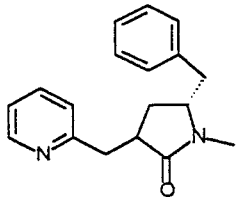
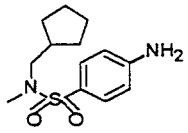
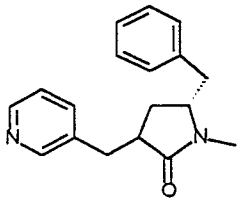
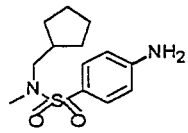
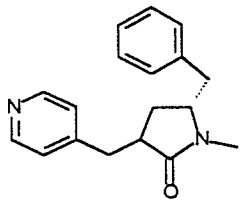
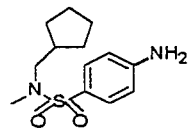
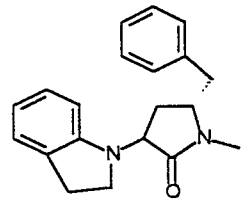
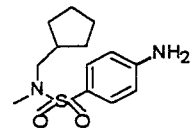
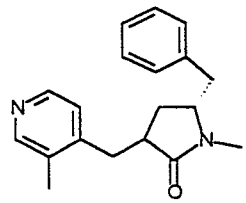
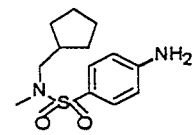
50		
51		
52		
53		
54		
62		
63		

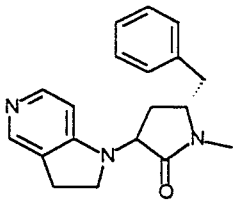
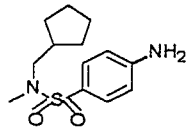
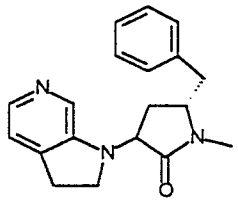
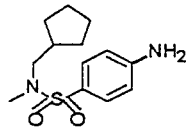
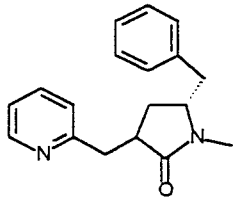
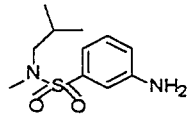
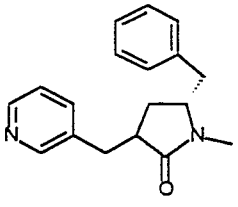
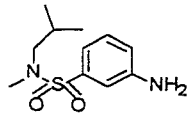
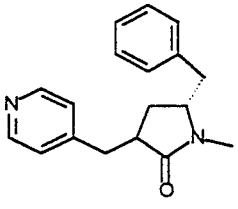
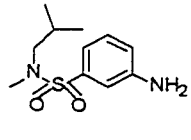
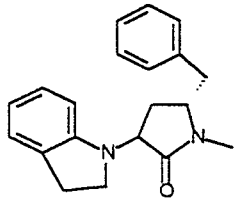
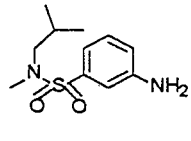
72		
75		
76		
123		
124		
126		

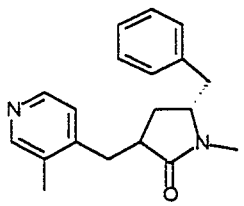
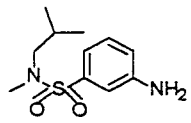
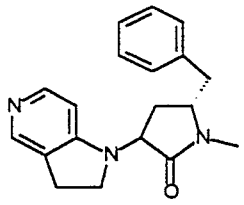
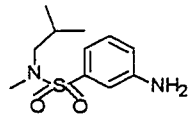
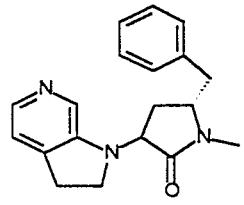
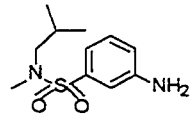
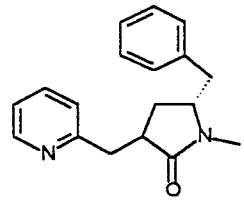
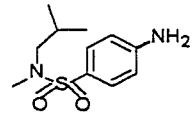
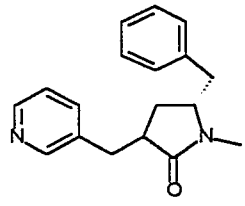
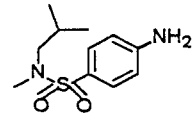
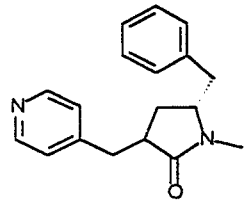
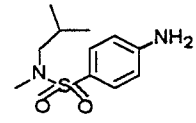
127		
128		
129		
131		
132		
133		

134		
135		
137		
138		
140		
141		

145		
146		
147		
149		
150		
155		

156		
160		
161		
162		
164		
165		

170		
171		
175		
176		
177		
179		

180		
185		
186		
190		
191		
192		

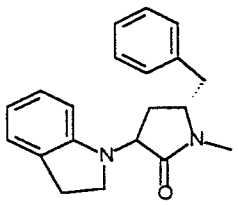
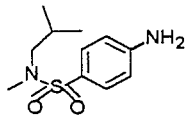
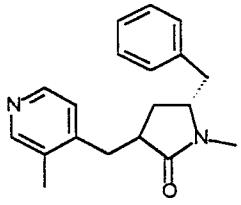
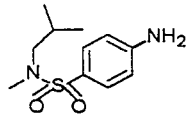
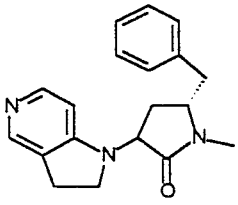
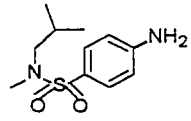
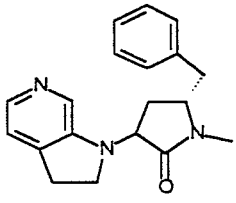
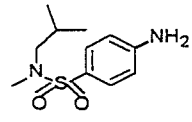
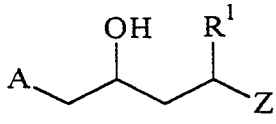
194		
195		
200		
201		

TABLE B



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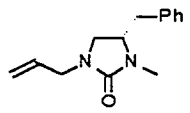
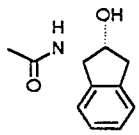
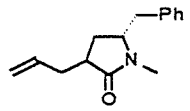
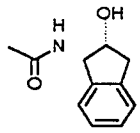
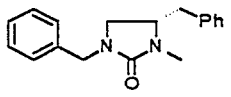
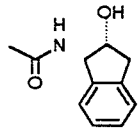
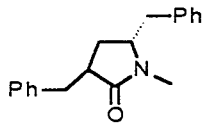
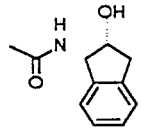
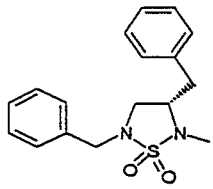
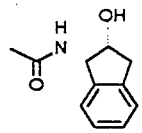
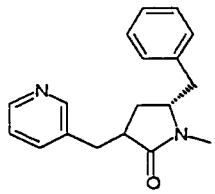
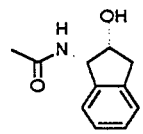
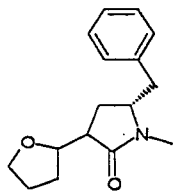
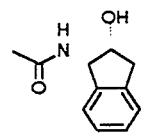
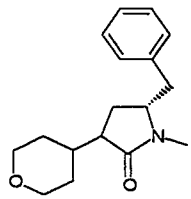
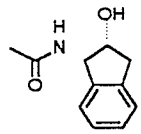
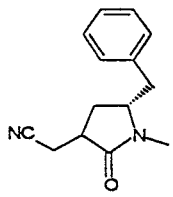
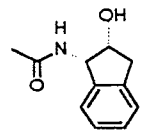
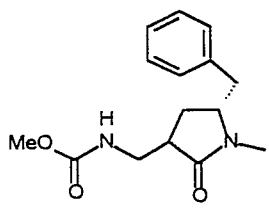
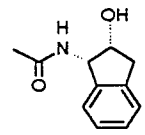
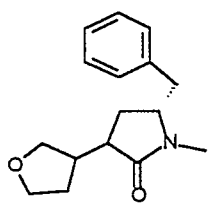
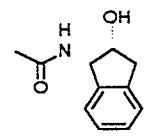
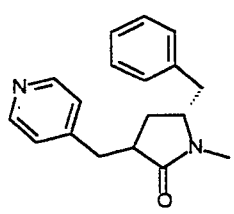
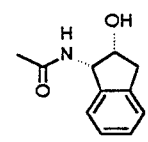
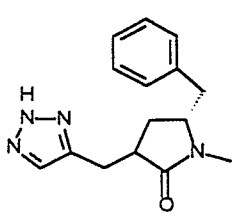
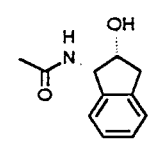
78		Bn	
80		Bn	
82		Bn	
83		Bn	
91		Bn	
92		Bn	
94		Bn	

95		Bn	
96		Bn	
208		Bn	
219		Bn	
220		Bn	
228		Bn	

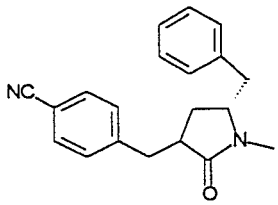
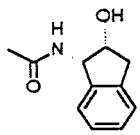
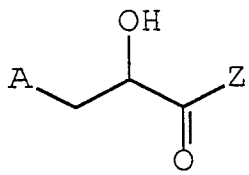
264		Bn	

TABLE C



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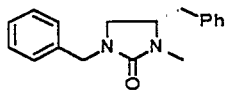
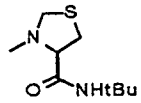
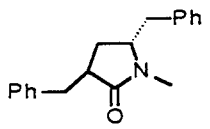
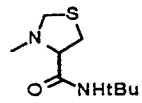
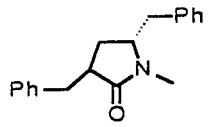
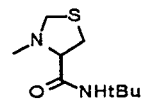
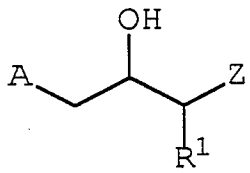
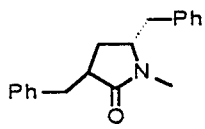
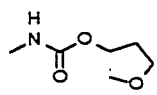
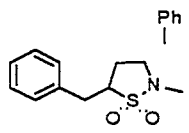
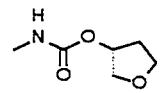
101		
102		
109		

TABLE D



121		Bn	

122		Bn	

61. The compound of claim 60, selected from the group consisting of compound numbers: 2, 7, 8, 9, 14, 18, 20, 25, 26, 32, 38, 45, 47, 48, 49, 50, 51, 53, 54, 62, 63, 72, 82, 83, 91, 92, 94, 95, 96, 123, 126, 140, 141, 219, 220, 228 and 264.

62. The compound of claim 61, selected from the group consisting of compound numbers: 7, 8, 9, 20, 45, 50, 51, 53, 54, 82, 83, 92, 94, 96, 219, 220, 228 and 264.

63. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective in inhibiting aspartyl protease and a pharmaceutically acceptable carrier, adjuvant or vehicle.

64. The pharmaceutical composition according to claim 67, wherein said pharmaceutical composition is orally administrable.

65. The pharmaceutical composition according to claim 67, further comprising one or more additional agents selected from the group consisting of other anti-viral agents and immunostimulators.

66. The pharmaceutical composition according to claim 69, wherein said other anti-viral agent is a

protease inhibitor or a reverse transcriptase inhibitor.

67. The pharmaceutical composition according to claim 70, wherein said protease inhibitor is a HIV protease inhibitor.

68. The pharmaceutical composition according to claim 71, wherein said HIV protease inhibitor or inhibitors are selected from the group consisting of VX-478, saquinavir, indinavir, ritonavir, nelfinavir, palinavir, U-103017, XM 412, XM 450, BMS 186318, CPG 53,437, CPG 61,755, CPG 70,726, ABT 378 , GS 3333, GS 3403, GS 4023, GS 4035, GS 4145, GS 4234 , and GS 4263.

69. The pharmaceutical composition according to claim 70, wherein said reverse transcriptase inhibitor is a nucleoside analog.

70. The pharmaceutical composition according to claim 73, wherein said nucleoside analog is selected from the group consisting of zidovudine (AZT), dideoxycytidine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89 and 524W91.

71. The pharmaceutical composition according to claim 70, wherein said reverse transcriptase inhibitor is a non-nucleoside analog.

72. The pharmaceutical composition according to claim 75, wherein said non-nucleoside reverse transcriptase inhibitor is delavirdine (U90) or nevirapine.

73. The pharmaceutical composition according to claim 67, wherein said pharmaceutical composition further comprises an agent capable of inhibiting the metabolic effects of one or more cytochrome P_{450} enzyme subtypes.

74. A method for inhibiting aspartyl protease activity comprising the step of contacting an aspartyl protease with the compound according to claim 1.

75. A method for reversibly binding an aspartyl protease comprising the step of contacting the aspartyl protease with the compound according to claim 1, said compound being covalently bound to a solid matrix.

76. A method for preventing HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to either claim 67 or 68.

77. A method for preventing HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to claim 69.

78. A method for treating HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutically effective amount of a pharmaceutical composition according to either claim 67 or 68.

79. A method for treating HIV infection in a mammal comprising the step of administering to said

mammal a pharmaceutical composition according to claim 69.

80. The method according to either claim 80 or 82, further comprising the step of administering, to the mammal one or more additional agents selected from the group consisting of other anti-viral agents and immunostimulators via a single or multiple dose.

81. The method according to claim 84, wherein said other anti-viral agent is a protease inhibitor or reverse transcriptase inhibitor.

82. The method according to claim 85, wherein said protease inhibitor is an HIV protease inhibitor.

83. The method according to claim 86, wherein said HIV protease inhibitor is selected from the group consisting of VX-478, saquinavir, indinavir , ritonavir, nelfinavir, palinavir, U-103017, XM 412 , XM 450, BMS 186318, CPG 53,437, CPG 61,755 , CPG 70,726, ABT 378, GS 3333, GS 3403, GS 4023, GS 4035, GS 4145 , GS 4234, and GS 4263.

84. The method according to claim 85, wherein said reverse transcriptase inhibitor is a nucleoside analog.

85. The method according to claim 88, wherein said nucleoside analog is selected from the group consisting of zidovudine (AZT), dideoxycytidine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89 and 524W91.

86. The method according to claim 85, wherein said reverse transcriptase inhibitor is a non-nucleoside analog.

87. The method according to claim 90, wherein said non-nucleoside reverse transcriptase inhibitor is delavirdine (U90) or nevirapine.

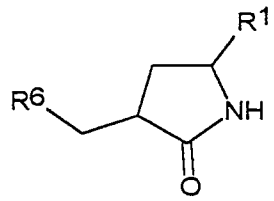
88. A method for treating or preventing of viral infection comprising the step of administering to said mammal a pharmaceutical composition according to either claim 67 or 68.

89. A method for treating or preventing HIV related disease effects, including tumors, CMV retinitis, candida infections, maternal fetal transmission, or AIDS related dementia, comprising the step of administering to said mammal a pharmaceutical composition according to either claim 67 or 68.

90. The composition according to claim 69, wherein the additional anti-viral agents are 3TC and zidovudine (AZT).

91. The composition according to claim 69, wherein the additional anti-viral agent is 1592U89.

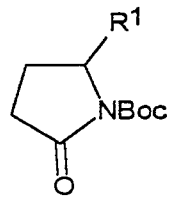
92. A process for preparing a compound of formula XIV:



XIV

wherein R^1 and R^6 are defined as in claim 1, comprising the steps of:

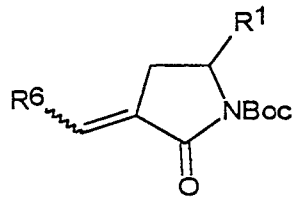
(1) reacting a compound of formula XV:



XV

wherein R^1 is defined as in claim 1,
in an inert solvent with a base;

(2) reacting the product of step (1) with an aldehyde of R^6CHO followed by an optional treatment with a dehyrating agent, wherein R^6 is defined as in claim 1 to give a compound of formula XVI:

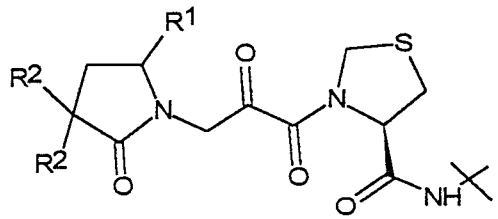


XVI

wherein R^1 and R^6 are defined as in claim 1;

(3) reacting the product of step (2) in an inert solvent with hydrogen gas in the presence of an hydrogenation catalyst followed by treatment with an anhydrous acid to give a product of formula XIV.

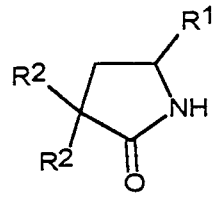
93. A process for preparing a compound of formula XVII:



XVII

wherein R^1 and R^2 are defined as in claim 1, comprising the steps of:

(1) reacting a compound of formula XVIII:



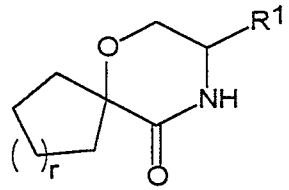
XVIII

wherein R^1 and R^2 are as defined in claim 1, in an inert solvent with a base, then bromomethylacrylic acid;

(2) reacting the product of step (1) with an oxidizing agent;

(3) reacting the product of step (2) in an inert solvent with thioproline t-butylamide and suitable amide-bond coupling reagents to give a product of formula XVII.

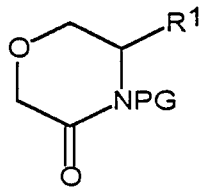
94. A process for preparing a compound of formula XIX:



XIX

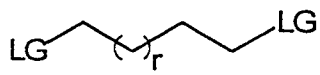
wherein R^1 and r are defined as in claim 1, comprising the steps of:

(1) reacting a compound of formula XX



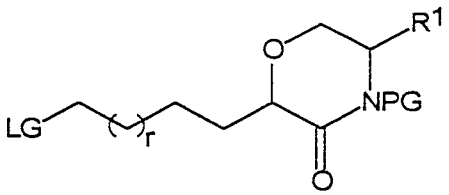
XX

in an inert solvent with a base, then a bis-leaving group al .e of formula XXI:



XXI

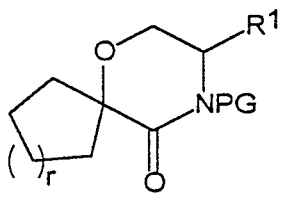
wherein LG is selected from halo, arylsulfonate esters and alkylsulfonate esters, and r is defined as in claim 1, to give a product of formula XXII:



XXII

wherein R^1 and PG are defined as in formula XX and LG and r are defined as in formula XXI;

(2) reacting the product of step (1) in an inert solvent with a base, to give a product of formula XXIII:

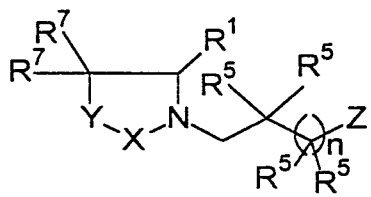


XXIII

wherein R^1 is defined as in claim 1 and PG is a N-protecting group;

(3) reacting the product of step (2) in an inert solvent with a reagent suitable for removal of the N-protecting group PG to give a compound of formula XIX.

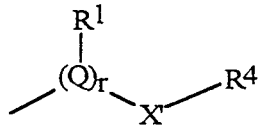
95. A compound according to formula I:



(I)

wherein:

each Z is

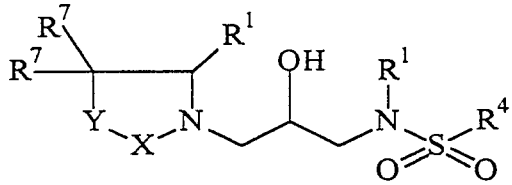


wherein Z is optionally fused with R^6;

Q, X, X', Y, R1, R4, R5, R7 and r as as defined in claim 1; and

provided that when Y is $-NR^2$ or $-(C(R^2)_2)_p$, p is 1, X is $-C(O)-$, Q is N and r is 1, then X' is not SO_2.

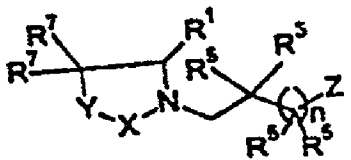
96. The compound according to claim 95, having the structure of formula IX:



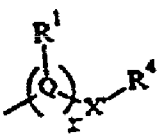
(IX)

wherein:

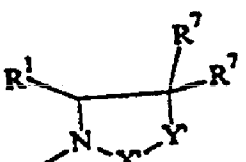
X is $-S(O)_2-$.



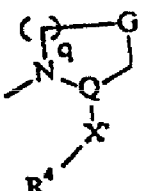
(I)



(a)



(b)



(c)