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(54) **INHIBITEURS DE CYSTEINE ET SERINE PROTEASES DERIVES D'ACIDE D-AMINE**

(54) **D-AMINO ACID DERIVED INHIBITORS OF CYSTEINE AND SERINE PROTEASES**

(57) L'invention concerne un nouvel acide (D)-aminé contenant des inhibiteurs de cystéine ou serine protéases. Elle concerne également des procédés d'utilisation de ces inhibiteurs de protéase.

(57) The present invention is directed to novel (D)-amino acid containing inhibitors of cysteine or serine proteases. Methods for the use of the protease inhibitors are also described.

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(54) Title: D-AMINO ACID DERIVED INHIBITORS OF CYSTEINE AND SERINE PROTEASES

(57) Abstract

The present invention is directed to novel (D)-amino acid containing inhibitors of cysteine or serine proteases. Methods for the use of the protease inhibitors are also described.

D-Amino Acid Derived Inhibitors of Cysteine and Serine Proteases

Cross Reference To Related Applications

This application claims benefit of U.S. Provisional Application Serial No. 60/007,651, filed November 28, 1995, the disclosure of which is hereby incorporated by reference in its entirety.

Field of the Invention

P2 (D)-amino acid inhibitors of cysteine or serine proteases, methods for making these compounds, and methods for using the same are disclosed.

Background of the Invention

Numerous cysteine and serine proteases have been identified in human tissues. A "protease" is an enzyme which degrades proteins into smaller components (peptides). The terms "cysteine protease" and "serine protease" refer to proteases which are distinguished by the presence therein of a cysteine or serine residue which plays a critical role in the catalytic process. Mammalian systems, including humans, normally degrade and process proteins via a variety of enzymes including cysteine and serine proteases. However, when present at elevated levels or when abnormally activated, cysteine and serine proteases may be involved in pathophysiological processes.

For example, calcium-activated neutral proteases ("calpains") comprise a family of intracellular cysteine proteases which are ubiquitously expressed in mammalian tissues. Two major calpains have been identified; calpain I and calpain II. While calpain II is the predominant form in many tissues, calpain I is thought to be the predominant form active in pathological conditions of nerve tissues. The calpain family of cysteine proteases has been implicated in many diseases and disorders, including neurodegeneration, stroke, Alzheimer's, amyotrophy, motor neuron damage, acute central nervous system injury, muscular dystrophy, bone resorption, platelet aggregation, cataracts and inflammation. Calpain I has been implicated in excitatory amino-acid induced neurotoxicity disorders including ischemia, hypoglycemia, Huntington's Disease, and epilepsy.

The lysosomal cysteine protease cathepsin B has been implicated in the following disorders: arthritis, inflammation, myocardial infarction, tumor metastasis, and muscular dystrophy. Other lysosomal cysteine proteases include cathepsins C, H, L and S. Interleukin-1β converting enzyme ("ICE") is a cysteine protease which catalyzes the formation of interleukin-1β. Interleukin-1β is an immunoregulatory protein implicated in the following disorders: inflammation, diabetes, septic shock, rheumatoid arthritis, and Alzheimer's disease. ICE has also been linked to apoptotic cell death of neurons, which is implicated in a variety of neurodegenerative disorders including Parkinson's disease, ischemia, and amyotrophic lateral sclerosis (ALS).

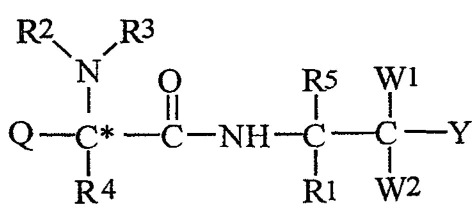
Cysteine proteases are also produced by various pathogens. The cysteine protease clostripain is produced by *Clostridium histolyticum*. Other proteases are produced by *Trypanosoma cruzi*, malaria parasites *Plasmodium falciparum* and *P.vinckei* and *Streptococcus*. Hepatitis A viral protease HAV C3 is a cysteine protease essential for processing of picornavirus structural proteins and enzymes.

Exemplary serine proteases implicated in degenerative disorders include thrombin, human leukocyte elastase, pancreatic elastase, chymase and cathepsin G. Specifically, thrombin is produced in the blood coagulation cascade, cleaves fibrinogen to form fibrin and activates Factor VIII; thrombin is implicated in thrombophlebitis, thrombosis and asthma. Human leukocyte elastase is implicated in tissue degenerative disorders such as rheumatoid arthritis, osteoarthritis, atherosclerosis, bronchitis, cystic fibrosis, and emphysema. Pancreatic elastase is implicated in pancreatitis. Chymase, an enzyme important in angiotensin synthesis, is implicated in hypertension, myocardial infarction, and coronary heart disease. Cathepsin G is implicated in abnormal connective tissue degradation, particularly in the lung.

Given the link between cysteine and serine proteases and various debilitating disorders, compounds which inhibit these proteases would be useful and would provide an advance in both research and clinical medicine. The present invention is directed to these, as well as other, important ends.

Summary of the Invention

The present invention is directed to novel cysteine and serine protease inhibitors which contain a (D)-amino acid at the P2 position. Exemplary compounds are represented by the following Formula I:



I

wherein:

C* denotes a carbon atom having a D-configuration;

Q has the formula G-B-$(CHR^{20})_q$- where R^{20} is independently H or alkyl having from 1 to 4 carbons;

q is 0, 1, or 2;

B is selected from the group consisting of C(=O), S(=O), $S(=O)_2$, S, CH_2, a bond, NH and O;

G is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, arylsulfonyl, alkylsulfonyl, aralkyloxy having from about 7 to about 15 carbons, amino, and a carbohydrate moiety optionally containing one or more alkylated hydroxyl groups, said aryl, heteroaryl, aralkyl, alkyl and amino groups being optionally substituted with one or more K groups;

K is selected from the group consisting of halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy, and amino, said amino group being optionally substituted with an acyl group or with 1 to 3 aryl or lower alkyl groups;

R^1 is selected from the group consisting of H, alkyl having from one to about 14 carbons, cycloalkyl having from 3 to about 10 carbons, aralkyl having from about 7 to about 15 carbons, heteroarylalkyl in which the heteroaryl ring contains from about 5 to about 14 ring atoms, a natural side chain of a D- or L-amino acid, and an unnatural side chain of a D- or L-amino acid, said alkyl, cycloalkyl, aralkyl, and heteroarylalkyl groups being optionally substituted with one or more K groups;

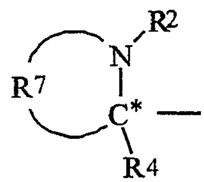
R^2 is selected from the group consisting of $C(=O)R^6$, $S(=O)_2R^6$, and a protecting group;

R^6 is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, said aryl, heteroaryl, aralkyl and alkyl groups being optionally substituted with one or more K groups, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, and amino optionally substituted with 1 or more alkyl groups;

R^3 is selected from the group consisting of H, lower alkyl, aralkyl, and a group of formula $-CO_2-R^{21}$ where R^{21} is a lower alkyl group;

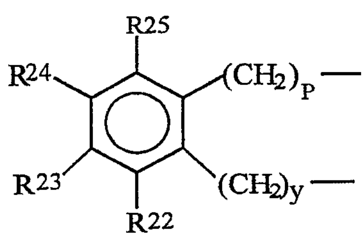
or R^3 may be taken together with R^2 to form a phthalimido group;

or Q and R^3 taken together with -C* and $-N(R^2)-$ may form a group of formula:



where R^7 is alkylene having from 2 to 5 carbons, said alkylene group optionally containing a carbon-carbon double bond, said alkylene group being optionally substituted with a group selected from the group consisting of aryl, azide, CN, a protected amino group, and OSO_2-aryl, wherein said aryl group is optionally substituted with one or more K groups, said aryl portion of said OSO_2-aryl group being optionally substituted with one or more K groups;

or R^7 may have the formula:



where p and y are independently 0 or 1, and R^{22}, R^{23}, R^{24}, and R^{25} are indepenedently H or a K group;

R^4 and R^5 are each independently selected from the group consisting of H and lower alkyl;

W^1 and W^2 are selected such that W^1 is H and W^2 is OC(=O)NH-R^{26} where R^{26} is alkyl, or W^1 and W^2 are both alkoxy, or W^1 is OH and W^2 is selected from the group consisting of aralkyl, aralkyloxy, aryloxy, heteroaryloxy, heteroaralkyloxy, and SO_3Z^1 where Z^1 which is preferably Group I or Group II counterion, preferably Na; or

W^1 and W^2 taken together may form a group selected from the group consisting of =O, =NR^8, =N(→O)R^9, -S$(CH_2)_2$O-, and -N(R^{12})$(CH_2)_2$N(R^{12})-;

R^8 is selected from the group consisting of NH(C=O)NH_2, hydroxyl, and lower alkoxy;

R^9 is selected from the group consisting of alkyl and aralkyl;

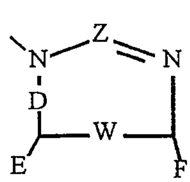
R^{12} is selected from the group consisting of alkyl having from 1 to 4 carbons, and phenyl;

Y is selected from the group consisting of H, C(=O)$NR^{10}R^{11}$, C(=O)OR^{10}, CH=N_2, and CH_2R^{13}; or

Y and R^1 taken together may form -$(CH_2)_4$N(Pr)- where Pr is H or a protecting group, provided that when Y and R^1 are taken together to form -$(CH_2)_4$N(Pr)-, then W^1 and W^2 are taken together to form =O;

R^{10} and R^{11} are each independently selected from the group consisting of H, alkyl having from 1 to about 10 carbons, said alkyl groups being optionally substituted with one or more K groups, aryl having from about 6 to about 14 carbons, and aralkyl having from about 7 to about 15 carbons;

R^{13} is selected from the group consisting of L, lower alkyl, aralkyl, halogen, and a group O-M, wherein M has the structure:



wherein:

Z is selected from the group consisting of N and CR^{14};

W is selected from the group consisting of a double bond and a single bond;

D is selected from the group consisting of C=O and a single bond;

E and F are independently selected from the group consisting of R^{14}, R^{15}, and J;

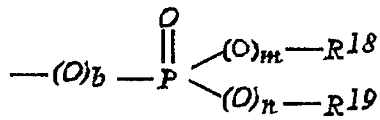
or E and F taken together comprise a joined moiety, said joined moiety being selected from the group consisting of an aliphatic carbocyclic ring having from 5 to 7 carbons, an aromatic carbocyclic ring having from 5 to 7 carbons, an aliphatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, and an aromatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, said aliphatic carbocyclic ring, aromatic carbocyclic ring, aliphatic heterocyclic ring, and aromatic heterocyclic ring each being optionally substituted with J;

R^{14} and R^{15} are independently selected from the group consisting of H, alkyl having from 1 to 10 carbons, heteroaryl having from 1 to 10 carbons, alkanoyl having from 1 to 10 carbons, and aroyl, wherein said alkyl, heteroaryl, alkanoyl and aroyl groups are optionally substituted with J;

J is selected from the group consisting of halogen, $C(=O)OR^{16}$, $R^{16}OC(=O)$, $R^{16}OC(=O)NH$, OH, CN, NO_2, $NR^{16}R^{17}$, $N=C(R^{16})R^{17}$, $N=C(NR^{16}R^{17})_2$, SR^{16}, OR^{16}, phenyl, napththyl, heteroaryl, and a cycloalkyl group having from 3 to 8 carbons;

R^{16} and R^{17} are independently H, alkyl having from 1 to 10 carbons, aryl, or heteroaryl, wherein said alkyl, aryl and heteroaryl groups are optionally substituted with K;

L is a phosphorus-containing enzyme reactive group, which preferably has the formula:



wherein:

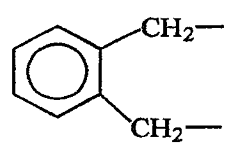
m, n, and b are each independently 0 or 1;

R^{18} and R^{19} are each independently selected from the group consisting of H, lower alkyl optionally substituted with K, aryl optionally substituted with K, and heteroaryl optionally substituted with K;

or R^{18} and R^{19} taken together with $-(O)_m-P(=O)-(O)_n-$ can form a 5-8 membered ring containing up to 3 hetero atoms,

or R^{18} and R^{19} taken together with $-(O)_m-P(=O)-(O)_n-$ can form a 5-8 membered ring optionally substituted with K.

In some preferred embodiments of the compounds of Formula I, G is alkyl, benzyl, tetrahydroisoquinolyl, 3-indolyl, phenyl, N-methylbenzylamino, substituted benzyl, 2-thienyl or p-benzyloxyphenyl. In other preferred embodiments of the compounds of Formula I Q and R^3 taken together have a formula selected from the group consisting of $-(CH_2)_3-$, $-CH_2-CH(OSO_2C_6H_5)-CH_2-$, $-CH_2-CH(OSO_2C_6H_4CH_3)-CH_2-$, $-CH_2-CH(N_3)-CH_2-$, $-CH_2-CH(CN)-CH_2-$, $-CH_2-CH=CH-$, and



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In other preferred embodiments of the compounds of Formula I, B is selected from the group consisting of $-C(=O)-$, $-O-$, $-S-$, $-S(=O)_2-$, and a bond.

In further preferred embodiments of the compounds of Formula I R^1 is selected from the group consisting of benzyl, substituted benzyl, a lysyl side chain, or a substituted lysyl side chain. In more preferred embodiments

R^1 is alkyl, preferably ethyl, isobutyl, or *t*-butyl, benzyl, p-benzyloxybenzyl, 2-pyridylmethyl, $-(CH_2)_4-NHC(=O)-O-CH_2-C_6H_5$, $-(CH_2)_4-NHC(=O)-O-t-C_4H_9$, or $-(CH_2)_4-NHSO_2-C_6H_5$.

In other preferred embodiments of the compounds of Formula I W^1 and W^2 taken together form -C(=O), and R^1 and Y together form $-(CH_2)_4-N(Pr)-$ where Pr is H or *t*-butoxycarbonyl.

In some preferred embodiments of the compounds of Formula I R^2 is selected from the group consisting of *t*-butyloxycarbonyl, $-S(=O)_2R^6$, and $-C(=O)CH_3$. More preferably, R^2 is$-S(=O)_2R^6$, said R^6 being selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In still more preferred embodiments of the compounds of Formula I R^2 is selected from the group consisting of $-S(=O)_2CH_3$, $-S(=O)_2CH_2CH_3$, *p*-fluorophenylsulfonyl, $-S(=O)_2N(CH_3)_2$, 2-thienylsulfonyl, 2-isoxazolesulfonyl, phenylsulfonyl, *p*-methylphenyl-sulfonyl, 4-(N-methylimidazole)sulfonyl, and 2-naphthylsulfonyl.

In other preferred embodiments of the compounds of Formula I Y is selected from the group consisting of H and CH_2F.

Preferably, W^1 and W^2 taken together form -C(=O), or W^1 and W^2 are selected such that W^1 is OH and W^2 is SO_3Z^1 where Z^1 is a group I counterion which is preferably Na, W^1 is H and W^2 is $OC(=O)NH-R^{26}$ where R^{26} is alkyl, W^1 is OH and W^2 is aralkyl, W^1 is OH and W^2 is aralkyloxy, W^1 is OH and W^2 is aryloxy, W^1 is OH and W^2 is heteroaryloxy, W^1 is OH and W^2 is heteroaralkyloxy, W^1 and W^2 are both alkoxy, or W^1 and W^2 taken together form a group selected from the group consisting of $=NR^8$, $=N(\rightarrow O)R^{9}$, $-S(CH_2)_2O-$, and $-N(R^{12})(CH_2)_2N(R^{12})-$.

In particularly preferred embodiments of the compounds of Formula I, B is selected from the group consisting of -(C=O)-, -O-, a bond, SO_2, and -S-; Y is selected from the group consisting of H and CH_2F; R^1 is selected from the group consisting of benzyl, substituted benzyl, a lysyl side chain, and a substituted lysyl side chain; and R^2 is selected from the group consisting of *t*-butyloxycarbonyl, $-C(=O)CH_3$, and $-S(=O)_2R^6$. Preferably, R^6 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted aryl, and substituted and unsubstituted heteroaryl.

In an especially preferred embodiment, Q is benzyloxymethyl; R^1 is benzyl; R^2 is $-SO_2CH_3$; R_3, R_4, R_5 and Y are each H; and W^1 and W^2 together form $-C(=O)-$.

The compounds of the invention are useful for the inhibition of cysteine and serine proteases. Beneficially, the compounds find utility in a variety of settings. For example, in a research arena, the claimed compounds can be used, for example, as standards to screen for natural and synthetic cysteine protease and serine protease inhibitors which have the same or similar functional characteristics as the disclosed compounds. In a clinical arena, the subject compounds can be used to alleviate, mediate, reduce and/or prevent disorders which are associated with abnormal and/or aberrant activity of cysteine proteases and/or serine proteases. Accordingly, compositions containing the subject compounds, and methods for using the subject compounds, such as methods for inhibiting serine proteases or cysteine proteases comprising contacting said proteases with an inhibitory amount of a compound of the invention are disclosed. Methodologies for making the present (D)-amino acid containing inhibitors are also disclosed. Other useful methodologies will be apparent to those skilled in the art, once armed with the present disclosure. These and other features of the compounds of the subject invention are set forth in more detail below.

Brief Description of the Drawings

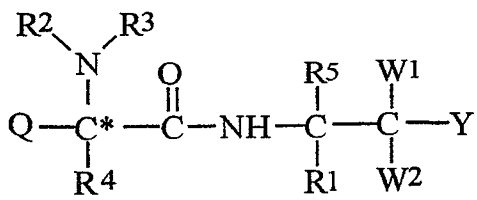
Figure 1 shows the effect of Compound 40 on spectrin breakdown in the CA1 hippocampal sectors of gerbils.

Figure 2 shows tht effect of Compound 40 on survival of CA1 neurons at four days after the ischemic insult.

Figure 3 shows the dose response for neuroprotective efficacy of Compound **40** when administered 3 hours after ischemia.

Detailed Description

Novel cysteine and serine protease inhibitors have been discovered which are represented by the general Formula I:



I

wherein:

C* denotes a carbon atom having a D-configuration;

Q has the formula G-B-$(CHR^{20})_q$- where R^{20} is independently H or alkyl having from 1 to 4 carbons;

q is 0, 1, or 2;

B is selected from the group consisting of C(=O), S(=O), $S(=O)_2$, S, CH_2, a bond, NH and O;

G is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, arylsulfonyl, alkylsulfonyl, aralkyloxy having from about 7 to about 15 carbons, amino, and a carbohydrate moiety optionally containing one or more alkylated hydroxyl groups, said aryl, heteroaryl, aralkyl, alkyl and amino groups being optionally substituted with one or more K groups;

K is selected from the group consisting of halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy, and amino, said amino group being optionally substituted with an acyl group or with 1 to 3 aryl or lower alkyl groups;

R^1 is selected from the group consisting of H, alkyl having from one to about 14 carbons, cycloalkyl having from 3 to about 10 carbons, aralkyl having from about 7 to about 15 carbons, heteroarylalkyl in which the heteroaryl ring contains from about 5 to about 14 ring atoms, a natural side chain of a D- or L-amino acid, and an unnatural side chain of a D- or L-amino acid, said alkyl, cycloalkyl, aralkyl, and heteroarylalkyl groups being optionally substituted with one or more K groups;

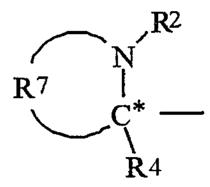
R^2 is selected from the group consisting of $C(=O)R^6$, $S(=O)_2R^6$, and a protecting group;

R^6 is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, said aryl, heteroaryl, aralkyl and alkyl groups being optionally substituted with one or more K groups, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, and amino optionally substituted with 1 or more alkyl groups;

R^3 is selected from the group consisting of H, lower alkyl, aralkyl, and a group of formula $-CO_2-R^{21}$ where R^{21} is a lower alkyl group;

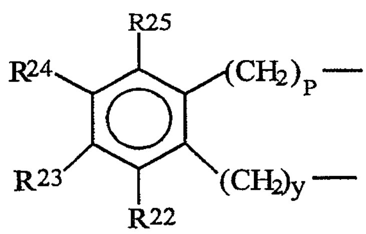
or R^3 may be taken together with R^2 to form a phthalimido group;

or Q and R^3 taken together with -C* and $-N(R^2)-$ may form a group of formula:



where R^7 is alkylene having from 2 to 5 carbons, said alkylene group optionally containing a carbon-carbon double bond, said alkylene group being optionally substituted with a group selected from the group consisting of aryl, azide, CN, a protected amino group, and OSO_2-aryl, wherein said aryl group is optionally substituted with one or more K groups, said aryl portion of said OSO_2-aryl group being optionally substituted with one or more K groups;

or R^7 may have the formula:



where p and y are independently 0 or 1, and R^{22}, R^{23}, R^{24}, and R^{25} are indepenedently H or a K group;

R^4 and R^5 are each independently selected from the group consisting of H and lower alkyl;

W^1 and W^2 are selected such that W^1 is H and W^2 is OC(=O)NH-R^{26} where R^{26} is alkyl, or W^1 and W^2 are both alkoxy, or W^1 is OH and W^2 is selected from the group consisting of aralkyl, aralkyloxy, aryloxy, heteroaryloxy, heteroaralkyloxy, and SO_3Z^1 where Z^1 which is preferably Group I or Group II counterion, preferably Na; or

W^1 and W^2 taken together may form a group selected from the group consisting of =O, =NR^8, =N(→O)R^9, -$S(CH_2)_2O$-, and -$N(R^{12})(CH_2)_2N(R^{12})$-;

R^8 is selected from the group consisting of $NH(C{=}O)NH_2$, hydroxyl, and lower alkoxy;

R^9 is selected from the group consisting of alkyl and aralkyl;

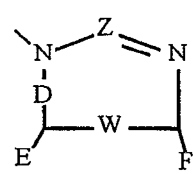
R^{12} is selected from the group consisting of alkyl having from 1 to 4 carbons, and phenyl;

Y is selected from the group consisting of H, $C(=O)NR^{10}R^{11}$, $C(=O)OR^{10}$, $CH{=}N_2$, and CH_2R^{13}; or

Y and R^1 taken together may form $-(CH_2)_4N(Pr)-$ where Pr is H or a protecting group, provided that when Y and R^1 are taken together to form $-(CH_2)_4N(Pr)-$, then W^1 and W^2 are taken together to form =O;

R^{10} and R^{11} are each independently selected from the group consisting of H, alkyl having from 1 to about 10 carbons, said alkyl groups being optionally substituted with one or more K groups, aryl having from about 6 to about 14 carbons, and aralkyl having from about 7 to about 15 carbons;

R^{13} is selected from the group consisting of L, lower alkyl, aralkyl, halogen, and a group O-M, wherein M has the structure:



wherein:

Z is selected from the group consisting of N and CR^{14};

W is selected from the group consisting of a double bond and a single bond;

D is selected from the group consisting of C=O and a single bond;

E and F are independently selected from the group consisting of R^{14}, R^{15}, and J;

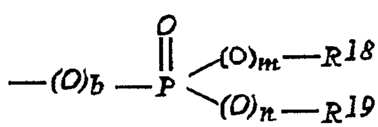
or E and F taken together comprise a joined moiety, said joined moiety being selected from the group consisting of an aliphatic carbocyclic ring having from 5 to 7 carbons, an aromatic carbocyclic ring having from 5 to 7 carbons, an aliphatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, and an aromatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, said aliphatic carbocyclic ring, aromatic carbocyclic ring, aliphatic heterocyclic ring, and aromatic heterocyclic ring each being optionally substituted with J;

R^{14} and R^{15} are independently selected from the group consisting of H, alkyl having from 1 to 10 carbons, heteroaryl having from 1 to 10 carbons, alkanoyl having from 1 to 10 carbons, and aroyl, wherein said alkyl, heteroaryl, alkanoyl and aroyl groups are optionally substituted with J;

J is selected from the group consisting of halogen, $C(=O)OR^{16}$, $R^{16}OC(=O)$, $R^{16}OC(=O)NH$, OH, CN, NO_2, $NR^{16}R^{17}$, $N=C(R^{16})R^{17}$, $N=C(NR^{16}R^{17})_2$, SR^{16}, OR^{16}, phenyl, napththyl, heteroaryl, and a cycloalkyl group having from 3 to 8 carbons;

R^{16} and R^{17} are independently H, alkyl having from 1 to 10 carbons, aryl, or heteroaryl, wherein said alkyl, aryl and heteroaryl groups are optionally substituted with K;

L is a phosphorus-containing enzyme reactive group, which preferably has the formula:



wherein:

m, n, and b are each independently 0 or 1;

R^{18} and R^{19} are each independently selected from the group consisting of H, lower alkyl optionally substituted with K, aryl optionally substituted with K, and heteroaryl optionally substituted with K;

or R^{18} and R^{19} taken together with $-(O)_m-P(=O)-(O)_n-$ can form a 5-8 membered ring containing up to 3 hetero atoms,

or R^{18} and R^{19} taken together with $-(O)_m-P(=O)-(O)_n-$ can form a 5-8 membered ring optionally substituted with K.

In some preferred embodiments of the compounds of Formula I, R^1 is selected from the group consisting of benzyl, p-benzyloxybenzyl, $-(CH_2)_4-NHC(=O)-O-CH_2-C_6H_5$, $-(CH_2)_4-NHC(=O)-O-t-C_4H_9$, and $-(CH_2)_4-NHSO_2-C_6H_5$; R_3, R_4, and R_5 are each H; W^1 and W^2 together form $-C(=O)-$; Y is H or CH_2F; B is CO, O, S, SO_2 or a bond; R^2 is $-C(=O)CH_3$, and $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl, dimethylamino, ethyl, 2-thienyl, 2-isoxazolyl, phenyl, *p*-methylphenyl, 4-N-methylimidazolyl, and 2-naphthyl; G is tetrahydroisoquinolinyl, benzyl, 3-indolyl, phenyl, N-methylbenzylamino, p-benzyloxyphenyl, 2-thienyl; or Q and R^3 together form $-(CH_2)_3-$.

In other preferred embodmients of the compounds of Formula I, q is 0; B is a bond; G is benzyl or 2-thienyl; Y is H; R^1 is benzyl; and R^2 is $-S(=O)_2R^6$ wherein R^6 is methyl, phenyl, or 2-thienyl.

In further preferred embodmients of the compounds of Formula I, q is 1; G is tetrahydroisoquinolinyl, benzyl, 3-indolyl, phenyl, N-methylbenzylamino, or p-benzyloxyphenyl; and R^2 is $-C(=O)CH_3$, or $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl, dimethylamino, ethyl, 2-thienyl, 2-isoxazolyl, *p*-methylphenyl, 4-N-methylimidazolyl, or 2-naphthyl.

In more preferred embodiments of the compounds of Formula I wherein q is 1, G is benzyl; and R^2 is $-C(=O)CH_3$, or $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl, dimethylamino, ethyl, 2-isoxazolyl, *p*-methylphenyl, 4-N-methylimidazolyl, or 2-naphthyl, with methyl being preferred.

In other preferred embodmients of the compounds of Formula I, q is 2; B is S; G is benzyl; Y is H; R^1 is benzyl; and R^2 is $-S(=O)_2CH_3$.

The term "P2" as used herein in connection with enzyme substrate nomenclature has the meaning described by Schechter et al., *Biochem. Biophys. Res. Comm.* 27: 157-162, 1967, the disclosure of which is hereby incorporated by reference in its entirety.

As used herein, the term "alkyl" includes straight-chain, branched and cyclic hydrocarbon groups such as, for example, ethyl, isopropyl and cyclopropyl groups. Preferred alkyl groups have 1 to about 10 carbon atoms. "Cycloalkyl" groups are cyclic alkyl groups. The term "alkylene" denotes divalent alkyl groups; i.e., methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), etc. "Aryl" groups are aromatic cyclic compounds including but not limited to phenyl, tolyl, naphthyl, anthracyl, phenanthryl, pyrenyl, and xylyl. Preferred aryl groups include phenyl and naphthyl. The term "carbocyclic", as used herein, refers to cyclic groups in which the ring portion is composed solely of carbon atoms. The term "heterocyclic" refers to cyclic groups in which the ring portion includes at least one heteroatom such as O, N or S. In general, the term "hetero" when used as a prefix denoted the presence of one or more hetero atoms. Thus, "heterocycloalkyl" groups are heterocycles containing solely single bonds within their ring portions, i.e. saturated heteroatomic ring systems. The term "lower alkyl" refers to alkyl groups of 1-4 carbon atoms. The term "halogen" refers to F, Cl, Br, and I atoms. The term "aralkyl" denotes alkyl groups which bear aryl groups, for example, benzyl groups.

As used herein, "alkoxy" groups are alkyl groups linked through an oxygen atom. Examples of alkoxy groups include methoxy ($-OCH_3$) and ethoxy ($-OCH_2CH_3$) groups. In general, the term "oxy" when used as a suffix denotes attachment through an oxygen atom. Thus, alkoxycarbonyl groups are carbonyl groups which contain an alkoxy substituent, i.e., groups of general formula -C(=O)-O-R, where R is alkyl. The term "aralkyloxy" denotes an aralkyl group linked through an oxygen atom. The term "heteroaryl" denotes aryl groups having one or more heteroatoms contained within an aromatic ring. The term "heteroarylaklyl" denotes a heteroaryl group attached through an alkyl group. "Heteroaralkyl" groups are aralkyl groups which have one or more heteroatoms in their aromatic ring portion. The term "carbohydrate" includes monosaccharides, disaccharides, and polysaccharides, as well as their protected derivatives, such as, for example, mono- and diisopropylidine, and benzylidene derivatives.

As used herein the term "alkanoyl" denotes an alkyl group attached through a carbonyl group, i.e., -C(=O)-R where R is alkyl. The term "aroyl" analogously denotes an aryl group attached through a carbonyl group. The term "sulfonyl" when used as a suffix denotes attachment through a $-SO_2-$ group. As used herein, the term group I counterion denotes Li^+, Na^+, K^+, Rb^+ and Cs^+.

As used herein, the term "amino acid" denotes a molecule containing both an amino group and a carboxyl group. As used herein the term "L-amino acid" denotes an α-amino acid having the L configuration around the α-carbon, that is, a carboxylic acid of general formula $CH(COOH)(NH_2)$-(side chain), having the L-configuration. The term "D-amino acid" similarly denotes a carboxylic acid of general formula $CH(COOH)(NH_2)$-(side chain), having the D-configuration around the α-carbon. Amino acid α-carbon atoms having the D-configuration are denoted herein by the symbol "C*". Side chains of L-amino acids include naturally occurring and non-naturally occurring moieties. Non-naturally occurring (i.e., unnatural) amino acid side chains are moieties that are used in place of naturally occurring amino acid side chains in, for example, amino acid analogs. *See*, for example, Lehninger, *Biochemistry*, Second Edition, Worth Publishers, Inc, 1975, pages 73-75. One representative amino acid side chain is the lysyl side chain, $-(CH_2)_4-NH_2$. Other representative α-amino acid side chains are shown below in Table 1.

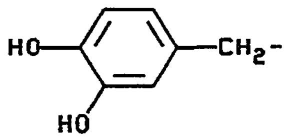
Table 1

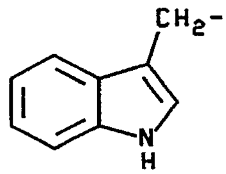
CH_3-

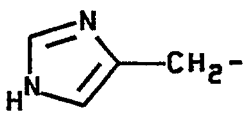
$HO-CH_2-$

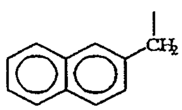
$C_6H_5-CH_2-$

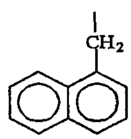
$HO-C_6H_4-CH_2-$











$HS-CH_2-$

$HO_2C-CH(NH_2)-CH_2-S-S-CH_2-$

CH_3-CH_2-

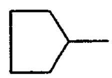
$CH_3-S-CH_2-CH_2-$

$CH_3-CH_2-S-CH_2-CH_2-$

$HO-CH_2-CH_2-$

$CH_3-CH(OH)-$

$HO_2C-CH_2-NHC(=O)-CH_2-$



$HO_2C-CH_2-CH_2-$

$NH_2C(=O)-CH_2-CH_2-$

$(CH_3)_2-CH-$

$(CH_3)_2-CH-CH_2-$

$CH_3-CH_2-CH_2-$

$H_2N-CH_2-CH_2-CH_2-$

$H_2N-C(=NH)-NH-CH_2-CH_2-CH_2-$

$H_2N-C(=O)-NH-CH_2-CH_2-CH_2-$

$CH_3-CH_2-CH(CH_3)-$

$CH_3-CH_2-CH_2-CH_2-$

$H_2N-CH_2-CH_2-CH_2-CH_2-$

Functional groups present on the compounds of Formula I may contain protecting groups. For example, the amino acid sidechain substituents of the compounds of Formula I can be substituted with protecting groups such as benzyloxycarbonyl or *t*-butoxycarbonyl groups. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. One such protecting group is the benzyloxycarbonyl (Cbz; Z) group. Other preferred protecting groups according to the invention may be found in Greene, T.W. and Wuts, P.G.M., "*Protective Groups in Organic Synthesis*" 2d. Ed., Wiley & Sons, 1991.

Because the D-amino acid-containing compounds of the invention inhibit cysteine proteases and serine proteases, they can be used in both research and therapeutic settings.

In a research environment, preferred compounds having defined attributes can be used to screen for natural and synthetic compounds which evidence similar characteristics in inhibiting protease activity. The compounds can also be used in the refinement of *in vitro* and *in vivo* models for determining the effects of inhibition of particular proteases on particular cell types or biological conditions. In a therapeutic setting, given the connection between cysteine proteases and certain defined disorders, and serine proteases and certain defined disorders, compounds of the invention can be utilized to alleviate, mediate, reduce and/or prevent disorders which are associated with abnormal and/or aberrant activity of cysteine proteases and/or serine proteases.

In preferred embodiments, compositions are provided for inhibiting a serine protease or a cysteine protease comprising a compound of the invention. In other preferred embodiments, methods are provided for inhibiting serine proteases or cysteine proteases comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory amount of a compound of the invention.

The disclosed compounds of the invention are useful for the inhibition of cysteine proteases and serine proteases. As used herein, the terms "inhibit" and "inhibition" mean having an adverse effect on enzymatic activity. An inhibitory amount is an amount of a compound of the invention effective to inhibit a cysteine and/or serine protease.

Pharmaceutically acceptable salts of the cysteine and serine protease inhibitors also fall within the scope of the compounds as disclosed herein. The term "pharmaceutically acceptable salts" as used herein means an inorganic acid addition salt such as hydrochloride, sulfate, and phosphate, or an organic acid addition salt such as acetate, maleate, fumarate, tartrate, and citrate. Examples of pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

Compounds provided herein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; or oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, via, for example, transdermal patches; or prepared in other suitable fashions for these and other forms of administration as will be apparent to those skilled in the art.

The composition may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteral administration may contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils and vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, a salicylate for rectal administration, or citric acid for vaginal administration. Formulations for transdermal patches are preferably lipophilic emulsions.

The materials for this invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients which could facilitate inhibition of cysteine and serine proteases in diseases or disorders.

As used herein, the phrase "enantiomerically enriched amount" when used in connection with a compound of Formula I in compositions of the invention, denotes the predominance (i.e., greater than 50%) of the compound of Formula I wherein the carbon atom designated by C* in Formula I has the D-configuration over the corresponding L-isomer at this position. In preferred embodiments of the compositions of the invention, the enantiomerically enriched amount of the compound of Formula I is an amount greater than about 75% (i.e., the D-isomer compound of Formula I constitutes greater than about 75% of the combined amount of compound of Formula I and the corresponding L-isomer). In more preferred embodiments of the compositions of the invention, the enantiomerically enriched amount of the compound of Formula I is an amount greater than about 85%, more preferably greater than about 90%, still more preferably greater than about 95%, and most preferably about 100%.

The concentrations of the compounds described herein in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. In general terms, the compounds of this invention may be provided in effective inhibitory amounts in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1μg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. Such formulations typically provide inhibitory amounts of the compound of the invention. The preferred dosage of drug to be administered is likely, however, to depend on such variables as the type or extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

As used herein, the term "contacting" means directly or indirectly causing at least two moieties to come into physical association with each other. Contacting thus includes physical acts such as placing a compound of the invention together with a protease in a container, or administering a compound of the invention to a patient. Thus, for example, administering a compound of the invention to a human patient evidencing a disease or disorder associated with abnormal and/or aberrant activity of such proteases falls within the scope of the definition of the term "contacting".

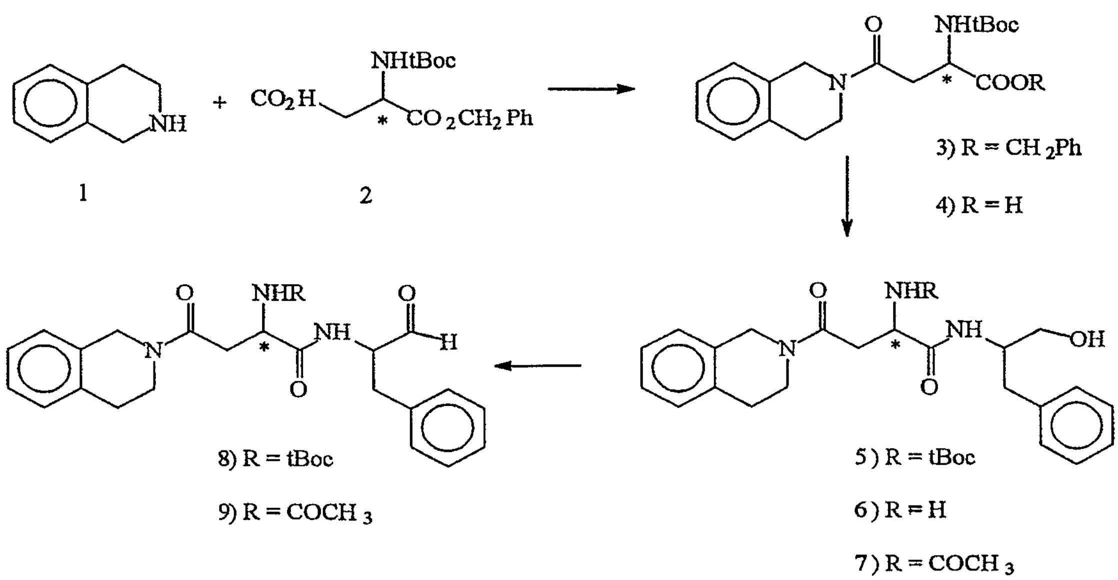
The invention is further illustrated by way of the following examples which are intended to elucidate the invention. These examples are not intended, nor are they to be construed, as limiting the scope of the disclosure.

Examples

Compounds of the invention were prepared by the following procedures. R_f values are reported using standard silica gel and analytical plates.

The synthesis of compounds of Formulae 1-9 are summarized in Scheme I below:

SCHEME 1



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Examples 1-5 show the synthesis of intermediate compounds 3-7. Examples 6 and 7 show the preparation of compounds 8 and 9 of the invention.

Example 1

Synthesis of Compound 3

To a stirring mixture of Compound 1 (0.65g, 2mmol) and Compound 2 (purchased from Bachem Bioscience, Inc., King of Prussia, PA) (0.27g, 2mmol) in methylene chloride (5mL), at room temperature, was added triethylamine (0.45g, 4.4 mmol) followed by bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl, 0.51g, 2mmol). The mixture was stirred for another 2h, slowly poured into ice-water (10mL) and extracted into ethyl acetate (3 x 10mL). The combined organic layer was successively washed with 2% citric acid solution (2 x 5mL), 2% $NaHCO_3$ solution (2 x 5mL), H_2O (1 x 5mL), brine (1 x 5mL), dried over Na_2SO_4 and concentrated to give a crude product. Purification by flash column chromatography (silica gel, 30% ethyl acetate in hexane) yielded 0.64g of Compound 3.

3: White gum; R_f (50% ethyl acetate in hexane): 0.60; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.05 (m, 9H), 5.90 (d, 1H), 5.25-5.10 (m, 2H), 4.70-4.55 (m, 3H), 3.80-3.55 (2 sets of t, 2H), 3.30-3.15 (m, 1H), 2.95-2.80 (m, 3H), 1.40 (s, 9H).

Example 2
Synthesis of Compound 4

A mixture of Compound 3 (0.61g, 1.40mmol) and 0.20g of 10% Pd-C (DeGussa type, 50% H_2O content) in methanol (40mL) was hydrogenated (40psi) in a Parr apparatus for 1 hour. Filtration through a Celite® pad and solvent evaporation gave 0.47g of Compound 4 which was used without further purification. ^{1}H-NMR spectrum of Compound 4 showed the absence of peaks for a benzyl group.

Example 3
Synthesis of Compound 5

To a cooled (0°C) solution of Compound 4 (0.20g, 0.574mmol) in anhydrous DMF (4mL) was added N-methylmorpholine (0.174g, 1.722mmol) followed by 1-HOBt (0.080g, 0.574mmol) and BOP (0.254g, 0.574mmol). The mixture was stirred for 15 minutes and to it was added (s)-phenylalaninol (0.112g, 0.7463mmol). The cooling bath was removed and the mixture was stirred for another 2h, poured into water (5mL) and extracted into ethyl acetate (3 x

10mL). The combined organic layer was successively washed with 2% citric acid solution (2 x 5mL), 2% $NaHCO_3$ solution (2 x 5mL), H_2O (1 x 5mL), brine (1 x 5mL), dried over Na_2SO_4 and concentrated to give a crude product. Purification by flash column chromatography (silica gel, 5% methanol in methylene chloride) yielded 0.212g of Compound 5.

5: White solid, mp 63-72 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.47; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.00 (m, 9H), 6.80 (broad, 1H), 5.90 (d, 1H), 4.80-4.45 (m, 4H), 4.30-4.10 (broad, 1H), 3.85-3.30 (m, 6H), 2.95-2.40 (m, 4H), 1.45 (s, 9H).

Example 4
Synthesis of Compound 6

A mixture of Compound 5 (0.190g, 0.3945mmol) and 90% TFA (1.2mL) in methylene chloride (3mL) was stirred at room temperature for 1 hour. Excess TFA was removed and the residue was diluted with methylene chloride (5mL) and washed with 2% $NaHCO_3$ solution (2 x 4mL), brine (1 x 5mL), dried over Na_2SO_4 and concentrated to give 0.15g of Compound 6 which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peak at δ 1.45 for a t-boc group.

Example 5
Synthesis of Compound 7

To a cooled (0 °C) solution of Compound 6 (0.150g, 0.3944mmol) in anhydrous methylene chloride (4mL) was added triethylamine (0.040g, 0.3944mmol). A solution of acetyl chloride (0.030g, 0.3944mmol) in methylene chloride (1mL) was added dropwise into the reaction flask over a period of 5 minutes. The cooling bath was removed and the reaction mixture was stirred for an additional 30 minutes, poured into ice-water (5mL) and the layers were separated. The organic layer was washed with 3% hydrochloric acid solution (2 x 4mL), saturated sodium bicarbonate solution (1 x 5mL), brine (1 x 5mL) and dried over anhydrous sodium sulfate.

Solvent evaporation gave a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 0.025g of Compound 7.

7: White solid, mp 64-79 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.34; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.00 (m, 10H), 4.95-4.80 (m, 1H), 4.75-4.40 (m, 2H), 4.30-4.15 (m, 1H) 3.90-3.50 (m, 4H),3.25-3.10 (m, 2H), 3.00-2.80 (m, 4H), 2.45-2.30 (m, 1H), 2.05 (m, 1H), 2.00 (d, 3H).

Example 6
Synthesis of Compound 8

To a cooled (0°C) solution of Compound 5 (0.100g, 0.21mmol) in anhydrous methylene chloride (2mL) and anhydrous dimethyl sulfoxide (2mL) was added triethylamine (0.085g, 0.839mmol). Sulfur trioxide-pyridine complex (0.133g, 0.839mmol) was slowly added to the stirred mixture over a period of 5 minutes and the ice-bath was removed. The mixture was stirred for another 1h, poured into water (10mL) and extracted into ethyl acetate (3 x 10mL). The organic layer was washed with 2% citric acid solution (2 x 5mL), saturated sodium bicarbonate solution (2 x 5mL), brine (1 x 5mL) and dried over anhydrous magnesium sulfate. Solvent evaporation gave a residue which was washed with n-pentane (20mL) and dried under vacuum to produce 0.055g of Compound **8** of the invention. A general description of this preparative procedure can be found in Luly, J. R. et al., *J. Org. Chem.* 1987, 1487-1492.

8: White solid, mp 70-80 °C (softening to melt); R_f (ethyl acetate): 0.69; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (d, 1H), 7.50 (broad, 1H), 7.25-7.00 (m, 9H), 6.05 (d, 1H), 4.75-4.45 (m, 4H), 3.85-3.00 (m, 5H), 2.95-2.40 (m, 3H), 1.45 (s, 9H).

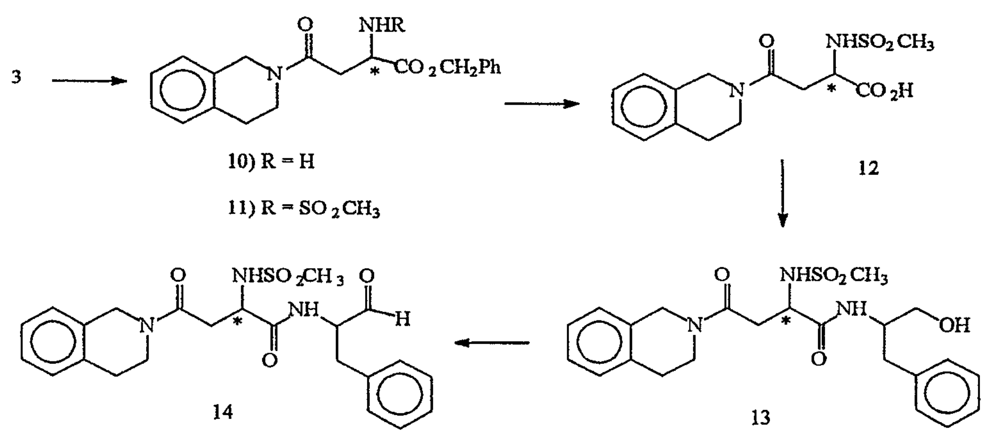
Example 7
Synthesis of Compound 9

This compound was synthesized following the general procedure described for the synthesis of Compound **8**. Thus the oxidation of 0.110g of Compound **7** by 0.145g of sulfur trioxide-pyridine complex in presence of 0.092g of triethylamine generated 0.060g of Compound **9** of the invention.

9: White solid, mp 80-120 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.31; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (d, 1H), 7.70-7.60 (t, 1H), 7.30-7.00 (m, 9H), 4.95-4.85 (m, 1H), 4.80-4.40 (m, 3H), 3.90-2.80 (m, 8H), 2.40-2.30 (m, 1H), 2.00 (s, 3H).

Scheme 2 Shows the synthesis of compounds 10-14:

SCHEME 2



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Examples 8-11 show the synthesis of intermediate compounds 10-13. Example 12 shows the preparation of compound 14 of the invention.

Example 8
Synthesis of Compound 10

This compound was synthesized following the general procedure described for the synthesis of Compound **6**. Thus deesterification of 2.10g of Compound **3** by 90% TFA

(3mL) in methylene chloride (7 mL) gave Compound **10** (1.47g) which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peak at δ 1.40 for a t-boc group.

Example 9
Synthesis of Compound 11

To a cooled (0 °C) solution of Compound **10** (1.393g, 4.1172mmol) in methylene chloride (15mL) was added triethylamine (0.445g, 4.3976mmol). A solution of methanesulfonyl chloride (0.504g, 4.3998mmol) in methylene chloride (4mL) was added dropwise into the reaction flask over a period of 5 minutes. The cooling bath was removed and the reaction mixture was stirred for an additional 30 minutes, poured into ice-water (20mL) and the layers were separated. The organic layer was washed with 2% citric acid solution (2 x 10mL), saturated sodium bicarbonate solution (2 x 10mL), brine (1 x 10mL) and dried over anhydrous sodium sulfate. Solvent evaporation gave a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 0.720g of Compound **11**.

11: White solid, mp 55-85 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.71; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 9H), 5.85 (dd, 1H), 5.25 -5.05 (2 sets of t, 2H), 4.65 (q, 1H), 4.50 (s, 1H), 4.40 (m, 1H), 3.85 (m, 1H), 3.60 (m, 1H), 3.30 (m, 1H), 3.00 (s, 3H), 3.00-2.80 (m, 3H).

Example 10
Synthesis of Compound 12

This compound was synthesized following the general procedure described for the synthesis of Compound **4**. Thus 0.69g of Compound **11** was hydrogenated to 0.50g of Compound **12** in a Parr apparatus, and the product was used without further purification. ^{1}H-NMR spectrum of an aliquot showed no peaks for a benzyl group.

Example 11
Synthesis of Compound 13

This compound was synthesized following the general procedure described for the synthesis of Compound **5**. Thus the reaction between 0.204g of Compound **12** and 0.113g of (S)-phenylalaninol generated a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 0.192g of Compound **13**.

13: White solid, mp 55-85 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.34; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.00 (m, 10H), 6.00 (broad, 1H), 4.75-4.40 (2 sets of q, 2H), 4.30 (m, 2H), 3.85- 3.45 (m, 4H), 3.35-3.25 (m, 1H), 3.05-2.60 (m, 6H), 2.85 (s, 3H).

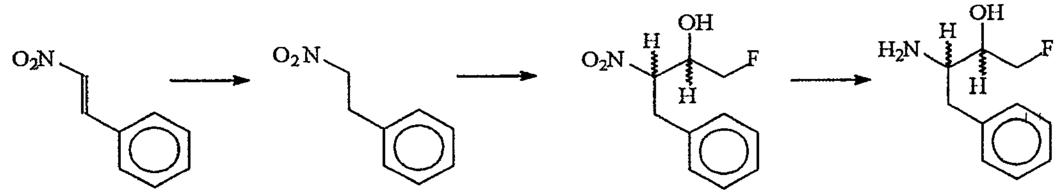
Example 12
Synthesis of Compound 14

This compound was synthesized following the general procedure described for the synthesis of Compound **8**. Thus the oxidation of 0.110g of Compound **13** by 0.133g of sulfur trioxide-pyridine complex in presence of 0.085g of triethylamine generated 0.080g of Compound **14** of the invention.

14: White solid, mp 80-110 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.36; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.80 (d, 1H), 7.35-7.00 (m 9H), 6.10 (d, 1H), 4.80 (m, 2H), 4.50 (m, 1H), 4.35 (m, 1H), 3.85-3.45 (m, 3H), 3.30-3.20 (m, 2H), 3.05-2.60 (m, 3H), 2.85 (s, 3H).

Scheme 3 shows the synthesis of compounds 16, 17a-b and 18a-b:

SCHEME 3



15 16 17a-b 18a-b

Examples 13 and 14 show the synthesis of intermediate compounds 16 and 17a-b. Example 15 shows the preparation of intermediate compounds 18a-b.

Example 13
Synthesis of Compound 16

To a stirring mixture of *trans*-β-nitrostyrene (Compound **15**, 5.25g, 0.035mol) and silica gel (10g, 230-400 mesh) in chloroform (400 mL) and isopropanol (75 mL) at room temperature, was slowly added sodium borohydride (5.50g, 0.145mol) over a period of 45 minutes. The reaction mixture was stirred for an additional 15 minutes and then carefully quenched with 10% hydrochloric acid (20mL). Separated solid was filtered and washed with chloroform (50mL). The combined filtrate and washings were washed with water (1 x 20mL), brine (1 x 20mL) and dried over anhydrous sodium sulfate. Solvent evaporation at reduced pressure gave a crude material which was purified by flash chromatography (silica gel, 8% ethyl acetate-hexane) to give 2.86g of Compound **16**.

16: Colorless oil (spicy odor); R_f (10% ethyl acetate in hexane) : 0.40; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 4.60 (t, 2H), 3.30 (t, 2H).

Example 14
Synthesis of Compounds 17a-b

To a cooled (-78°C) solution of oxalyl chloride (2M) in methylene chloride (11.60mL, 0.0232mol) was added slowly dimethyl sulfoxide (3.65g, 3.32mL, 0.0467mol). The reaction mixture was stirred for 15 minutes. A solution of 2-fluoroethanol (1.16g, 0.0181mol) in methylene chloride (10mL) was then slowly introduced into the reaction flask. After stirring for another 15 minutes, the reaction mixture was diluted with anhydrous methylene chloride (180mL), and triethylamine (9.20g, 12.63mL, 0.090mol) was added. Stirring was continued for another 2h at which time the reaction mixture had warmed to room temperature. At this time, a solution of Compound **16** (2.74g, 0.0181mol) in anhydrous methylene chloride (10mL) was added to the reaction mixture and stirring was continued overnight. The mixture was then washed with water (1 x 30mL), 4% hydrochloric acid (3 x 20mL), water (1 x 20mL), saturated sodium bicarbonate solution (2 x 20mL) and brine (1 x 20mL). Drying over anhydrous sodium sulfate and solvent evaporation gave a crude material which was purified by flash chromatography (silica gel, 25% ethyl acetate-hexane) to give Compounds **17a** and **17b** as erythro / threo isomers. Combined yield was 3.01g. In another set of experiments, 13.94 g of Compound **16** was converted to 12.5g of Compounds **17a-b** which, without any separation, were used in the subsequent steps. A general description of this preparative procedure can be found in Imperiali, B. et al., *Tetrahedron Lett.* 27(2), 135, 1986 and in Revesz, L. et al., *Tetrahedron Lett.* 35(52), 9693, 1994.

17a: White solid, mp 71-73 °C; R_f (30% ethyl acetate in hexane) : 0.46; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40-7.10 (m, 5H), 4.90 (m, 1H), 4.60 (m, 1H), 4.50-4.30 (m, 2H), 3.45-3.25 (m, 2H), 2.70 (d, 1H).

17b: Colorless oil; R_f (30% ethyl acetate in hexane) : 0.42; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 4.90 (m, 1H), 4.65 (m,1H), 4.50 (m, 1H), 4.20 (m, 1H), 3.40-3.30 (m, 2H), 2.90 (d,1H).

Example 15
Synthesis of Compounds 18a-b

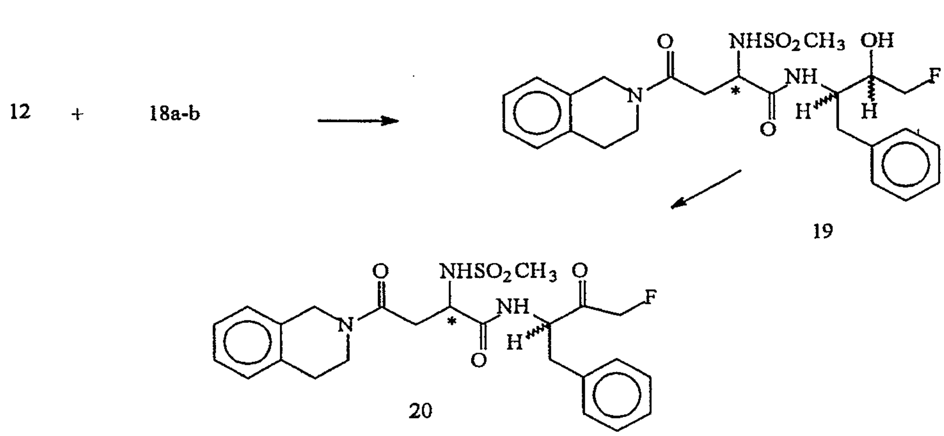
A mixture of Compound **17a** (0.48g, 2.25mmol), absolute ethanol (20mL) and Raney-Nickel (catalytic) was hydrogenated (60psi) in a Parr apparatus for 5 hours. Filtration through a Celite® pad and solvent evaporation gave 0.41g of Compound **18a**. Similar treatment of Compound **17b** (0.80g, 3.75mmol) gave 0.51g of Compound **18b**. Finally, a combined mixture of Compounds **17a-b** (10.00g) was hydrogenated to give 7.20g of a mixture of Compounds **18a-b** which was used in all the experiments, described below.

18a: White solid, mp 64-67 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40-7.10 (m, 5H), 4.70 (d, 1H), 4.50 (d, 1H), 3.90-3.70 (m, 1H), 3.30-3.10 (m, 1H), 2.95 (dd, 1H), 2.60-2.45 (q, 1H), 2.20-1.70 (broad, 3H).

18b: White solid, mp 67-70 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.40-7.10 (m, 5H), 4.70 (d, 1H), 4.55 (d, 1H), 3.70-3.50 (m, 1H), 3.20-3.00 (m, 1H), 2.95 (dd, 1H), 2.60-2.45 (q, 1H), 2.20-1.65 (broad, 3H).

Scheme 4 shows the synthesis of compounds 19 and 20:

SCHEME 4



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Example 16 shows the synthesis of intermediate compound 19. Example 17 shows the preparation of compound 20 of the invention.

Example 16
Synthesis of Compound 19

This compound was synthesized following the general procedure described for the synthesis of Compound **5**. Thus the reaction between 0.142g of Compound **12** and 0.088g of Compounds **18a-b** generated a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 0.138g of Compound **19** as a mixture of diastereoisomers.

19: White solid, mp 75-115 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.44; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.05 (m, 10H), 6.15-5.75 (m, 1H), 4.70-3.40 (m, 11H), 3.30-2.50 (m, 8H).

Example 17
Synthesis of Compound 20

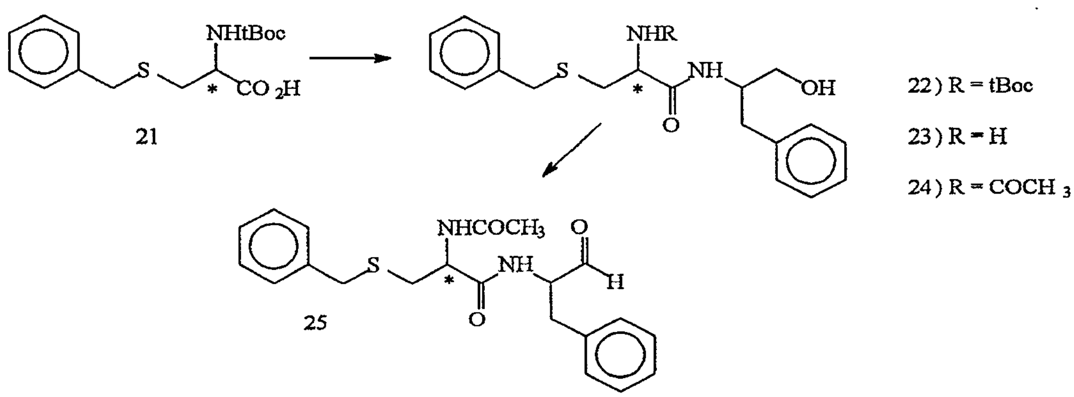
To a cooled (0°C) solution of Compound **19** (0.126g, 0.2563mmol) in anhydrous methylene chloride (8 mL) was added Dess-Martin periodinane reagent (0.217g, 0.5126mmol). The cooling bath was removed and the mixture was stirred for an additional 45 minutes. It was then diluted with methylene chloride (15mL) and washed with 10% sodium thiosulfate solution (4 x 10mL), saturated sodium bicarbonate solution (1 x 10mL) and brine (1 x 10mL). Drying over anhydrous sodium sulfate and solvent removal under reduced pressure gave a crude material which was purified by flash column chromatography (silica, 70% ethyl acetate-hexane) to generate 0.094g of Compound **20** of the invention as a mixture of two diastereoisomers. A general description of this preparative procedure can be found in Patel, D. V. et al, *J. Med. Chem.* 1993, 36, 2431-2447.

20: White solid; R_f (70% ethyl acetate in hexane): 0.44; ^{1}H-

NMR (300 MHz, $CDCl_3$) δ 7.80-7.65 (m, 1H), 7.40-7.05 (m, 9H), 6.10-6.00 (t, 1H), 5.10-4.40 (m, 6H), 4.35-4.25 (m, 1H), 3.90-3.50 (m, 2H), 3.30-2.50 (m, 5H), 2.85 (m, 3H).

Scheme 5 shows the synthesis of compounds 22-25:

SCHEME 5



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Examples 18-20 show the synthesis of intermediate compounds 22-24. Example 21 shows the preparation of compound 25 of the invention.

Example 18
Synthesis of Compound 22

This compound was synthesized following the general procedure described for the synthesis of Compound **5**. Thus the reaction between 1.095g of Compound **21** (purchased from Advanced ChemTech, Louisville, KY) and 0.532g of (s)-phenylalaninol generated a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 1.06g of Compound **22**.

22: White solid, mp 105-108 °C; R_f (5% methanol in methylene chloride): 0.44; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 10H), 6.40 (d, 1H), 5.10 (broad, 1H), 4.25-4.05 (m, 2H), 3.75 (s, 2H), 3.70-3.50 (2 sets of m, 2H), 2.95-2.55 (m, 5H). 1.45 (s, 9H).

Example 19
Synthesis of Compound 23

This compound was synthesized following the general procedure described for the synthesis of Compound **6**. Thus the reaction between 0.512g of Compound **21** and 1mL of 90% TFA in 3mL methylene chloride generated 0.38g of Compound **23** which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peak at δ 1.45 for a t-boc group.

Example 20
Synthesis of Compound 24

This compound was synthesized following the general procedure (except that acetyl bromide was used in place of acetyl chloride) described for the synthesis of Compound **7**. Thus the reaction between 0.377g of Compound **23** and 0.121g of acetyl bromide in the presence of 0.10g of triethylamine in 5mL methylene chloride gave a crude product which was purified by flash column chromatography (silica gel, 4% methanol in methylene chloride) to yield 0.158g of Compound **24**.

24: White solid, mp 149-151 °C; R_f (5% methanol in methylene chloride): 0.32; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.05 (m, 10H), 6.80 (d, 1H), 6.45 (d, 1H), 4.45 (q, 1H), 4.20 (m, 1H), 3.70 (s, 2H), 3.75-3.50 (2 sets of m, 2H), 3.20-3.00 (m, 1H), 2.90-2.75 (m, 2H), 2.70-2.50 (2 sets of q, 2H), 1.95 (s, 3H).

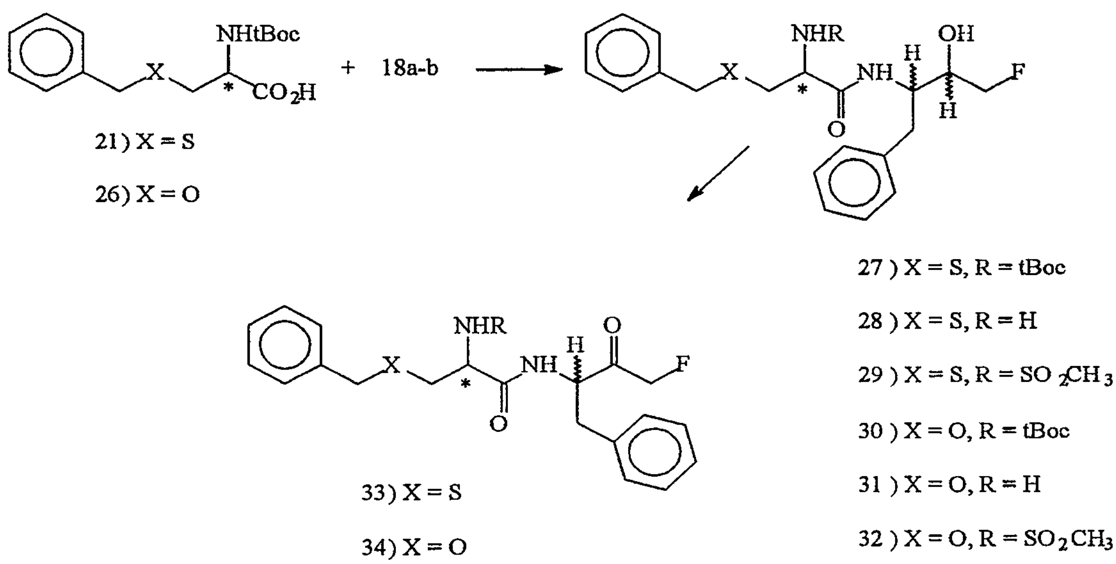
Example 21
Synthesis of Compound 25

This compound was synthesized following the general procedure described for the synthesis of Compound **8**. Thus the oxidation of 0.167g of Compound **24** by 0.240g of sulfur trioxide-pyridine complex in the presence of 0.153g of triethylamine generated 0.085g of Compound **25** of the invention.

25: White solid, mp 45-70 °C (softening to melt); R_f (ethyl acetate): 0.34; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.05 (m, 10H), 6.80 (d, 1H), 6.20 (d, 1H), 4.70-4.40 (2 sets of q, 2H), 3.70 (s, 2H), 3.10 (d, 1H), 2.90-2.50 (2 sets of m, 2H), 1.95 (s, 3H).

Scheme 6 shows the synthesis of compounds 27-34:

SCHEME 6



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Examples 22-27 show the synthesis of intermediate compounds 27-32. Examples 28 and 29 show the preparation of compounds 33 and 34 of the invention.

Example 22
Synthesis of Compound 27

This compound was synthesized following the general procedure described for the synthesis of Compound 5. Thus the reaction between 1.033g of Compound **21** and 0.668g of Compound **18a-b** generated a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 1.38g of Compound **27** as a mixture of diastereoisomers.

27: White solid, mp 120-138 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.72 and 0.61 (overlapping 2 sets of erythro and threo isomers); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 10H), 6.60-6.30 (2 sets of t, 1H), 5.20-5.05 (broad, 1H), 4.60-3.90 (5 sets of m, 5H), 3.75-3.60 (2 sets of d, 2H), 3.00-2.80 (m, 3H), 2.75-2.55 (m, 2H), 1.50-1.30 (m, 9H).

Example 23
Synthesis of Compound 28

This compound was synthesized following the general procedure described for the synthesis of Compound **6**. Thus the reaction between 1.02g of Compound **27** and 3mL of 90% TFA in 5mL methylene chloride generated 0.77g of Compound **28** which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peaks for a t-boc group at δ 1.50-1.30.

Example 24
Synthesis of Compound 29

This compound was synthesized following the general procedure described for the synthesis of Compound **11**. Thus the reaction between 0.644g of Compound **28** and 0.183g of methanesulfonyl chloride in the presence of 0.162g of triethylamine in 5mL methylene chloride generated a crude product which was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.347g of Compound **29** as a mixture of diastereoisomers.

29: White solid, mp 135-150 °C (softening to melt); R_f (5% methanol in methylene chloride): 0.63 and 0.59 (2 sets of overlapping erythro and threo isomers); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 6.70-6.30 (2 sets of m, 1H), 5.40-5.00 (2 sets of m, 1H), 4.70-4.10 (m, 4H), 4.00-3.85 (m, 1H), 3.80-3.60 (m, 2H), 3.10-2.50 (m, 8H).

Example 25
Synthesis of Compound 30

This compound was synthesized following the general procedure described for the synthesis of Compound **5**. Thus the reaction between 0.633g of Compound **26** (purchased from Advanced ChemTech, Louisville, KY) and 0.432g of Compound **18a-b** generated a crude product which was purified by flash column chromatography (silica gel, 3% methanol in methylene chloride) to yield 0.865g of Compound **30** as a mixture of diastereoisomers.

30: White semi-solid; R_f (5% methanol in methylene chloride): 0.72 and 0.65 (overlapping 2 sets of erythro and threo isomers); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.05 (m, 10H), 6.85-6.50 (1 set of d and 1 set of t, 1H), 5.40-5.20 (broad, 1H), 4.60-4.30 (m, 4H), 4.30-4.05 (m, 2H), 3.95-3.70 (m, 2H), 3.60-3.40 (m, 2H), 3.05-2.85 (m, 2H), 1.40 (2s, 9H).

Example 26
Synthesis of Compound 31

This compound was synthesized following the general procedure described for the synthesis of Compound **6**. Thus the reaction between 0.820g of Compound **30** and 2mL of 90% TFA in 4mL methylene chloride generated 0.506g of Compound **31** which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peak at δ 1.40 for a t-boc group.

Example 27
Synthesis of Compound 32

This compound was synthesized following the general procedure described for the synthesis of Compound **11**. Thus the reaction between 0.50g of Compound **31** and 0.175g of methanesulfonyl chloride in the presence of 0.155g of triethylamine in 6mL methylene chloride generated a crude product which was purified by flash column chromatography (silica gel, 4% methanol in methylene chloride) to yield 0.32g of Compound **32** as a mixture of diastereoisomers.

32: White solid, mp 118-121 °C; R_f (5% methanol in methylene chloride): 0.43; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 7.10-6.90 (2 sets of d, 1H), 5.40 (broad t, 1H), 4.60-4.10 (m, 5H), 4.05-3.80 (m, 2H), 3.80-3.50 (2 sets of m, 2H), 3.30-3.20 (m, 1H), 3.00-2.60 (m, 5H).

Example 28
Synthesis of Compound 33

This compound was synthesized following the general procedure described for the synthesis of Compound **20**. Thus the oxidation of 0.296g of Compound **29** by 0.276g of Dess-Martin reagent in 10mL methylene chloride generated a crude product which was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.15g of Compound **33** of the invention as a mixture of diastereoisomers.

33: White solid, mp 40-70 °C (softening to melt); R_f (70% ethyl acetate in hexane): 0.75; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 6.85 (t, 1H), 5.25-4.75 (m, 4H), 3.90-3.75 (m, 1H), 3.70 (s, 2H), 3.30-3.10 (m, 1H), 3.05-2.90 (m, 1H), 2.85-2.60 (m, 5H).

Example 29
Synthesis of Compound 34

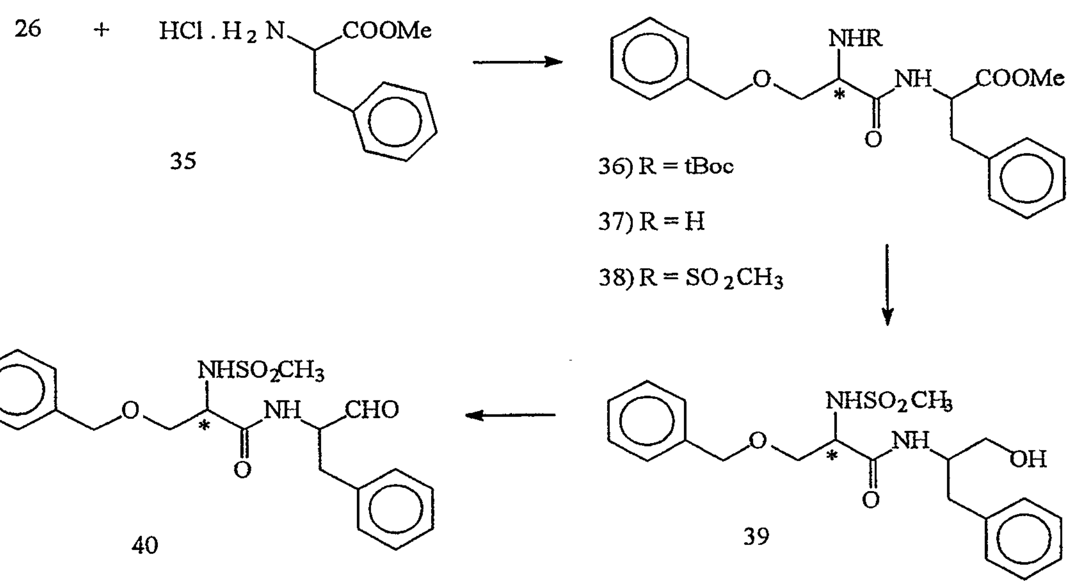
This compound was synthesized following the general procedure described for the synthesis of Compound **20**. Thus the oxidation of 0.30g of Compound **32** by 0.725g of Dess-Martin reagent in 10mL methylene chloride generated 0.25g of Compound **34** of the invention as a mixture of two diastereoisomers.

34: White gum; R_f (50% ethyl acetate in hexane): 0.38; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 11H), 5.40 (m, 1H), 5.10-

4.70 (m, 3H),4.60-4.40 (t, 2H), 4.05 (m, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.80 (s, 3H).

Scheme 7 shows the synthesis of compounds 36-40:

SCHEME 7



The symbol "*" denotes a D-configuration around the indicated carbon atom.

Examples 30-33 show the synthesis of intermediate compounds 36-39.

Example 34 shows the preparation of compound 40 of the invention.

Example 30

Synthesis of Compound 36

This compound was synthesized following the general procedure described for the synthesis of Compound **5**. Thus the reaction between 5.221g of Compound **26** and 4.20g of Compound **35** generated 7.80g of Compound **36**, most of which was used in the next step without further purification. An aliquot of the crude product was purified by flash column chromatography (silica gel, 40% ethyl acetate in hexane) to yield an analytical sample.

36: White solid, mp 80-83 °C; R_f (30% ethyl acetate in hexane): 0.37; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 10H), 6.90 (broad d, 1H), 5.40 (broad, 1H), 4.90 (q, 1H), 4.50 (q, 2H), 4.30 (broad, 1H), 3.90 (broad q, 1H), 3.70 (s, 3H), 3.50 (dd, 1H), 3.10 (m, 2H), 1.40 (s, 9H).

Example 31
Synthesis of Compound 37

This compound was synthesized following the general procedure described for the synthesis of Compound **6**. Thus the reaction between 7.70g of Compound **36** and 10mL of 90% TFA in 15mL of methylene chloride generated 6.00g of Compound **37** which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of an aliquot showed no peak at δ 1.40 for t-boc group.

Example 32
Synthesis of Compound 38

This compound was synthesized following the general procedure described for the synthesis of Compound **11**. Thus the reaction between 6.00g of Compound **37** and 2.70g of methanesulfonyl chloride in the presence of 2.386g of N-methylmorpholine (instead of triethylamine) in 20mL methylene chloride generated a crude product which was purified by flash column chromatography (silica gel, 45% ethyl acetate in methylene chloride) to yield 5.86g of Compound **38**.

38: White solid, mp 92-98 °C (softening to melt); R_f (50% ethyl acetate in hexane): 0.33; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 11H), 5.30 (d, 1H), 4.85 (m 1H), 4.45 (q, 2H), 4.10 (q, 1H), 3.80 (dd,1H), 3.75 (s, 3H), 3.60 (dd, 1H), 3.20-3.00 (2 sets of q, 2H), 2.85 (s, 3H).

Example 33
Synthesis of Compound 39

To a stirred solution of Compound **38** (2.501g, 5.7569mmol) in anhydrous THF (10mL) at room temperature, a 2(M) solution of $LiBH_4$ in THF (4.31mL) was added slowly over a period of 30 minutes. The mixture was stirred for another 30 minutes, slowly poured over ice-water (ca. 20g), acidified (0°C) with 4(N) hydrochloric acid and extracted into ethyl acetate (3 x 75mL). The combined organic layer was successively washed with 2% $NaHCO_3$ solution (2 x 20mL), H_2O (1 x 10mL), brine (1 x 20mL), dried over Na_2SO_4 and concentrated to give a crude product. Purification by flash column chromatography (silica gel, 20% methylene chloride in ethyl acetate) yielded 1.275g of Compound **39**.

39: White solid, mp 140-142 °C; R_f (ethyl acetate): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 6.90 (d, 1H), 5.50 (d, 1H), 4.50 (q, 2H), 4.20 (m, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.70-3.45 (m, 3H), 2.90-2.70 (m, 2H), 2.85 (s, 3H), 2.60 (t, 1H).

Example 34

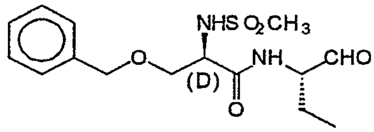
Synthesis of Compound 40

This compound was synthesized following the general procedure described for the synthesis of Compound **20**. Thus the oxidation of 0.813g of Compound **39** by 1.70g of Dess-Martin reagent in 20mL of methylene chloride generated 0.77g of Compound **40** of the invention.

40: White solid, mp 75-85 °C (softening to melt); R_f (ethyl acetate): 0.62; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 5.30 (d, 1H), 4.70 (q, 1H), 4.50 (q, 2H), 4.10 (q, 1H), 3.85 (dd, 1H), 3.60 (dd, 1H), 3.15 (m, 2H), 2.85 (s, 3H).

Example 35

Synthesis of Compound 41

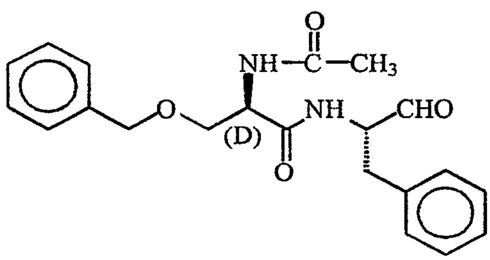


This compound was synthesized following Scheme 7, as described above, except that (L)-Abu-OMe hydrochloride salt instead of (L)-Phe-OMe hydrochloride salt was used in the first step.

41: White solid, mp 75-83 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.52; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.30 (m, 6H), 5.65 (d, 1H), 4.55 (q, 2H), 4.45 (q, 1H), 4.20 (q, 1H), 3.85 (q, 1H), 3.75 (q, 1H), 2.95 (s, 3H), 1.95 (m, 1H), 1.70 (m, 1H), 0.90 (t, 3H).

Example 36

Synthesis of Compound 42

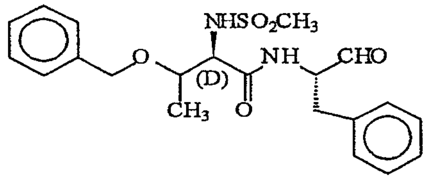


This compound was synthesized following Scheme 7, as described above, except that acetyl chloride, instead of methanesulfonyl chloride, was used in the preparation of the analog of Compound **38**.

42: White solid, mp 118-123 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.45; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.30 (m, 8H), 7.10 (dd, 2H), 6.95 (d, 1H), 6.30 (d, 1H), 4.70 (q, 1H), 4.60 (m, 1H), 4.50 (q, 2H), 3.85

(dd, 1H), 3.45 (dd, 1H), 3.10 (d, 2H), 2.00 (s, 3H).

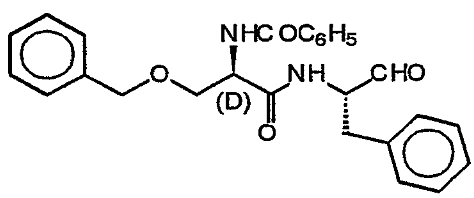
Example 37
Synthesis of Compound 43



This compound was synthesized following Scheme 7, as described above, except that Boc-(D)-Thr(Bzl), instead of Boc-(D)-Ser(Bzl), was used in the first step.

43: White solid, mp 102-108 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.57; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 5.40 (d, 1H), 4.75 (q, 1H), 4.50 (d, 2H), 4.00 (m 2H), 3.20 (q, 1H), 3.00 (q, 1H), 2.80 (s, 3H), 1.05 (d, 3H).

Example 38
Synthesis of Compound 44

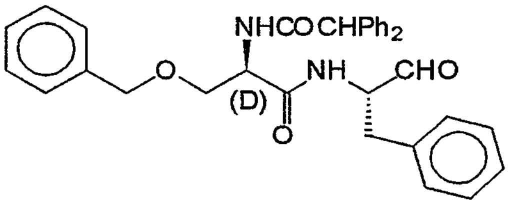


This compound was synthesized following Scheme 7, as described above, except that benzoyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

44: White solid, mp 142-147 °C (softening to melt); R_f (90%

CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.54; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.80 (d, 2H), 7.60-7.00 (m, 15H), 4.80 (m, 1H), 4.70 (q, 1H), 4.50 (d, 2H), 4.00 (dd, 1H), 3.55 (dd, 1H), 3.10 (d, 2H).

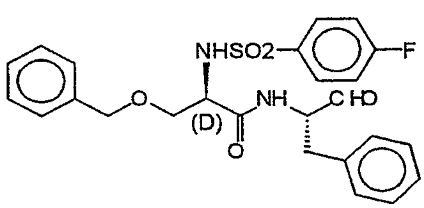
Example 39
Synthesis of Compound 45



This compound was synthesized following Scheme 7, as described above, except that diphenylacetic acid (in the presence of DCC and HOBt), instead of methanesulfonyl chloride and NMM, was used in preparation of the analog of Compound **38**.

45: White solid, mp 148-153 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.60; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.40-7.00 (m, 20H), 6.85 (d, 1H), 6.45 (d, 1H), 4.95 (s, 1H), 4.65 (m, 2H), 4.40 (q, 2H), 3.85 (dd, 1H), 3.45 (dd, 1H), 3.10 (m, 2H).

Example 40
Synthesis of Compound 46

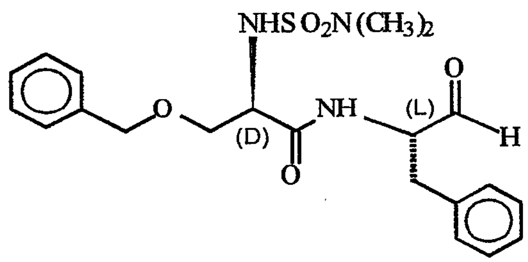


This compound was synthesized following Scheme 7, as described above, except that 4-fluorobenzenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

46: White solid, mp 132-136 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.54; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.80 (q, 2H), 7.40-7.00 (m, 13H), 5.60 (d, 1H), 4.60 (q, 1H), 4.35 (q, 2H), 3.80 (m, 2H), 3.25 (dd, 1H), 3.10 (d, 2H).

Example 41

Synthesis of Compound 47

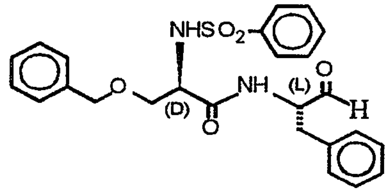


This compound was synthesized following Scheme 7, as described above, except that dimethylsulfamoyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

47: White solid, mp 90-100 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.54; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.10 (m, 11H), 5.25 (d, 1H), 4.70 (q, 1H), 4.45 (q, 2H), 4.00 (m, 1H), 3.90 (dd, 1H), 3.55 (dd, 1H), 3.15 (m, 2H), 2.70 (s, 6H).

Example 42

Synthesis of Compound 48

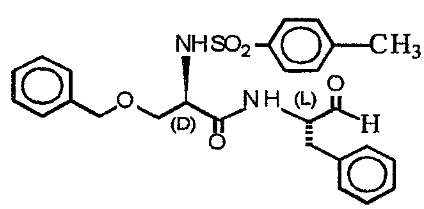


This compound was synthesized following Scheme 7, as described above, except that benzenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**. The compound contained a minor amount of another diasteromer.

48: White solid, mp 110-115 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.63; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 and 9.50 (2 singlets, 84:16, 1H), 7.80-7.00 (m, 16H), 5.60 (d, 1H), 4.60 (q, 1H), 4.30 (q, 2H), 3.80 (m, 2H), 3.30 and 3.20 (2 sets of dd, 84:16, 1H), 3.10 and 3.05 (2 sets of d, 84:16, 2H).

Example 43

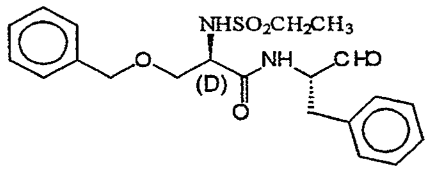
Synthesis of Compound 49



This compound was synthesized following Scheme 7, as described above, except that p-toluenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

49: White solid, mp 113-124 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.58; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.35 (d, 2H), 7.40-7.20 (m, 9H), 7.15 (m, 4H), 5.50 (d, 1H), 4.60 (q, 1H), 4.40 (d, 1H), 4.20 (d, 1H), 3.80 (m, 2H), 3.20 (dd, 1H), 3.10 (d, 2H), 2.40(s, 3H).

Example 44
Synthesis of Compound 50

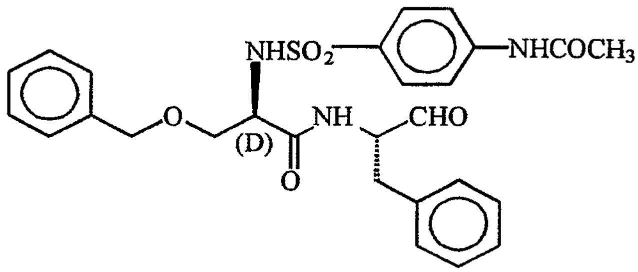


This compound was synthesized following Scheme 7, as described above, except that ethanesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

50: White solid, mp 125-127 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.51; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 5.25 (d, 1H), 4.70 (q, 1H), 4.45 (q, 2H), 4.05 (m, 1H), 3.85 (dd, 1H), 3.60 (dd, 1H), 3.15 (m, 2H), 2.90 (q, 2H), 1.25 (t, 3H).

Example 45

Synthesis of Compound 51

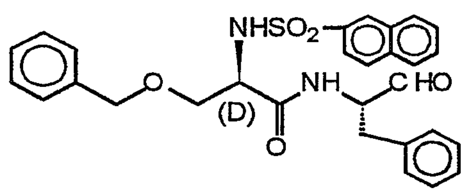


This compound was synthesized following Scheme 7, as described above, except that 4-acetamidobenzenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**. Compound **51** contained a minor amount of another diasteromer.

51: White solid, mp 150-156 °C (decomp.); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.36; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.40 and 9.30 (2 sets of singlets, 86:14, 1H), 8.70 (2 overlapping d, 1H), 8.20 (t, 1H), 7.85 (m, 3H), 7.45 (m, 4H), 7.35 (m, 8H), 4.50-4.30 (m, 2H), 4.20 (m, 1H), 3.60 and 3.45 (2 sets of d, 2H), 3.20 (m, 1H), 2.85 (m, 1H), 2.20 (s, 3H).

Example 46

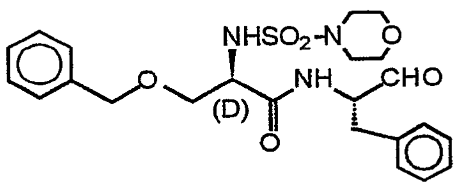
Synthesis of Compound 52



This compound was synthesized following Scheme 7, as described above, except that 2-naphthalenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

52: White solid, mp 95-105 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.54; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.40 (s, 1H), 7.90 (m, 4H), 7.70 (m, 4H), 7.40-7.00 (m, 9H), 65 (d, 1H), 4.55 (q, 1H), 4.30 (q, 2H), 3.80 (m, 2H), 3.20 (dd, 1H), 3.05 (d, 2H).

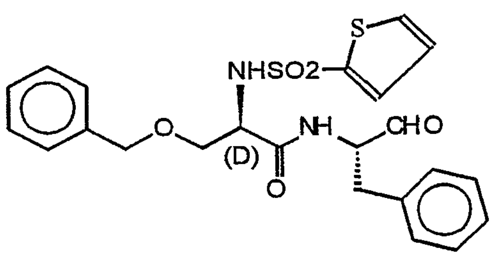
Example 47
Synthesis of Compound 53



This compound was synthesized following Scheme 7, as described above, except that morpholinosulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

53: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.51; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.10 (m, 11H), 5.35 (d, 1H), 4.75 (q, 1H), 4.50 (q, 2H), 4.00 (m, 1H), 3.85 (m, 1H), 3.80-3.50 (m, 5H), 3.30-3.00 (m, 6H).

Example 48
Synthesis of Compound 54

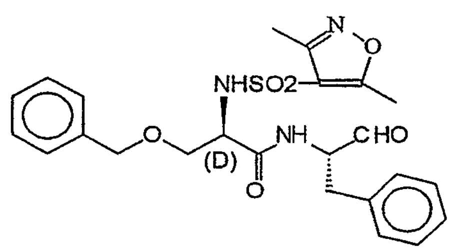


This compound was synthesized following Scheme 7, as described above, except that 2-thiophenesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

54: White solid, mp 105-115 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.56; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.60 (m, 2H), 7.40-7.00 (m, 12H), 5.65 (d, 1H), 4.60 (q, 1H), 4.35 (q, 2H), 3.90 (m, 2H), 3.30 (m, 1H), 3.10 (d, 2H).

Example 49

Synthesis of Compound 55

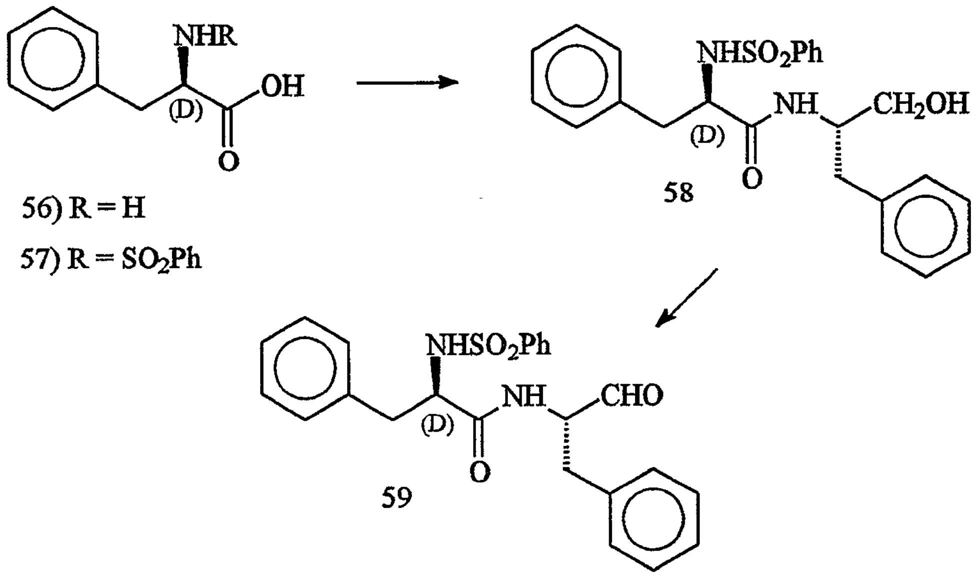


This compound was synthesized following Scheme 7, as described above, except that 3,5-dimethyl-4 isoxazolesulfonyl chloride, instead of methanesulfonyl chloride, was used in preparation of the analog of Compound **38**.

55: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.39; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.30-7.10 (m, 11H), 5.65 (d, 1H), 4.60 (q, 1H), 4.30 (q, 2H), 3.70 (m, 1H), 3.60 (m, 1H), 3.35 (t, 1H), 3.05 (d, 2H), 2.50 (s, 3H), 2.25 (s, 3H).

Scheme 8 shows the synthesis of Compound **59**.

Scheme 8



Example 50

Synthesis of Compound 59

To a stirred suspension of (D)-Phe (Compound **56**, 2.00g, 0.012 mol) in water (10 mL) was slowly added 1 N NaOH (20 mL), followed by benzenesulfonyl chloride (3.20g, 0.018 mol); pH of the reaction mixture was maintained at approx. 10~11 by periodic addition of 1 N NaOH. After 2 h, the reaction mixture was acidified (pH approx. 2~3) with conc. hydrochloric acid and extracted into ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (1 x 10 mL), brine (1 x 20 mL), dried ($MgSO_4$) and concentrated to give 2.00g of crude Compound **57** which was used directly in the next step; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80-7.00 (m, 11H), 5.10 (d, 1H), 4.25 (m, 1H), 3.10 (dd, 1H), 3.00 (dd, 1H).

One g of Compound **57** was coupled with 0.5g of (s)-phenylalaninol, following the coupling procedure of Scheme 1, to generate 1.00g of Compound **58** ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.10 (a series of m, 13H), 6.90 (d, 2H), 6.40

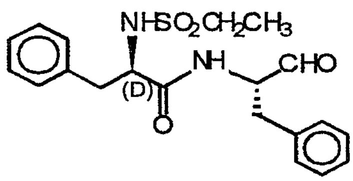
(d, 1H), 5.05 (d, 1H), 4.05 (m, 1H), 3.85 (m, 1H), 3.50 (m, 2H), 2.85 (m, 2H), 2.75 (m, 2H), 2.30 (t, 1H).

Compound **58** was oxidized to Compound **59** by Dess-Martin reagent, as described above in Scheme 7, for the preparation of Compound **40**.

59: White solid, mp 70-75 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.50; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.60 (m, 4H), 7.40 (t, 3H), 7.30-7.10 (m, 6H), 6.90 (d, 2H), 6.70 (d, 1H), 4.90 (d, 1H), 4.60 (q, 1H), 3.90 (q, 1H), 3.15 (dd, 1H), 3.00 (dd, 1H), 2.90 (d, 2H).

Example 51

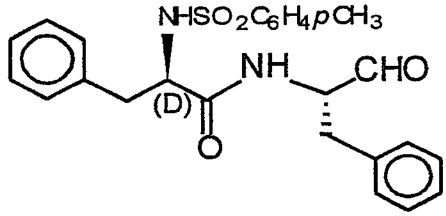
Synthesis of Compound 60



This compound was synthesized following Scheme 8, as described above, except that ethanesulfonyl chloride, instead of benzenesulfonyl chloride, was used in the first step.

60: White solid, mp 112-116 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.20 (m, 8H), 7.10 (d, 2H), 6.65 (d, 1H), 5.10 (d, 1H), 4.70 (q, 1H), 4.15 (q, 1H), 3.20-2.90 (m, 4H), 2.70-2.50 (m, 2H), 1.00 (t, 3H).

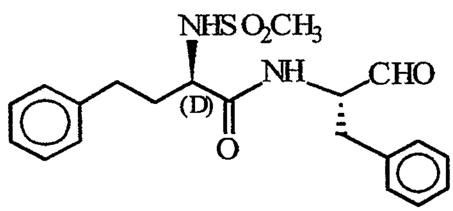
Example 52
Synthesis of Compound 61



This compound was synthesized following Scheme 8, as described above, except that p-toluenesulfonyl chloride, instead of benzenesulfonyl chloride, was used in the first step.

61: White solid, mp 130-135 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.47; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.50 (d, 2H), 7.40-7.10 (m, 10H), 6.90 (d, 2H), 6.80 (d, 1H), 4.85 (d, 1H), 4.60 (q, 1H), 3.85 (q, 1H), 3.15 (dd, 1H), 3.00 (dd, 1H), 2.90 (d, 2H), 2.40 (s, 3H).

Example 53
Synthesis of Compound 62



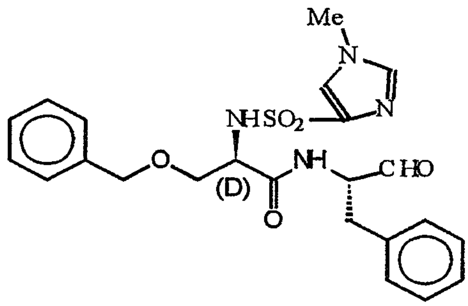
This compound was synthesized following Scheme 8, as described above, except that (D)-Homophe and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride, respectively, were used in the first step.

62: White solid, mp 125-130 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.45; ^{1}H-NMR (300 MHz, $CDCl_3$)

δ 9.65 (s, 1H), 7.40-7.00 (m, 10H), 6.30 (d, 1H), 5.05 (d, 1H), 4.80 (q, 1H), 3.90 (m, 1H), 3.20 (m, 2H), 2.80 (s, 3H), 2.65 (m, 2H), 1.90 (m, 2H).

Example 54

Synthesis of Compound 63

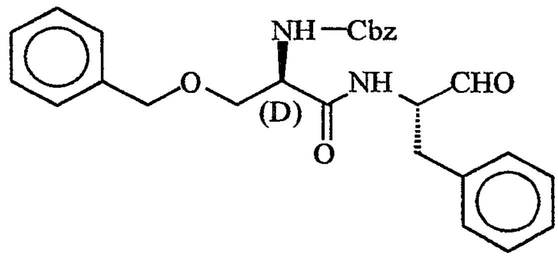


This compound was synthesized following Scheme 8, as described above, except that (D)-Ser(Bzl) and N-methyl-4-imidazolesulfonyl chloride, instead of (D)-Phe and methanesulfonyl chloride, respectively, were used in the first step.

63: White solid, mp 47-56 °C (softening to melt);; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.40; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.60 (d, 1H) 7.40-7.10 (m, 12H), 5.85 (d, 1H), 4.60 (q, 1H), 4.40 (q, 2H), 4.15 (m, 1H), 4.00 (dd, 1H), 3.70 (s, 3H), 3.50 (m, 1H), 3.10 (m, 2H).

Example 55

Synthesis of Compound 64

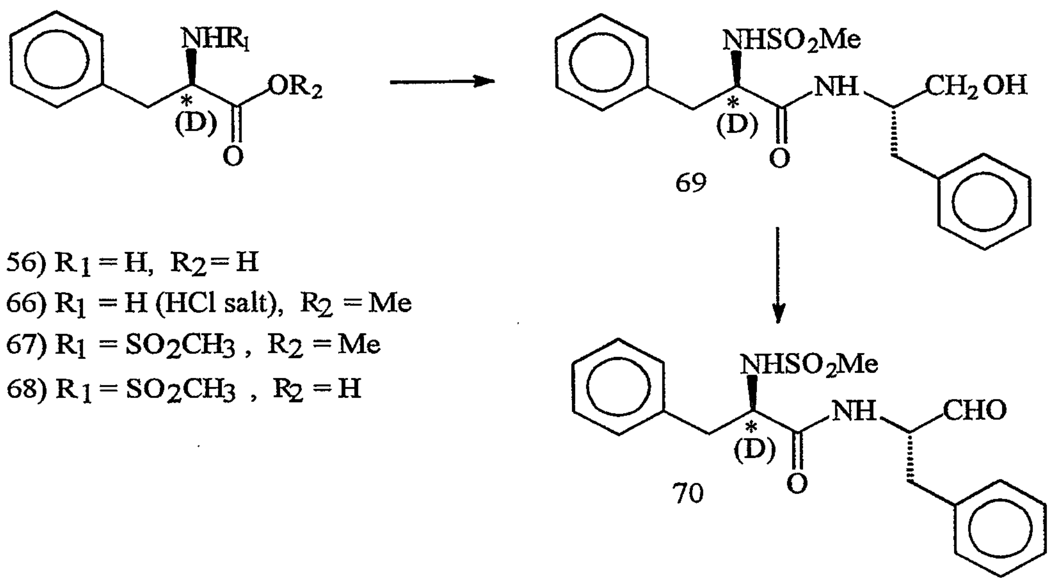


This compound was synthesized following Scheme 8, as described above, except that (D)-Ser(Bzl) and Cbz-OSuc, instead of (D)-Phe and methanesulfonyl chloride, respectively, were used in the first step.

64: White solid, mp 115-120 °C (softening to melt);; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.75; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.10 (m, 15H), 6.95 (broad d, 1H), 5.60 (broad d, 1H), 5.10 (s, 2H), 4.70 (broad q, 1H), 4.45 (q, 2H), 4.40 (m, 1H), 3.90 9d, 1H), 3.50 (dd, 1H), 3.10 (d, 2H).

Scheme 9 shows the synthesis of Compound **70**.

Scheme 9



Example 56
Synthesis of Compound 70

To a stirred solution of (D)-Phe (Compound **56**, 2.00g, 0.012 mol), or Boc-(D)-Phe (Compound **65**), in methanol

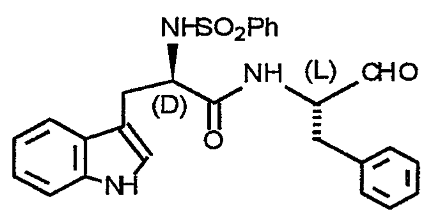
(40 mL), at 0 °C was added slowly thionyl chloride (2.90g, 0.024 mol). The mixture was stirred at 0 °C for 1h and then at room temperature overnight. Excess solvent and reagents were removed in vacuo to give 2.50g of crude Compound **66**. This product was treated with methanesulfonyl chloride, in the presence of triehylamine and methylene chloride, to generate Compound **67**; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 4.85 (d, 1H), 4.40 (m, 1H), 3.80 (s, 3H), 3.15 (dd, 1H), 3.05 (dd, 1H), 2.65 (s, 3H).

Compound **67** was quantitatively hydrolyzed (LiOH, THF-H_2O, room temperature, 3h) to Compound **68** which in turn was converted to Compound **70** via Compound **69** using the procedures described in Scheme 7 for the preparation of Compound **40**.

70: White solid, mp 65-70 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.44; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.40-7.00 (m, 10H), 6.80 (d, 1H), 5.30 (d, 1H), 4.75 (q, 1H), 4.10 (m, 1H), 3.20-3.00 (m, 3H), 2.90 (dd, 1H), 2.40 (s, 3H).

Example 57

Synthesis of Compound 71

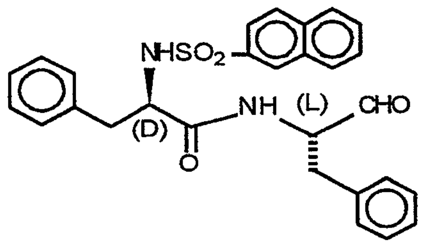


This compound was synthesized following Scheme 9, as described above, except that (D)-Trp and benzenesulfonyl chloride, instead of (D)-Phe and methanesulfonyl chloride, respectively, were used in the first step.

71: White solid, mp 125-135 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.55; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.40 (broad, 1H), 7.40-6.80 (m, 16H), 5.35 (d, 1H), 4.55 (q, 1H), 4.00 (q, 1H), 3.20-2.90 (m, 4H).

Example 58

Synthesis of Compound 72

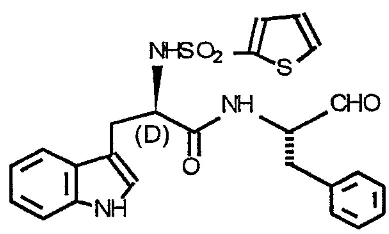


This compound was synthesized following Scheme 9, as described above, except that 2-naphthalenesulfonyl chloride, instead of methanesulfonyl chloride, was used in the first step.

72: White solid, mp 120-130 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.51; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.05 (s, 1H), 7.90 (d, 2H), 7.80 (d, 1H), 7.65 (m, 2H), 7.55 (dd, 1H), 7.30 (m, 3H), 7.00 (m, 5H), 6.80 (m, 3H), 5.00 (d, 1H), 4.50 (q, 1H), 3.95 (q, 1H), 3.10 (dd, 1H), 2.95 (dd, 1H), 2.90 (m, 2H).

Example 59

Synthesis of Compound 73

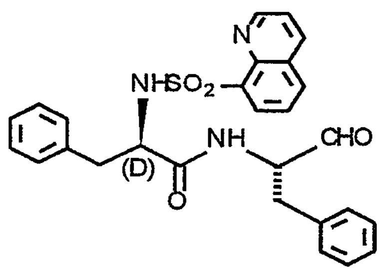


This compound was synthesized following Scheme 9, as described above, except that (D)-Trp and 2-thiophenesulfonyl chloride, instead of (D)-Phe and methanesulfonyl chloride, respectively, were used in the first step.

73: White solid, mp 90-100 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.39; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.10 (s, 1H), 7.40-7.00 (m, 11H), 6.85 (m, 2H), 6.75 (d, 1H), 5.15 (d, 1H), 4.60 (q, 1H), 4.05 (q, 1H), 3.10 (m, 3H), 3.00 (dd, 1H).

Example 60

Synthesis of Compound 74

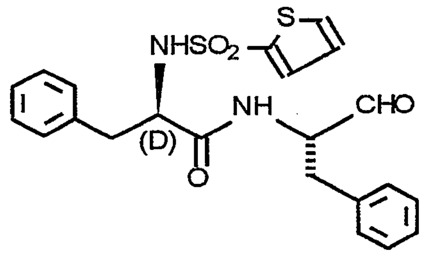


This compound was synthesized following Scheme 9, as described above, except that 8-quinolinesulfonyl chloride, instead of methanesulfonyl chloride, was used in the first step.

74: White solid, mp 80-90 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.57; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.70 (m, 1H), 8.30 (m, 1H), 8.20 (m, 1H), 8.00 (m, 1H), 7.60 (t, 1H), 7.45 (q, 1H), 7.40-7.10 (m, 6H), 6.90-6.60 (m, 6H), 4.60 (q, 1H), 4.10 (m, 1H), 3.20 (dd, 1H), 3.05 (m, 2H), 2.80 (dd, 1H).

Example 61

Synthesis of Compound 75

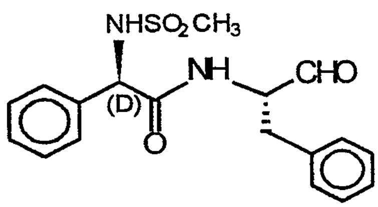


This compound was synthesized following Scheme 9, as described above, except that 2-thiophenesulfonyl chloride, instead of methanesulfonyl chloride, was used in the first step.

75: White solid, mp 55-65 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.43; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.60 (dd, 1H), 7.40 (dd, 1H), 7.35-7.05 (m, 8H), 7.00 (t, 1H), 6.95 (m, 2H), 6.65 (d, 1H), 5.00 (d, 1H), 4.65 (q, 1H), 4.00 (q, 1H), 3.15 (dd, 1H), 3.00 (dd, 1H), 2.95 (d, 2H).

Example 62

Synthesis of Compound 76

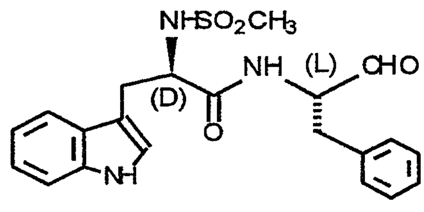


This compound was synthesized following Scheme 9, as described above, except that (D)-phenylglycine, instead of (D)-phenylalanine, was used in the first step.

76: White solid, mp 140-145 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.45; ^{1}H-NMR (300 MHz, $CDCl_3$)

δ 9.60 (s, 1H), 7.40-7.05 (m, 8H), 6.75 (d, 2H), 6.00 (d, 1H), 5.85 (d, 1H), 5.05 (d, 1H), 4.80 (q, 1H), 3.05 (q, 2H), 2.65 (s, 3H).

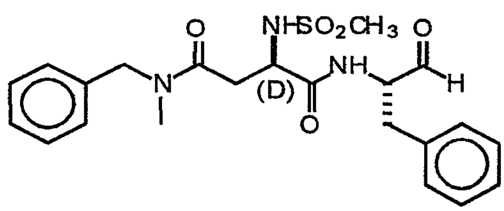
Example 63
Synthesis of Compound 77



This compound was synthesized following Scheme 9, as described above, except that (D)-Trp, instead of (D)-phenylalanine, was used in the first step.

77: White solid, mp 105-115 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.35; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.15 (s, 1H), 7.60 (d, 1H), 7.40-7.00 (m, 9H), 6.50 (d, 1H), 4.95 (d, 1H), 4.65 (q, 1H), 4.20 (q, 1H), 3.25 (m, 2H), 3.10 (dd, 1H), 2.95 (dd, 1H), 2.50 (s, 3H).

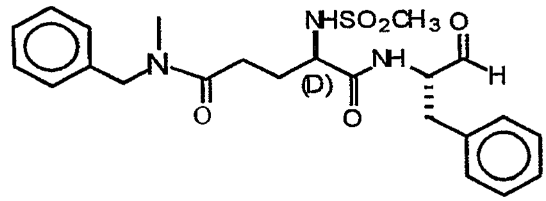
Example 64
Synthesis of Compound 78



This compound was synthesized following Schemes 1 and 2, as described above, except that *N*-benzylmethylamine, instead of 1,2,3,4-tetrahydroisoquinoline, was used in the first step.

78: White solid, mp 75-85 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.30; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.65 and 9.55 (2 singlets, rotomeric 1H), 7.70 (m, 1H), 7.40-7.00 (m, 10H), 6.20 (m, 1H), 4.70-4.30 (m, 4H), 3.30-2.90 (m, 4H), 2.85 (2 sets of d, 6H)

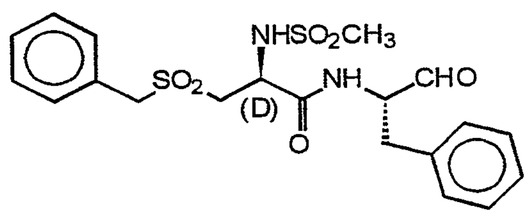
Example 65
Synthesis of Compound 79



This compound was synthesized following Schemes 1 and 2, as described above, except that *N*-benzylmethylamine and Boc-(D)-Glu-OBz, instead of 1,2,3,4-tetrahydroisoquinoline and Boc-(D)-Asp-OBz, respectively, were used in the first step.

79: White solid, mp 75-85 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.42; ^{1}H-NMR (300 MHz, $CDCl_3$) of this compound is a complex one due to the presence of rotamers.

Example 66
Synthesis of Compound 80

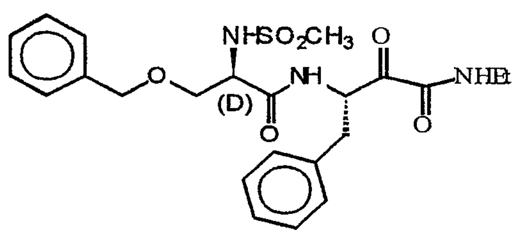


This compound was synthesized following the procedure of Scheme 7, as described above, with the following changes: Boc-(D)-Cys(Bzl) (Compound **21**) was used instead of Boc-(D)-Ser(Bzl) (Compound **26**), in the first step of the synthesis; and the sulfide moiety was converted to a sulfonyl moiety by Oxone® in MeOH before the final oxidation of the alcohol to the aldehyde by Dess-Martin reagent was carried out.

80: White solid, mp 125-135 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.41; ^1H-NMR (300 MHz,DMSO-d_6) δ 9.60 (s, 1H), 8.90 (d, 1H), 8.05 (d, 1H), 7.50-7.20 (m, 10H), 4.50 (m, 4H), 3.30 (d, 2H), 3.10 (m, 1H), 2.95 (s, 3H), 2.90 (m, 1H).

Example 67

Synthesis of Compound 81

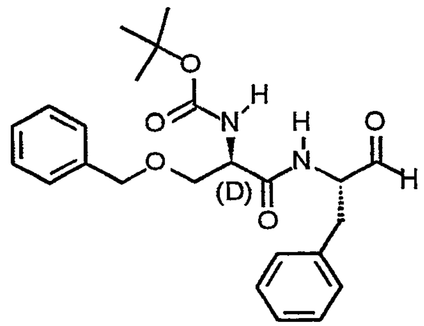


This compound was synthesized following the procedure outlined in Scheme 6, above, except that 3(S)-amino-2(R,S)-hydroxy-4-phenylbutanoic acid ethyl amide (prepared by the method of Harbeson et al. *J. Med. Chem.* **1994**, *37*, 2918) was used instead of Compound **18a-b** in the synthesis.

81: White solid, mp 137-143 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.56; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 9H), 7.00 (m, 2H), 6.80 (broad, 1H), 5.60 (m, 1H), 5.15 (d, 1H), 4.50 (s, 1H), 4.45 (d, 1H), 4.00 (M, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.35 (m, 3H), 3.05 (m, 1H), 2.80 (s, 3H), 1.20 (t, 3H).

Example 68

Synthesis of Compound 82

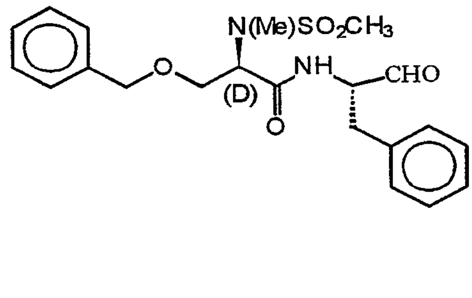


This compound was synthesized by coupling Boc-(D)-Ser(Bzl) and (S)-phenylalaninol, followed by oxidation, using the processes described in Scheme 1.

82:White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.65; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 5.30 (broad, 1H), 4.70 (m, 1H), 4.50 (m, 2H), 4.30 (m, 1H), 3.90 (m, 1H), 3.50 (m, 1H), 3.15 (d, 2H), 1.50 (s, 9H).

Example 69

Synthesis of Compound 83

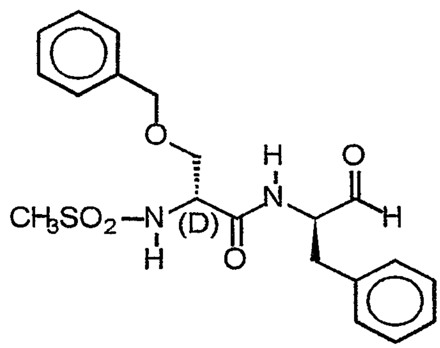


This compound was generated by N-methylation (MeI, K_2CO_3, DMF) of Compound **38** (Scheme 7), followed by reduction of the methyl ester to the corresponding alcohol and oxidation of the alcohol to the product aldehyde.

83:White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 4.60 (m, 2H), 4.45 (q, 2H), 3.95 (dd, 1H), 3.70 (t, 1H), 3.10 (m, 2H), 2.85 (s, 3H), 2.75 (s, 3H).

Example 70

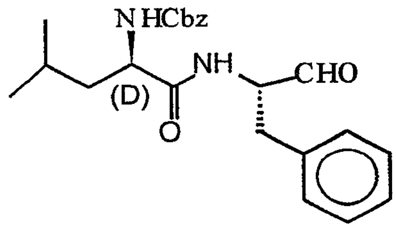
Synthesis of Compound 84



This compound was synthesized following Scheme 9, as described above, except that (D)-Ser(Bzl) instead of (D)-Phe was used in the first step, and (R)-phenylalaninol, instead of (S)-phenylalaninol, was used in the coupling step.

84:White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.41; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.00 (m, 11H), 5.30 (d, 1H), 4.75 (m, 1H), 4.50 (s, 2H), 4.10 (m, 1H), 3.85 (dd, 1H), 3.60 (dd,1H), 3.10 (m, 2H), 2.90 (s, 3H).

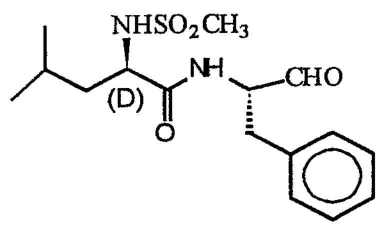
Example 71
Synthesis of Compound 85



This compound was synthesized by coupling Cbz-(D)-Leu and (S)-phenylalaninol, followed by oxidation (Scheme 9).

85:White solid; mp 40-50 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.65; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.10 (m, 10H), 6.50 (broad, 1H), 5.15 (s, 2H), 5.10 (broad, 1H), 4.70 (broad q, 1H), 4.20 (broad, 1H), 3.15 (d, 2H), 1.60-1.20 (m, 3H), 0.85 (broad d, 6H).

Example 72
Synthesis of Compound 86

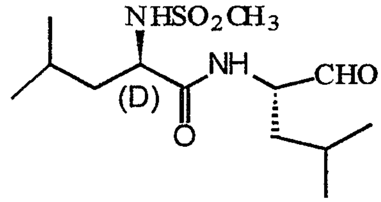


This compound was synthesized following the procedures of Scheme 8, as described above, except that (D)-Leu, instead of (D)-Phe, was used in the first step.

86:White solid; mp 95-100 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.33; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.40-7.10 (m, 5H), 6.30 (d, 1H), 4.80 (m, 2H), 3.90 (m, 1H), 3.25 (dd, 1H), 3.15(dd, 1H), 2.85 (s, 3H), 1.65-1.20 (m, 3H), 0.90 (t, 6H).

Example 73

Synthesis of Compound 87

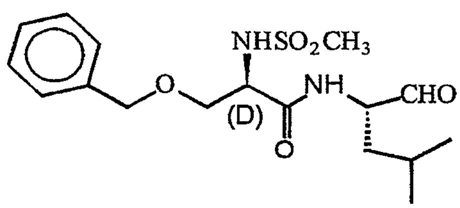


This compound was synthesized following the procedures of Scheme 7, as described above, except that Boc-(D)-Leu instead of Boc-(D)-Ser(Bzl) was used in the first step, and (S)-leucinol instead of (S)-phenylalaninol was used in the coupling step.

87:White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.40; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.15 (d, 1H), 5.00 (d, 1H), 4.60 (m, 1H), 4.00 (m, 1H), 3.00 (s, 3H), 1.90-1.40 (m, 6H), 1.00 (m, 12H).

Example 74

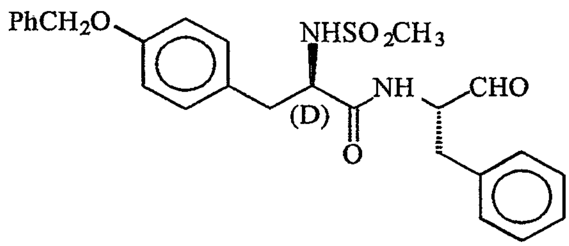
Synthesis of Compound 88



This compound was synthesized following the procedures of Scheme 9, as described above, except that Boc-(D)-Ser(Bzl), instead of (D)-Phe was used in the first step and (S)-leucinol, instead of (S)-phenylalaninol, was used in an intermediate step.

88:White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.46; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.20 (m, 5H), 6.95 (d, 1H), 5.30 (d, 1H), 4.55 (m, 3H), 4.15 (m, 1H), 3.90 (m, 1H), 3.75 (dd,1H), 2.95 (s, 3H), 1.70-1.20 (m, 3H), 0.90 (m, 6H).

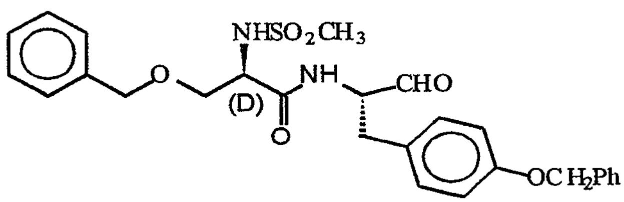
Example 75
Synthesis of Compound 89



This compound was synthesized following the procedures of Scheme 9, as described above, except that Boc-(D)-Tyr(Bzl) instead of (D)-Phe was used in the first step.

89:White solid; mp 140-145 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.34; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.45-7.20 (m, 5H), 7.10 (d, 4H), 6.90 (d, 2H), 6.55 (d, 1H), 5.05 (s, 2H), 4.85 (q, 1H), 4.70 (q, 1H), 4.05 (q, 1H), 3.10 (m, 2H), 2.90 (q, 1H), 2.45 (s, 3H).

Example 76
Synthesis of Compound 90



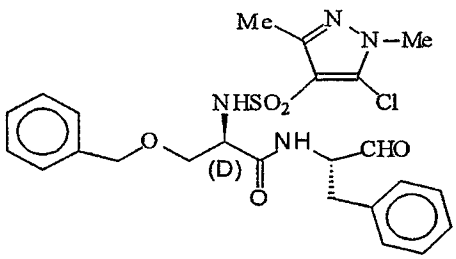
This compound was synthesized following the procedures of Scheme 9, as described above, with the following changes: Boc-(D)-Ser(Bzl) was used instead of (D)-Phe in the first step; (L)-Tyr(Bzl)-OMe, was used instead of

(S)-phenylalaninol in an intermediate step; and the ester moiety was subsequently reduced ($NaBH_4$, EtOH) to the alcohol moiety before the final oxidation step.

90:White solid; mp 105-106 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.38; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.45-7.20 (m, 10H), 7.15 (d, 1H), 7.00 (d, 2H), 6.85 (d, 2H), 5.25 (d, 1H), 5.00 (s, 2H), 4.70 (q, 1H), 4.45 (q, 2H), 4.10 (m, 1H), 3.85 (dd, 1H), 3.60 (dd, 1H), 3.10 (m, 2H), 2.85 (s, 3H).

Example 77

Synthesis of Compound 91

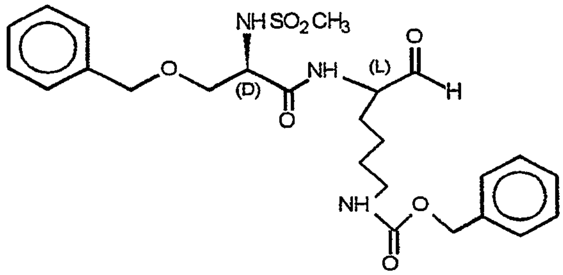


This compound was synthesized using the procedures of Scheme 7, as described above, except that 5-chloro-1,3-dimethylpyrazole-4-sulfonyl chloride instead of methanesulfonyl chloride was used in the first step.

91:White solid; mp 50-60 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.57; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.60 and 9.55 (2 singlets, 5:1, 1H), 7.40-7.00 (m, 11H), 5.70 (d, 1H), 4.65 (q, 1H), 4.40 (q, 2H), 3.90-3.60 (m, 2H), 3.80 (s, 3H), 3.40 (dd, 1H), 3.10 (2 sets of d, 5:1, 2H), 2.40 (s, 3H).

Example 78

Synthesis of Compound 92

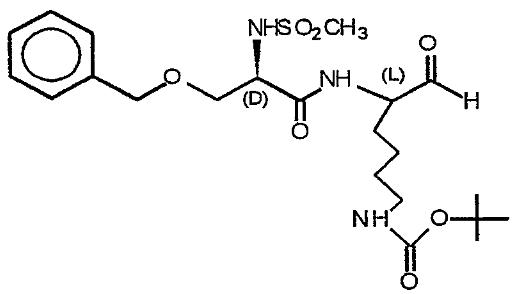


This compound was synthesized using the procedures of Scheme 8, as described above, with the following changes: (D)-Ser(Bzl) and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride were used in the first step; (L)-Lys(Cbz)-OMe hydrochloride salt, instead of (S)-phenylalaninol, was used in an intermediate step; and the ester moiety was subsequently reduced ($NaBH_4$, EtOH) to the alcohol before the final oxidation step.

92:White solid; mp 125-135 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.40; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.40-7.15 (m, 11H), 5.25 (d, 1H), 5.10 (s, 2H), 4.90 (broad, 1H), 4.55 (q, 2H), 4.45 (m, 1H), 4.15 (q, 1H), 3.85 (dd, 1H), 3.70 (dd, 1H), 3.15 (q, 2H), 2.90 (s, 3H), 1.90 (m, 1H), 1.70 (m, 1H), 1.50 (m, 2H), 1.30 (m, 2H).

Example 79

Synthesis of Compound 93

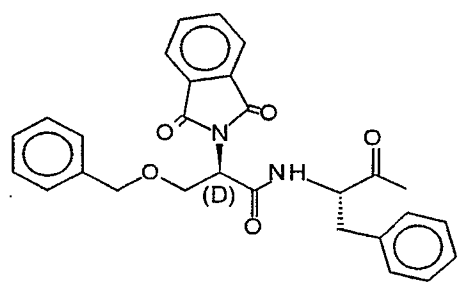


This compound was synthesized following the procedures of Scheme 8, as described above, with the following changes: (D)-Ser(Bzl) and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride, were used in the first step; (L)-Lys(Boc)-OMe hydrochloride salt, instead of (S)-phenylalaninol, was used in an intermediate step; and the ester moiety was subsequently reduced ($NaBH_4$, EtOH) to the alcohol before the final oxidation step.

93: White solid; mp 130-135 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.47; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.40-7.20 (m, 6H), 5.50 (broad d, 1H), 4.65-4.40 (m, 4H), 4.15 (q, 1H), 3.85 (dd, 1H), 3.75 (dd, 1H), 3.05 (m, 2H), 2.95 (s, 3H), 1.90 (m, 1H), 1.65 (m, 1H), 1.60-1.20 (m, 4H), 1.45 (s, 9H).

Example 80

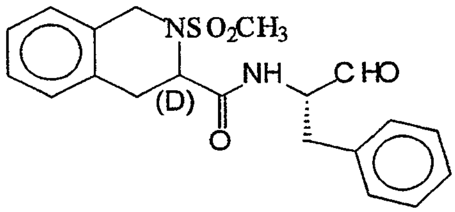
Synthesis of Compound 94



This compound was synthesized following the procedures of Scheme 8, as described above, except that (D)-Ser(Bzl) and N-carbethoxyphthalimide (in the presence of aqueous Na_2CO_3), were used in the first step, instead of (D)-Phe and benzenesulfonyl chloride. The final product showed some racemization had occurred.

94: White solid; mp 40-50 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.70; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.65 and 9.60 (2 singlets, 7:3, 1H), 7.80 (m, 2H), 7.70 (m, 2H), 7.60 (t, 1H), 7.40-7.10 (m, 10H), 5.00 (m, 1H), 4.75 (q, 1H), 4.60-4.30 (m, 3H), 3.70 (m, 1H), 3.25 and3.15 (2 sets of doublets, 2H).

Example 81
Synthesis of Compounds 95 and 96



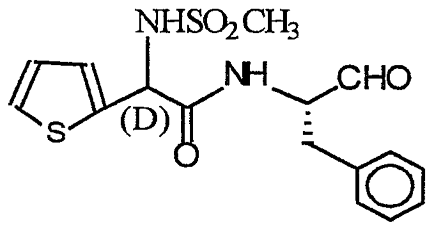
These compounds were synthesized following the procedures of Scheme 7, as described above, except that Boc-(D)-Tic, instead of Boc-(D)-Ser(Bzl) was used in the first step. However, racemization was observed during the synthesis, and the isomers were separated after the sulfonylation step. Individual isomers were converted separately in the final two steps to give the product aldehydes.

Isomer I (95): Pale yellow solid; mp 55-65 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.70; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.30-7.10 (m, 9H), 7.00 (d, 1H), 7.55 (m, 3H), 7.35 (d, 1H), 3.20 (d, 2H), 3.10 (d, 2H), 2.60 (s, 3H).

Isomer II (96): Pale yellow solid; mp 65-75 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.30-7.00 (m, 10H), 4.60-4.40 (m, 3H), 4.05 (d, 1H), 3.20-3.05 (m, 3H), 3.00 (q, 1H), 2.60 (s, 3H).

Example 82

Synthesis of Compounds 97 and 98



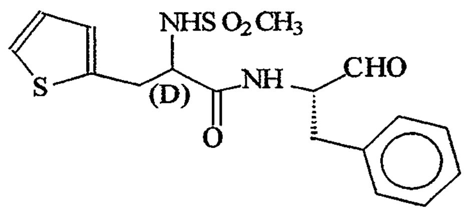
These compounds were synthesized following the procedures of Scheme 8, as described above, except that (D and L)-thiopheneglycine, instead of (D)-Phe, was used in the first step. Diastereomers were separated after the first step. Individual isomers were converted separately to the product aldehydes. Stereochemistry around the chiral center in isomers I and II was tentatively assigned (L) and (D) respectively, based on comparison of their enzyme inhibitory activity with that of other members of the series with known configuration.

Isomer I (97): Pale yellow solid; mp 65-75 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.38; ^{1}H-NMR (300 MHz, Acetone-d_6) δ 9.65 (s, 1H), 8.10 (d, 1H), &.50-7.00 (m, 8H), 6.85 (d, 1H), 5.45 (d, 1H), 4.55 (m, 1H), 3.30 (dd, 1H), 3.00 (dd, 1H), 2.70 (s, 3H).

Isomer II (98): Pale yellow solid; mp 151-154 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.33; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.05 (d, 1H), 8.30 (d, 1H), 7.65 (d, 1H), 7.35 (m, 5H), 7.10 (t, 1H), 6.95 (d, 1H), 5.55 (d, 1H), 4.70 (m, 1H), 3.40 (dd, 1H), 3.00 (dd, 1H), 2.95 (s, 3H).

Example 83

Synthesis of Compounds 99 and 100



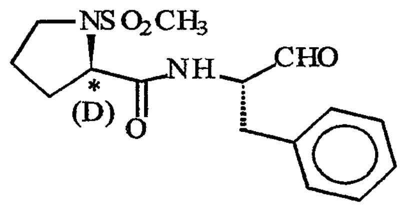
These compounds were synthesized following the procedures of Scheme 8, as described above, except that (D and L)-thiophenealanine instead of (D)-Phe was used in the first step. Diastereomers were separated after the first step. Individual isomers were converted separately to the product aldehydes. Isomer I was also prepared separately starting with (L)- thiophenealanine. Thus isomer II, Compound **100**, has the (D)-configuration at the P_2 position.

Isomer I (99): White solid; mp 93-98 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.20 (m, 4H), 7.15 (d, 2H), 6.95 (dd, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 5.00 (d, 1H), 4.70 (q, 1H), 4.15 (q, 1H), 3.30 (m, 2H), 3.10 (m, 2H), 2.65 (s, 3H).

Isomer II (100): White solid; mp 124-128 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.49; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.20 (m, 4H), 7.15 (d, 2H), 6.95 (dd, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 5.20 (d, 1H), 4.75 (q, 1H), 4.15 (m, 1H), 3.30 (dd, 1H), 3.20 (dd, 1H), 3.10 (m, 2H), 2.60 (s, 3H).

Example 84

Synthesis of Compound 101

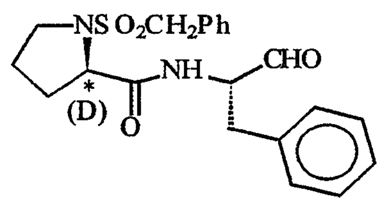


This compound was synthesized following the procedures of Scheme 8, as described above, except that (D)-proline and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride, were used in the first step;

101: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.33; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.40-7.10 (m, 5H), 7.05 (d, 1H), 4.65 (q, 1H), 4.20 (dd, 1H), 3.50 (m, 1H), 3.35 (q, 1H), 3.20 (d, 2H), 2.85 (s, 3H), 2.30 (m, 1H), 2.10 (m, 1H), 1.90 (m, 2H).

Example 85

Synthesis of Compound 102



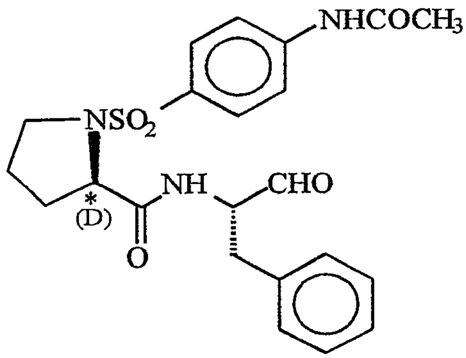
This compound was synthesized following the procedures of Scheme 7, as described above, except that Boc-(D)-proline instead of Boc-(D)-Ser(Bzl) was used in the first step, and α-toluenesulfonyl chloride instead of methanesulfonyl chloride was used for preparation of the N-sulfonyl intermediate compound.

102: White solid; mp 40-50 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.66; ^{1}H-NMR (300 MHz, $CDCl_3$)

δ 9.55 (s, 1H), 7.45-7.10 (m, 10H), 6.85 (d, 1H), 4.55 (q, 1H), 4.25 (s, 2H), 4.05 (dd, 1H), 3.15 (m, 2H), 3.10 (dd, 2H), 2.10 (m, 1H), 1.90 (m, 1H), 1.80 (m, 2H).

Example 86

Synthesis of Compound 103

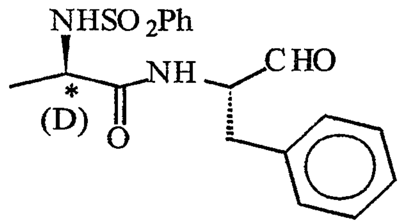


This compound was synthesized following the procedures of Scheme 7, as described above, except that Boc-(D)-proline instead of Boc-(D)-Ser(Bzl) was used in the first step, and 4-acetamidobenzenesulfonyl chloride, instead of methanesulfonyl chloride, was used for preparation of the N-sulfonyl intermediate compound.

103: White solid; mp 75-85 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.26; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.65 (m, 5H), 7.40-7.20 (m, 6H), 4.65 (q, 1H), 4.05 ((dd, 1H), 3.45 (m, 1H), 3.20 (m, 2H), 3.15 (m, 1H), 2.20 (s, 3H), 2.10 (m, 1H), 1.80-1.50 (m, 3H).

Example 87

Synthesis of Compound 104

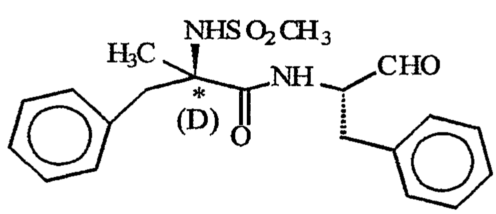


This compound was synthesized following the procedures of Scheme 8, as described above, except that (D)-Ala instead of (D)-Phe was used in the first step.

104: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.33; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.85 (d, 2H), 7.55 (m, 3H), 7.30 (m, 3H), 7.15 (d, 2H), 6.60 (d, 1H), 5.25 (d, 1H), 4.60 (q, 1H), 3.80 (m, 1H), 3.10 (d, 2H), 1.20 (d, 3H).

Example 88

Synthesis of Compound 105

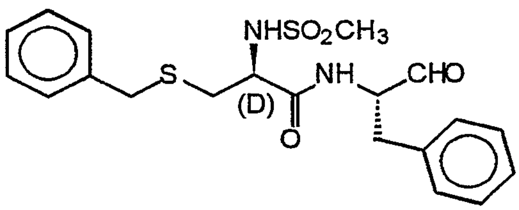


This compound was synthesized following the procedures of Scheme 8, as described above, except that (D)-α-Me-Phe and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride, were used in the first step. Crude product showed the presence of one product aldehyde. However, racemization occurred during purification of the product by chromatography through a florisil column.

105: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.42;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 and 9.50 (2 singlets, 1H), 7.40-7.00 (m, 10H), 6.65 and 6.60 (2 sets of d, 1H), 4.85 (d, 1H), 4.65 (q, 1H), 3.20-2.90 (m, 7H), 1.70 and 1.60 (2 singlets, 3H).

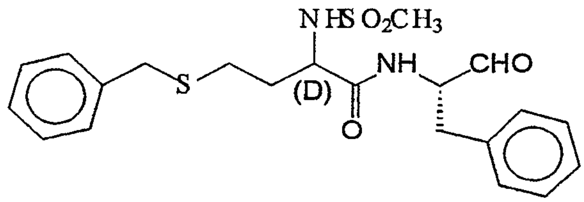
Example 89
Synthesis of Compound 106



The synthesis of this compound was initiated by following the procedures of Scheme 9, as described above, with the following changes: Boc-(D)-Cys (Bzl), instead of (D)-Phe, was used in the first step; Phe-N(Me)OMe (prepared from Boc-Phe and HN(Me)OMe following the general procedure of Fehrentz et al. *Synthesis*, **1983**, 676, followed by acidic hydrolysis) was used instead of (S)-phenylalaninol in the condensation step. The dipeptide Weinreb amide intermediate was subsequently reduced to the target aldehyde by lithium aluminium hydride, following a general procedure from the above-mentioned reference.

106: Waxy solid; R_f (EtOAc): 0.55; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.10 (m, 10H), 6.90 (d, 1H), 5.50 (d, 1H), 4.75 (q, 1H), 3.95 (q, 1H), 3.70 (s, 2H), 3.15 (m, 2H), 3.00-2.60 (m, 2H), 2.80 (s, 3H), Example 90

Synthesis of Compounds 107 and 108



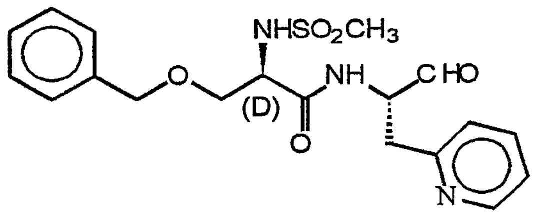
The synthesis of these compounds was initiated by following the procedures of Scheme 8, as described above, with the following changes: (D and L)- homocysteine(Bzl) and methanesulfonyl chloride, instead of (D)-Phe and benzenesulfonyl chloride, were used in the first step; and Phe-N(Me)OMe, instead of (S)-phenylalaninol, was used in the condensation step. The separated diastereomeric dipeptide Weinreb amide intermediates were subsequently reduced to the target aldehydes by lithium aluminium hydride.

Isomer I (107): White solid, mp 54-56 °C; R_f (EtOAC): 0.60; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.05 (m, 10H), 6.55 (d, 1H), 5.30 (d, 1H), 4.75 (q, 1H), 4.05 (m, 1H), 3.65 (m, 2H), 3.20 (dd, 1H), 3.00 (dd, 1H), 2.70 (s, 3H), 2.40 (m, 2H), 1.90 (m, 2H).

Isomer II (108): Waxy solid; R_f (EtOAc): 0.50; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.40-7.05 (m, 10H), 6.60 (d, 1H), 5.50 (d, 1H), 4.75 (q, 1H), 4.05 (m, 1H), 3.65 (m, 2H), 3.20 (dd, 1H), 3.00 (dd, 1H), 2.85 (s, 3H), 2.40 (m, 2H), 1.80 (m, 2H).

Example 91

Synthesis of Compound 109

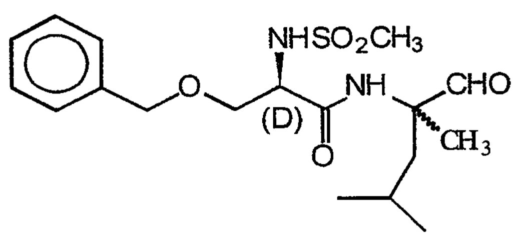


This compound was synthesized following Scheme 8, as described above, except that (D)-Ser(Bzl) instead of (D)-Phe was used in the first step, and (s)-pyridylalaninol, instead of (s)-phenylalaninol, was used in the coupling step.

109: Pale yellow foam; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.51; ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum was complex, possibly due to the presence of a cyclized form along with the parent molecule; mass spectrum showed M+H-ion peak at m/e 406.

Example 92

Synthesis of Compound 110

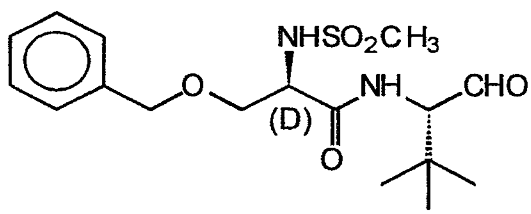


This compound was synthesized following Scheme 8, as described above, except that (D)-Ser(Bzl) instead of (D)-Phe was used in the first step, and racemic α-methylleucinol, instead of (S)-phenylalaninol, was used in the coupling step. Thus the product aldehyde was a diastereomeric mixture, epimeric at P_1.

110: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.71 and 0.62 (diastereomers); ^1H-NMR (300 MHz, $CDCl_3$) δ 9.30 and 9.25 (2 singlets, 1H), 7.45 (d, 1H), 7.40-7.20 (m, 5H), 5.40 (d, 1H), 4.55 (m, 2H), 4.10 (m, 1H), 3.90 (m, 1H), 3.70 (dd, 1H), 2.95 and 2.90 (2 singlets, 3H), 1.60-1.20 (m, 3H), 1.40 (s, 3H), 0.90 and 0.70 (2 sets of doublet, 6H).

Example 93

Synthesis of Compound 111

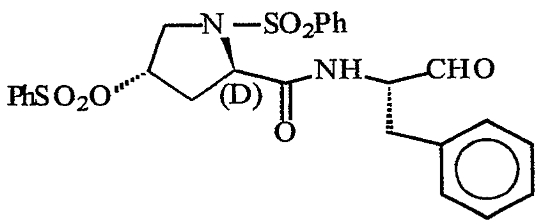


This compound was synthesized following Scheme 8, as described above, except that (D)-Ser(Bzl) instead of (D)-Phe was used in the first step, and (s)-tert-butylglycinol instead of (S)-phenylalaninol was used in the coupling step.

111: White foam; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.60; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.45-7.25 (m, 5H), 7.20 (d, 1H), 5.40 (d, 1H), 4.60 (q, 2H), 4.50 (d, 1H), 4.15 (q, 1H), 3.90 (dd, 1H), 3.75 (dd, 1H), 2.95 (s, 3H), 1.00 (s, 9H).

Example 94

Synthesis of Compound 112

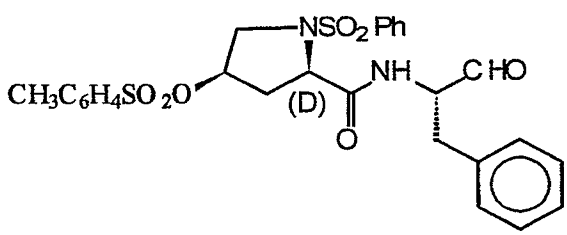


This compound was synthesized following Scheme 8, as described above, except that cis-4-hydroxy-(D)-proline instead of (D)-Phe was used in the first step, and both NH and OH groups were simultaneously sulfonylated.

112: White solid, mp 160-165 °C ; R_f (50% CH_2Cl_2-50% EtOAc): 0.61; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.80 -7.25 (m, 16H), 4.90 (t, 1H), 4.55 (q, 1H), 4.25 (d, 1H), 3.55 (dd, 1H), 3.35 (dd, 1H), 3.10 (d, 2H), 2.45 (d, 1H), 1.70 (m, 1H).

Example 95

Synthesis of Compound 113

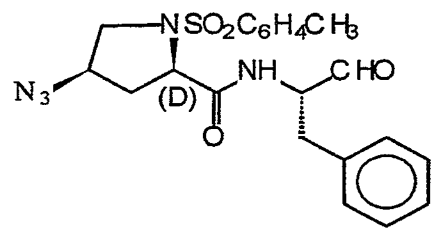


This compound was synthesized following Scheme 9, as described above, except that cis-4-hydroxy-(D)-proline instead of (D)-Phe was used in the first esterification step. Selective phenylsulfonylation of the NH-group, and Mitsunobu displacement (with inversion, in the presence of Ph_3P and diethyl azidocarboxylate; Mitsunobu, O. *Synthesis*, **1981**, 1) of the OH-group with methyl-p-toluenesulfonate gave the bis-sulfonylated intermediate. The remainder of the synthesis followed the route described in Scheme 9.

113: White solid, mp 75-80 °C; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.43; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.80-7.20 (m, 14H), 7.10 (d, 1H), 4.80 (m, 1H), 4.65 (q, 1H), 4.15 (t, 1H), 3.60 (m, 2H), 3.15 (m, 2H), 2.40 (s, 3H), 2.10 (m, 2H).

Example 96

Synthesis of Compound 114

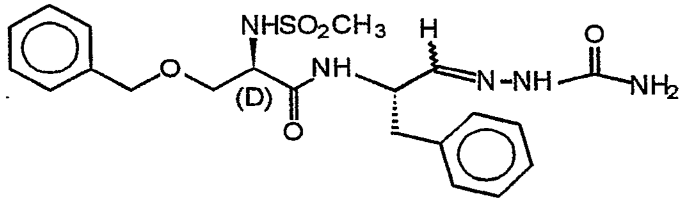


This compound was synthesized following Scheme 8, as described above, with the following changes: cis-4-hydroxy-(D)-proline instead of (D)-Phe was used in the first step; both NH and OH groups were sulfonylated with p-toluenesulfonyl chloride; the disulfonylated derivative was coupled with (S)-phenylalaninol, and the tosyl group in the dipeptide intermediate was displaced in an S_N2 fashion by the azido group (NaN_3, DMF). Oxidation to generate the product aldehyde was carried out as described.

114: White solid, mp 65-75 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.59; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.70 (d, 2H), 7.40-7.15 (m, 7H), 4.70 (q, 1H), 4.15 (dd, 1H), 4.00 (m, 1H), 3.60 (dd, 1H), 3.20 (m, 4H), 2.45 (s, 3H), 2.25 (m, 1H), 1.85 (m, 1H).

Example 97

Synthesis of Compound 115

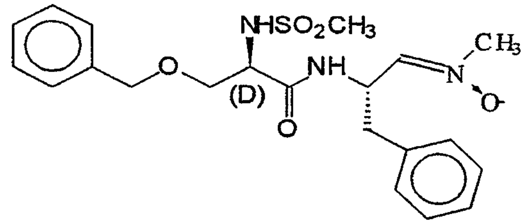


A mixture of Compound **40** (0.20 g, 0.50 mmol), semicarbazide hydrochloride (0.056 g, 0.50 mmol), sodium acetate (0.040 g, 0.50 mmol), ethanol (7 mL) and water (3 mL) was stirred at 0 °C for 1h, and then at room temperature overnight. The reaction mixture was concentrated, taken into water (15 mL) and extracted into methylene chloride (3 x 15 mL). The combined organic layer was washed with brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to give a crude product. It was purified by flash column chromatography (5% MeOH in methylene chloride) to give 0.048 g of Compound **115**.

115: White solid, mp 168-173 °C ; R_f (90% CH_2Cl_2-10% CH_3OH): 0.44; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.45 -7.10 (m, 11H), 7.15 (d, 2H), 7.00 (d, 1H), 6.40 (d, 1H), 4.80 (m, 1H), 4.50 (q, 2H), 4.10 (m, 1H), 3.80 (dd, 1H), 3.70 (dd, 1H), 3.00 (m, 2H), 2.90 (s, 3H).

Example 98

Synthesis of Compound 116

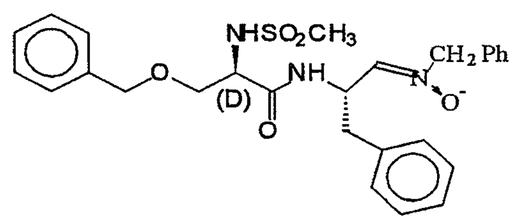


This compound was generated following the same synthetic protocol, as described above, for the synthesis of Compound **115**, Example **97** , except that N-methylhydroxylamine hydrochloride instead of semicarbazide hydrochloride was used in the synthesis.

116: White solid, mp 148-153 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.53; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H), 7.40-7.10 (m, 10H), 6.70 (d, 1H), 5.25 (d, 1H), 4.95 (m, 1H), 4.50 (dd, 2H), 4.05 (m, 1H), 3.80 (dd, 1H), 3.65 (s, 3H), 3.60 (m, 1H), 3.20 (dd, 1H), 3.10 (dd, 1H), 2.90 (s, 3H).

Example 99

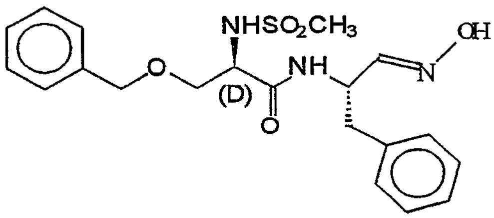
Synthesis of Compound 117



This compound was generated following the same synthetic protocol, as described above, for the synthesis of Compound **115** , except that N-benzylhydroxylamine hydrochloride instead of semicarbazide hydrochloride was used in the synthesis.

117: White solid, mp 154-156 °C; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.56; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H), 7.40-7.20 (m, 13H), 7.00 (m, 2H), 6.65 (d, 1H), 5.30 (d, 1H), 4.95 (m, 1H), 4.80 (s, 2H), 4.50 (s, 2H), 4.00 (m, 1H), 3.80 (dd,1H), 3.60 (dd, 1H), 3.15 (dd, 1H), 3.00 (dd, 1H), 2.90 (s, 3H).

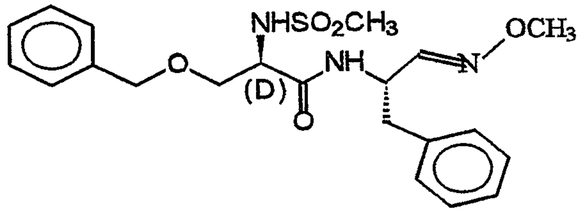
Example 100
Synthesis of Compound 118



This compound was synthesized by coupling Compound **40** and hydroxylamine hydrochloride, in the presence of pyridine and ethanol (without sodium acetate and water), following the general synthetic protocol for the synthesis of Compound **115**.

118: White foam; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.51; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 7.10 (t, 2H), 5.35 (d, 1H), 4.85 (m, 1H), 4,45 (dd, 2H), 4.05 (m, 1H), 3.85 (dd, 1H), 3.60 (dd, 1H), 3.00 (d, 2H), 2.85 (s, 3H), 1.55 (broad, 1H).

Example 101
Synthesis of Compound 119

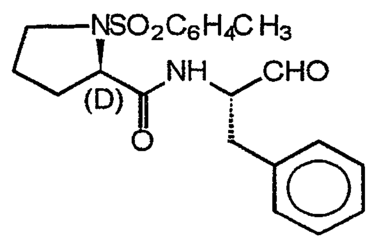


This compound was synthesized by coupling Compound **40** and methoxylamine hydrochloride, in the presence of pyridine and ethanol (without sodium acetate and water), following the general synthetic protocol for the synthesis of Compound **115**.

119: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.86; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 12H), 5.20 (2 sets of d, 1H), 4.85 (m, 1H), 4.45 (q, 2H), 4.00 (m, 1H), 3.90 and 3.75 (2 singlets, 3H), 3.80 (m, 1H), 3.60 (m, 1H), 3.00 (d, 2H), 2.85 and 2.80 (2 singlets, 3H).

Example 102

Synthesis of Compound 120

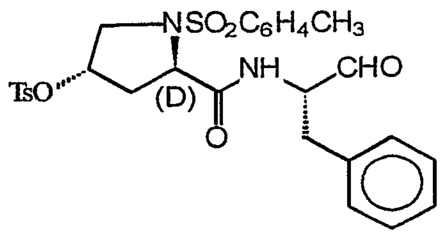


This compound was synthesized following Scheme 8, as described above, except that (D)-Pro and p-toluenesulfonyl chloride, instead of (D)-Phe and methanesulfonyl chloride, were used in the first step.

120: White solid; mp 55-60 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.42; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.70 (d, 2H), 7.30 (m, 7H), 4.65 (q, 1H), 4.10 (dd, 1H), 3.45 (m, 1H), 3.15 (m, 4H), 2.40 (s, 3H), 2.05 (m, 1H), 1.80-1.50 (m, 3H).

Example 103

Synthesis of Compound 121

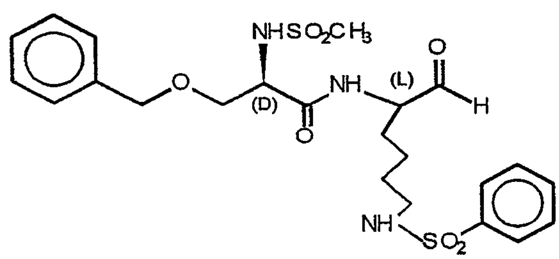


This compound was synthesized following Scheme 8, as described above, except that cis-4-hydroxy-(D)-proline instead of (D)-Phe was used in the first step, and both NH and OH groups were sulfonylated with p-toluenesulfonyl chloride.

121: White solid; mp 160-165 °C (softening to melt); R_f (EtOAc : CH_2Cl_2 2 :1): 0.65; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.65 (t, 4H), 7.45-7.20 (m, 10H), 4.85 (m, 1H), 4.50 (q, 1H), 4.20 (d, 1H), 3.65 (d, 1H), 3.30 (dd, 1H), 3.10 (d, 2H), 2.45 and 2.40 (2 singlets, 6H), 1.65 (m, 2H).

Example 104

Synthesis of Compound 122

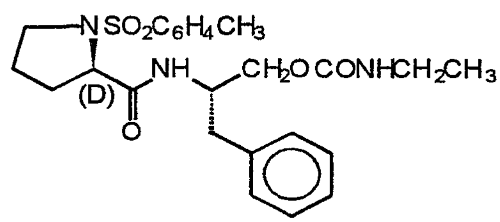


The synthesis of this compound was initiated by coupling (EDCI, HOBt, DMF) methanesulfonyl-(D)-Ser(Bzl) and (L)-Lys(Boc)-OMe hydrochloride salt; NHBoc was converted (90% TFA, CH_2Cl_2) to free NH_2 which, in turn, was converted to $NHSO_2Ph$ ($PhSO_2Cl$, NMM, THF- CH_2Cl_2). Finally, the COOMe group was converted to CHO, following the procedure described in Scheme 7. The final product showed that some racemization had occurred.

122: White solid; mp 50-55 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.41; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 and 9.50 (2 singlets, 1:9, 1H), 7.85 (d, 2H), 7.55 (m, 3H), 7.30 (m, 5H), 5.60 (d, 1H), 4.90 (broad t, 1H), 4.50 (m, 4H), 4.20 (m, 1H), 3.90 (dd, 1H), 3.80 (dd, 1H), 3.00 and 2.95 (2 singlets, 9:1, 3H), 2.85 (m, 2H), 1.95-1.30 (m, 6H).

Example 105

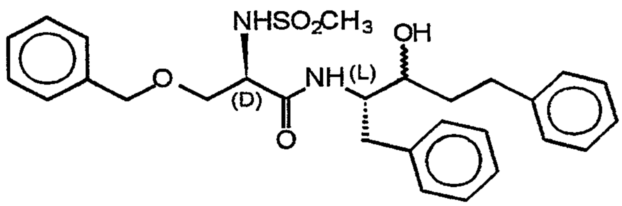
Synthesis of Compound 123



The synthesis of this compound was initiated following Scheme 8, as described above, except that (D)-Pro and p-toluenesulfonyl chloride, instead of (D)-Phe and methanesulfonyl chloride, were used in the first step. The intermediate dipeptide alcohol was treated with ethyl isocyanate in the presence of triethylamine to generate the final product.

123: White solid; mp 45-55 °C (softening to melt); R_f (EtOAc : CH_2Cl_2 2 :1): 0.57; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 2H), 7.30 (m, 7H), 4.85 (broad, 1H), 4.30 (m, 1H), 4.10 (m, 3H), 3.50 (m, 1H), 3.25 (m, 2H), 3.15 (m, 1H), 3.00 (dd, 1H), 2.85 (dd, 1H), 2.45 (s, 3H), 2.10 (m, 1H), 1.80-1.40 (m, 4H), 1.15 (t, 3H).

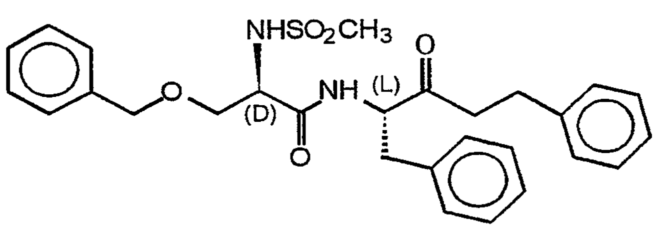
Example 106
Synthesis of Compound 124



This compound was synthesized by coupling (EDCI, HOBt, DMF) methanesulfonyl-(D)-Ser(Bzl) and 4-(S)-amino-3-(R,S)-hydroxy-1,5-biphenylpentane (prepared by coupling Boc-Phe-H and benzylmagnesium chloride, followed by deprotection of the Boc group).

124: White solid; mp 108-110 °C; R_f (90% CH_2Cl_2-10%EtOAc): 0.27; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.05 (m, 15H), 6.90 (d, 1H), 5.25 (d, 1H), 4.50 (q, 2H), 4.20 (q, 1H), 4.00 (q, 1H), 3.80 (dd, 1H), 3.65 (m, 1H), 3.50 (m, 2H), 2.85 (m, 4H), 2.65 (q, 2H), 2.00 (d, 1H), 1.70 (q, 2H).

Example 107
Synthesis of Compound 125

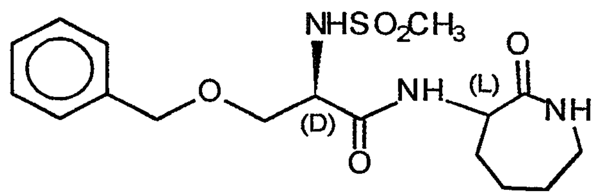


This compound was synthesized by Dess-Martin oxidation of Compound **124** prepared in Example 106.

125: White solid; mp 112-113 °C; R_f (90% CH_2Cl_2-10% EtOAc): 0.42; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 14H), 7.00 (m, 2H), 5.30 (d, 1H), 4.75 (q, 1H), 4.45 (q, 2H), 4.00 (q, 1H), 3.80 (dd, 1H), 3.55 (dd, 1H), 3.05 (dd, 1H), 3.00-2.75 (m, 3H), 2.80 (s, 3H), 2.75 (m 2H).

Example 108

Synthesis of Compound 126

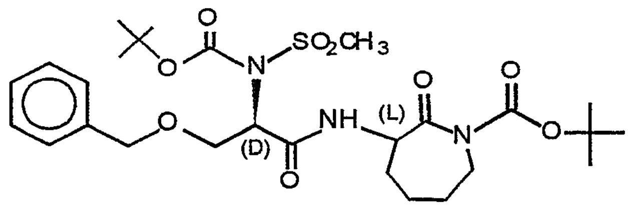


This compound was synthesized by coupling (EDCI, HOBt, DMF) methanesulfonyl-(D)-Ser(Bzl) and (L)-α-amino-ε-caprolactam.

126: White solid; mp 45-50 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.55; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H), 7.30 9m, 5H), 6.35 (broad t, 1H), 5.80 (d, 1H), 4.55 (m, 3H), 4.25 (m, 1H), 3.80 (dd, 1H), 3.70 (dd, 1H), 3.20 (m, 2H), 3.00 (s, 3H), 2.00 (m, 2H), 1.80 (m, 2H), 1.40 (m, 2H).

Example 109

Synthesis of Compound 127

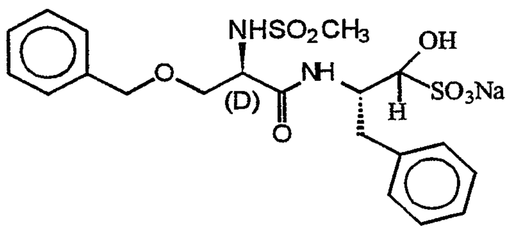


This compound was synthesized by treatment of Compound 126 prepared in Example 108 with Boc_2O in the presence of Et_3N and 4-dimethylaminopyridine, following the procedure of Grieco et al. *J. Org. Chem.* **1983**, *48*, 2426.

127: White solid; mp 55-60 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.90; ^1H-NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1H), 7.50-7.20 (m, 5H), 5.05 (q, 1H), 4.70 (m, 2H), 4.30 (m, 2H), 3.75 (q, 1H), 3.40 (s, 3H), 3.30 (m, 2H), 2.05-1.40 (a series of m, 6H), 1.55 (s, 9H), 1.45 (s, 9H).

Example 110

Synthesis of Compound 128

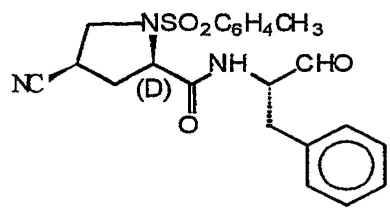


This compound was synthesized by reaction of Compound **40** with sodium bisulfite in a biphasic system of methylene chloride and water.

128: White solid (hygroscopic); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25 and 7.85 (2 sets of d, 1H), 7.40-7.00 (m, 10H), 5.75 and 5.60 (2 sets of d, 1H), 4.50-4.20 (m, 4H), 4.00 (m, 2H), 3.80 (m, 1H), 3.50-3.20 (m, 3H), 2.80 and 2.75 (2 singlets, 3H). Anal. calcd. for $C_{20}H_{25}N_2O_8S_2Na \cdot 0.3NaHSO_3$: C, 44.51; H, 4.67, N, 5.19. Found: C, 44.62; H, 4.75; N, 5.20.

Example 111

Synthesis of Compound 129

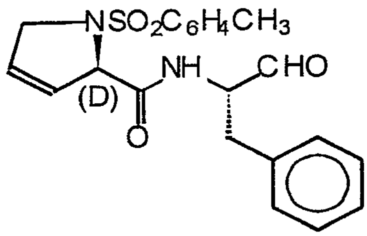


This compound was synthesized following the procedures of Scheme 8, as described above, except that cis-4-hydroxy-(D)-proline instead of (D)-Phe was used in the first step and both NH and OH groups were sulfonylated with p-toluenesulfonyl chloride. The disulfonylated derivative was coupled with (S)-phenylalaninol and the OTs group in the dipeptide intermediate was displaced in an S_N2 fashion by the cyano group (KCN, DMSO, 65 °C, overnight). Finally, oxidation of the alcohol moiety generated the target aldehyde, Compound **129**.

129: White solid; mp 65-75 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.44; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.70 (d, 2H), 7.40-7.15 (m, 8H), 4.70 (q, 1H), 4.20 (d, 1H), 3.75 (dd, 1H), 3.30-3.10 (m, 3H), 3.00 (m, 1H), 2.55 (dd, 1H), 2.45 (s, 3H), 1.70 (m, 1H).

Example 112

Synthesis of Compound 130

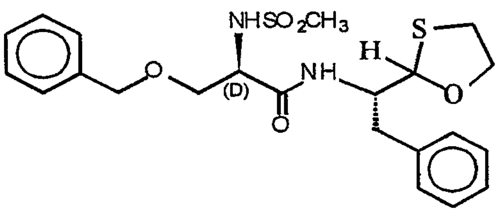


The precursor alcohol for this aldehyde was isolated as a minor product from the cyanation step Example 111. Subsequent Dess-Martin oxidation of the alcohol generated the target aldehyde, Compound **130**.

130: White solid; mp 55-65 °C (softening to melt); R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.52; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.70 (d, 2H), 7.40-7.20 (m, 8H), 5.70 (m, 2H), 4.85 (m, 1H), 4.60 (q, 1H), 4.15 (m, 2H), 3.20 (m, 2H), 2.45 (s, 3H).

Example 113

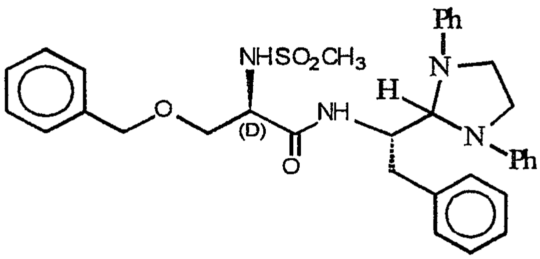
Synthesis of Compound 131



This compound was synthesized by coupling Compound **40** with 2-mercaptoethanol in the presence of $ZnCl_2$ and Na_2SO_4 in THF-Et_2O.

131: White gum; R_f (90% CH_2Cl_2-9% CH_3OH-1% conc. NH_4OH): 0.31; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 5.60 (d, 1H), 4.60 (m, 1H), 4.50 (q, 2H), 4.15 (d, 1H), 4.00 (broad d, 1H), 3.80 (m, 2H), 3.70 (t, 2H), 3.50 (dd, 1H), 3.20 (dd, 1H), 3.00-2.70 (m, 4H), 2.85 (s, 3H).

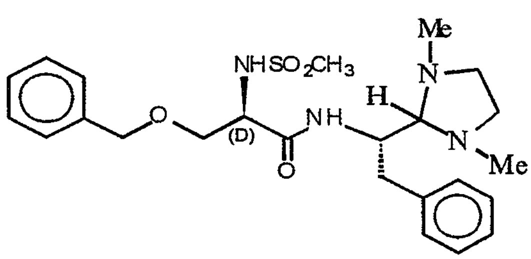
Example 114
Synthesis of Compound 132



This compound was synthesized by coupling Compound **40** with 1,2-dianilinoethane.

132: White solid; mp 138-140 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 and 6.90-6.70 (2 sets of m, 21H), 5.75 (d, 1H), 4.75 (d, 2H), 4.30 (s, 2H), 3.90 (q, 1H), 3.75 (m, 3H), 3.45 (m, 2H), 3.35 (dd, 1H), 3.05 (dd, 1H), 2.70 (s, 3H), 2.50 (t, 1H).

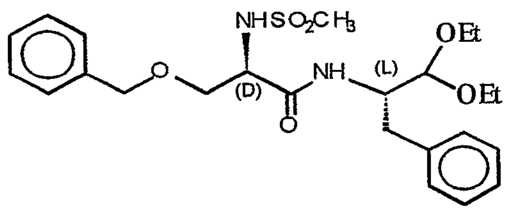
Example 115
Synthesis of Compound 133



This compound was synthesized by coupling Compound 40 with N, N'-dimethylethylenediamine.

133: White gum; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 5.25-4.90 (broad, 3H), 4.30 (q, 1H), 4.00 (t, 1H), 3.75 (dd, 1H), 3.50 (m, 4H), 3.10-2.70 (m, 5H), 2.85 (s, 3H), 2.50 (d, 6H).

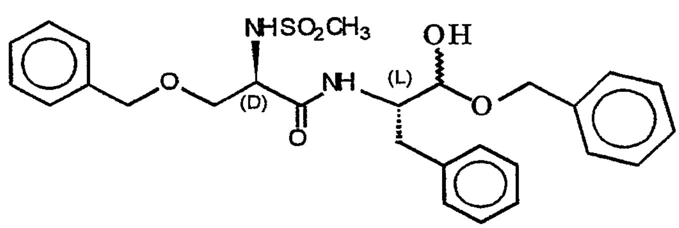
Example 116
Synthesis of Compound 134



This compound was synthesized by coupling methanesulfonyl-(D)-Ser(Bzl) and Phe-H diethyl acetal; the final product showed that some racemization had occurred.

134: White gum; R_f (EtOAc-hexane: 1:1): 0.30; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.00 (m, 11H), 6.80 (d, 1H), 5.15 (t, 1H), 4.50-4.25 (m, 4H), 3.90 (m, 1H), 3.70-3.30 (m, 5H), 2.90 (m, 1H), 2.80 and 2.70 (2 singlets, 3H), 2.65 (m, 1H), 1.10 (m, 6H).

Example 117
Synthesis of Compound 135



This compound was synthesized by stirring overnight at room temperature Compound **40** with excess benzyl alcohol. Excess alcohol was removed by repeated washing with hexane, and the residue was triturated with EtOAc-hexane to give Compound **135** as a solid material, mp 87-89°C, which was immediately subjected to biological testing. ^{1}H-NMR (300MHz, DMSO-d_6) spectrum of an aliquot showed the absence of aldehyde moiety in the molecule.

Example 118
Inhibition and Rate of Inactivation of Cysteine Protease Activity

To evaluate inhibitory activity, stock solutions (40 times concentrated) of exemplary compounds of the invention were prepared in 100% anhydrous DMSO and 5 µL of each inhibitor preparation were aliquoted into each of three wells of a 96-well plate. Recombinant human calpain I, prepared by the method of Meyer et al. (*Biochem. J.* **314**: 511-519 (1996)), was diluted into assay buffer (i.e., 50mM Tris, 50mM NaCl, 1mM EDTA, 1mM EGTA, and 5mM-mercaptoethanol, pH 7.5 including 0.2mM Succ-Leu-Tyr-MNA) and 175 µL aliquoted into the same wells containing the independent inhibitor stocks as well as to positive control wells containing 5 µL DMSO, but no compound. To start the reaction, 20 µL of 50 mM $CaCl_2$ in assay buffer was added to all wells of the plate, excepting three, which were used as background signal baseline controls. Substrate hydrolysis was monitored every 5 minutes for a total of 30 minutes. Substrate hydrolysis in the absence of inhibitor was linear for up to 15 minutes.

Inhibition of calpain I activity was calculated as the percent decrease in the rate of substrate hydrolysis in the presence of inhibitor (V_I) relative to the rate in its absence (V_o). Comparison between V_o and V_I was made within the linear range for substrate hydrolysis. For screening, compounds were tested at 10, 1.0, and 0.1 µM. Compounds having 50% inhibition at 10 µM were considered active. The IC50s of inhibitors (concentration yielding 50% inhibition) were determined from the percent decrease in the rates of substrate hydrolysis in the presence of five to seven different concentrations of the test compound. The results were plotted as % inhibition versus log inhibitor concentration and the IC50 was calculated from linear regression of the data. Apparent second order rate constants were determined from analysis of reaction progress curves under pseudo-first order conditions. Each determination represents the means of three or more independent single cuvette analyses continually monitored via a Perkin-Elmer LS50B spectrofluorimeter. The rate of inhibition of hydrolysis was obtained by fitting the curve to the exponential equation (1):

$$y = Ae^{-(Kobs \cdot t)} + B \qquad (1)$$

where y is the product formed at time t. K_{obs} is the pseudo-first order rate constant for inactivation. A and B are constants. A, the amplitude of the reaction, is given by $[P_o-P_\infty]$ and B (= P_∞) is the maximal product formed when the reaction is complete. The apparent second order rate constant k_{app} was determined as $K_{obs}/[I]$. This was corrected for the presence of substrate to give the second order rate constant k_2 according to equation (2):

$$k_2 = k_{app} (1 + [S] / K_m) \qquad (2)$$

To demonstrate activity against two other cysteine proteases, cathepsin B (Calbiochem, catalog # 219364) and cathepsin L (Calbiochem, catalog # 219402), assays were performed substantially the same as outlined above except that the cathepsin B and cathepsin L were diluted into a different assay buffer consisting of 50mM sodium acetate (pH 6.0)/1mM EDTA/1mM dithiothreitol and the substrate used was Cbz-Phe-Arg-AMC (Bachem catalog # I-1160; 0.1mM for cathepsin B; 0.006mM for cathepsin L). Additionally, the order of reagents added to the plate was altered because both enzymes are constitutively active. Following inhibitor addition to the plates, appropriate 2x concentrated stock dilutions of the enzyme preparations were made in assay buffer and 100µl added to each well. The assay was initiated by addition of 100ul of 2x concentrated stock dilution of substrate in assay buffer. Substrate hydrolysis was monitored using a Fluoroskan II (ex=390 nm; em=460 nm). Results are presented in Tables II and III.

Example 119
Inhibition of Serine Protease Activity

To demonstrate activity against the serine protease α-chymotrypsin (Sigma Chem. Co. catalog # C-3142) the protocol of Example 118 was followed except that the enzyme was diluted into assay buffer consisting of 50mM Hepes (pH 7.5)/0.5M NaCl and the final substrate concentration used was 0.03mM Succ-Ala-Ala-Pro-Phe-AMC (Bachem catalog #I-1465). Additionally, because α-chymotrypsin is not a calcium sensitive enzyme and is constitutively active, following addition of inhibitor stocks to the 96 well plates, 100µl of a 2-fold concentrated stock of enzyme in dilution buffer was first added and the reaction started by addition of 100µl of a 2-fold concentrated stock of substrate in assay buffer. Substrate hydrolysis was monitored every 5 minutes up to 30 minutes using a Fluoroskan II (em=390nm ex=460nm). Results, expressed as inhibition of α-chymotrypsin at 10 µM, are presented in Tables II and III.

Inhibition of thrombin (Sigma Chem. Co. catalog # T-7009) was evaluated as described for chymotrypsin except that the assay was performed in 50 mM Tris, 10 mM $CaCl_2$, pH 7.5 and the substrate was 25 µM Bz-Phe-Val-Arg-AMC (Bachem catalog # I-1080). Results are presented in Tables II and III.

Table II

Cpd	Chemical Name	Calpain IC50 (nM)	Calpain Inacti-vation Rates (M^{-1}/S^{-1})	Cat B IC50 (nM)	Cat L IC50 (nM)	Thrombin % I @ 10 uM	Chymotrypsin % I @ 10 uM
8	(R)-2-THIQ-C(=O)CH_2CH(NHBoc)C(=O)-Phe-H	≈20,000	--		24,000	0	32
9	2-THIQ-C(=O)CH_2CH(NHC(=O)CH_3)C(=O)-Phe-H	83	--	11,000	2,000	0	2
25	BnS-CH_2CH(NHC(=O)CH_3)C(=O)-Phe-H	26	--	5,000	48	0	3
14	2-THIQ-C(=O)CH_2CH(NHS(=O)$_2CH_3$)C(=O)-Phe-H	20	--	145	56	0	11
33	BnS-CH_2CH(NHS(=O)$_2CH_3$)C(=O)-Phe-CH_2F	--	26,600			0	14
20	THIQ-2-C(=O)CH_2CH(NHS(=O)$_2CH_3$)C(=O)-Phe-CH_2F	--	2,800		1,800	0	7
34	BnO-CH_2CH(NHS(=O)$_2CH_3$)C(=O)-Phe-CH_2F	--	21,000		1,800	0	14
40	BnO-CH_2CH(NHS(=O)$_2CH_3$)C(=O)-Phe-H	11		42	9	0	23

Table III

Cpd.	Cal-pain % I @ 0.1 uM	Cal-pain IC50 (nM)	Cat B % I @ 1 uM	Cat B IC50 (nM)	Cat L %I @ 1 uM	Throm-bin % I @ 10 uM	Chymo-trypsin % I @ 10 uM
41	67	50	42		100	2	0
42	87	17	90		96	7	14
43	95	12	98	58	68	0	3
44	29	280	62		100	7	0
45	55	85	100		100	7	5
46	90	24	100		100	15	6
47	91	9	96		98	6	2
48	87	31	99	11	100	3	0
49	75	27	99		100	4	1
50	95	12	99		98	9	15
51	92	32	100	14	100	21	3
52	93	28	100	4	100	10	0
53	25	72	98		100	0	0
54	95	13	100		100	4	3
55	87	25	90		100	2	12
59	86	20	100	5	100	0	4
60	74	33	97		100	0	0
61	83	22	100		100	0	0
62	71	39	85		89	0	4
63	41	75			100	1	40
64	68		87		100	0	10
70	85	16	90		100	0	12
71	92	31	100		100	11	5
72	91	14	100		100	13	7
73	95	14	100		100	12	16
74	83	33	100		100	6	13
75	91	20	100		99	10	2
76	88	13	79	250	90	1	30

77	91	14	90		93	0	0
78	94	12	100	6	100	0	0
79	47	1000	99		93	1	8
80	90	15	99	46	100	4	8
81	18	180	73		100	0	2
82	4		60		93	6	8
83	37	520	62		53	7	0
84	2		22		93	0	0
85	44	110	44		89	0	6
86	72	40	78		100	0	8
87	23	95	86		96		
88	40	93	88		91	5	0
89	82	15	100		97	0	4
90	99	5	100		99	0	0
91	30		68		100	0	53
92	100	4	100		100	0	0
93	95	9	99		100	0	0
94	14		0		93	0	1
95	17	278	38		100	1	0
96	49	174	90		100	0	14
97	79	37	89		100	4	25
98	96	8	98	16	100	16	49
99	66	62	96		100	0	13
100	96	15	97	31	100	0	0
101	84	53	46		100	0	2
102	63	72	69		73	7	0
103	37	71	40		56	3	26
104	45	93	86		97	7	6
105	9		45		71	0	10
106	95	8	92		100	7	16
107	63	67	97		100	2	11
108	83	25	96		100	0	0

109	59	40	70		98	0	0
110	10		12		83	0	0
111	27		10		91	0	16
112	7		25		100	0	9
113	11		47		94	0	0
114	85	28	24		100	3	9
115	0		47		94	0	0
116	4		96		100	0	0
117	21		95		100	0	0
118	31		33		99	0	8
119	19		68		98	0	3
128	89	8	99		100	0	1
120	87	14	50		65	0	12
121	28		83		17	3	18
122	98	3	100		100	0	13
123	7		16		14	0	2
124	20		27		17	2	0
125	0		47		39	4	0
126	5		2		16	0	6
127	6		36		7	0	1
129	73	28	64		100	1	6
130	90	10	62		97	9	0
131	6		21		55	11	0
132	63		78		100	0	0
133	93	13	100		100	0	1
134	0		19		98	0	10
135	91	11	98		100	0	4

Example 120

Suppression by Compound 40 of Spectrin Breakdown in Gerbil Global Ischemia Model

Gerbils were anesthetized using 4% isolflurane volatilized using a gas mixture consisting of 30% O_2 and 70% N_2. After the induction of anesthesia, a preferred compound of the invention, compound **40** (Example 34), was administered either immediately before the induction of ischemia or three hours after the initiation of reperfusion. To induce ischemia, the common carotid arteries were exposed and occluded bilaterally for 7 minutes. Gerbil core temperature was carefully regulated at 38°C by a thermostatically controlled heat lamp. Reperfusion was initiated by the release of the arterial occlusion, whereupon anesthesia was terminated so that the gerbils began to breath room air. The neck incision was closed, and the gerbils were returned to the incubator for one hour to maintain their core temperature. At 1 hour of reperfusion, anesthesia was induced by inhalation of CO_2 and the gerbils were sacrificed. The CA1 hippocampal sector was dissected using a hole punch (0.3 mm), and spectrin breakdown products (BDP) were determined by Western Blotting. Spectrin breakdown was quantified by image analysis, and percent inhibition was calculated by integrated optical density. Calpain activation and elevated levels of spectrin breakdown products have been associated with several neurodegenerative conditions including those caused by ischemia. Detection of calpain activation by detection of calpain activated spectrin breakdown is described in detail in U.S. Patent 5,536,639, the disclosures of which are hereby incorporated by reference in their entirety.

To quantify histopathological damage, the gerbils were returned to their home cages after one hour reperfusion in the incubator and then sacrificed, as described above, four days later. The brains were rapidly removed, frozen on dry ice, and then sectioned using a cryostat. Twenty micron sections were stained with thionin, and surviving neurons in the hippocampal CA1 sector were counted using computer assisted image analysis.

In order to facilitate solvation and administration, Compound **40** was formulated for use as an emulsion. The emulsion was prepared by mixing 1,2-dimyristoyl-sn-glycero-3-phosphocholine (Sygena, Inc., Cambribge, Mass.), cholesterol (Genzyme Corp., Cambribge, Mass.), and Compound **40** in a ratio of 4:2:1 parts by weight. Chloroform (1 ml) and ethanol (0.5 ml) were added, and the contents were mixed until all solutes were dissolved in the organic phase. Volatile solvents were then evaporated with a stream of nitrogen. Phosphate buffered saline (50°C) was added to the residual mixture in an amount to give a concentration of compound **40** of 6 mg/ml. The components of the residue were mixed using a Pasteur pipet to give a coarse emulsion, and a fine emulsion was obtained using a high pressure emulsifier.

Analysis of spectrin breakdown in the CA1 hippocampal sectors of vehicle-treated control gerbils and gerbils treated with Compound **40** showed a statistically significant suppression of spectrin breakdown in gerbils treated with Compound **40** ($p<.0001$; Figure 1).

Figure 2 shows with statistical significance ($p<.01$) that Compound **40** was neuroprotective at four days after the ischemic insult, a time when most of the hippocampal CA1 neurons had degenerated in vehicle-treated gerbils. Intact hippocampal CA1 neurons were counted and expressed as a percent of the number of intact neurons found at that level of the dorsal hippocampus in control gerbils.

Figure 3 shows with statistical significance ($p<.02$) the neuroprotective effect of Compound **40** when administered 3 hours after ischemia.

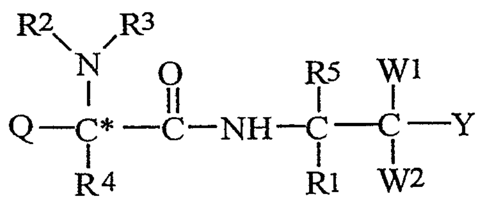
As shown in Figure 1, compound **40** reduced spectrin breakdown by approximately 50%. Compound **40** also more than doubled the number of surviving hippocampal CA1 neurons relative to controls, as shown in Figure 2.

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



wherein:

C* denotes a carbon atom having a D-configuration;

Q has the formula G-B-$(CHR^{20})_q$- where R^{20} is independently H or alkyl having from 1 to 4 carbons;

q is 0, 1, or 2;

B is selected from the group consisting of C(=O), S(=O), $S(=O)_2$, S, CH_2, a bond, NH and O;

G is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, arylsulfonyl, alkylsulfonyl, aralkyloxy having from about 7 to about 15 carbons, amino, and a carbohydrate moiety optionally containing one or more alkylated hydroxyl groups, said aryl, heteroaryl, aralkyl, alkyl and amino groups being optionally substituted with one or more K groups;

K is selected from the group consisting of halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy, and amino, said amino group being optionally substituted with an acyl group or with 1 to 3 aryl or lower alkyl groups;

R^1 is selected from the group consisting of H, alkyl having from one to about 14 carbons, cycloalkyl having from 3 to about 10 carbons, aralkyl having from about 7 to about

15 carbons, heteroarylalkyl in which the heteroaryl ring contains from about 5 to about 14 ring atoms, a natural side chain of a D- or L-amino acid, and an unnatural side chain of a D- or L-amino acid, said alkyl, cycloalkyl, aralkyl, and heteroarylalkyl groups being optionally substituted with one or more K groups;

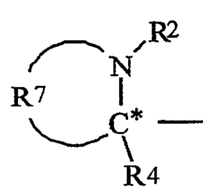
R^2 is selected from the group consisting of $C(=O)R^6$, $S(=O)_2R^6$, and a protecting group;

R^6 is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, said aryl, heteroaryl, aralkyl and alkyl groups being optionally substituted with one or more K groups, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, and amino optionally substituted with 1 or more alkyl groups;

R^3 is selected from the group consisting of H, lower alkyl, aralkyl, and a group of formula $-CO_2-R^{21}$ where R^{21} is a lower alkyl group;

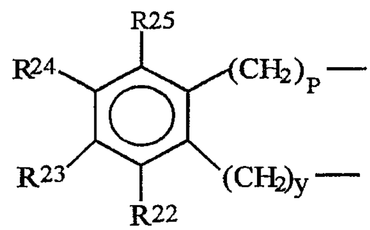
or R^3 may be taken together with R^2 to form a phthalimido group;

or Q and R^3 taken together with -C* and $-N(R^2)-$ may form a group of formula:



where R^7 is alkylene having from 2 to 5 carbons, said alkylene group optionally containing a carbon-carbon double bond, said alkylene group being optionally substituted with a group selected from the group consisting of aryl, azide, CN, a protected amino group, and OSO_2-aryl, wherein said aryl group is optionally substituted with one or more K groups, said aryl portion of said OSO_2-aryl group being optionally substituted with one or more K groups;

or R^7 may have the formula:



where p and y are independently 0 or 1, and R^{22}, R^{23}, R^{24}, and R^{25} are indepenedently H or a K group;

R^4 and R^5 are each independently selected from the group consisting of H and lower alkyl;

W^1 and W^2 are selected such that W^1 is H and W^2 is OC(=O)NH-R^{26} where R^{26} is alkyl, or W^1 and W^2 are both alkoxy, or W^1 is OH and W^2 is selected from the group consisting of aralkyl, aralkyloxy, aryloxy, heteroaryloxy, heteroaralkyloxy, and SO_3Z^1 where Z^1 is a Group I or Group II counterion; or

W^1 and W^2 taken together may form a group selected from the group consisting of =O, =NR^8, =N(→O)R^9, -$S(CH_2)_2O$-, and -N(R^{12})$(CH_2)_2$N(R^{12})-;

R^8 is selected from the group consisting of NH(C=O)NH_2, hydroxyl, and lower alkoxy;

R^9 is selected from the group consisting of alkyl and aralkyl;

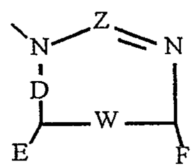
R^{12} is selected from the group consisting of alkyl having from 1 to 4 carbons, and phenyl;

Y is selected from the group consisting of H, C(=O)$NR^{10}R^{11}$, C(=O)OR^{10}, CH=N_2, and CH_2R^{13}; or

Y and R^1 taken together may form -$(CH_2)_4$N(Pr)- where Pr is H or a protecting group, provided that when Y and R^1 are taken together to form -$(CH_2)_4$N(Pr)-, then W^1 and W^2 are taken together to form =O;

R^{10} and R^{11} are each independently selected from the group consisting of H, alkyl having from 1 to about 10 carbons, said alkyl groups being optionally substituted with one or more K groups, aryl having from about 6 to about 14 carbons, and aralkyl having from about 7 to about 15 carbons;

R^{13} is selected from the group consisting of L, lower alkyl, aralkyl, halogen, and a group O-M, wherein M has the structure:



wherein:

Z is selected from the group consisting of N and CR^{14};

W is selected from the group consisting of a double bond and a single bond;

D is selected from the group consisting of C=O and a single bond;

E and F are independently selected from the group consisting of R^{14}, R^{15}, and J;

or E and F taken together comprise a joined moiety, said joined moiety being selected from the group consisting of an aliphatic carbocyclic ring having from 5 to 7 carbons, an aromatic carbocyclic ring having from 5 to 7 carbons, an aliphatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, and an aromatic heterocyclic ring having from 5 to 7 atoms and containing from 1 to 4 heteroatoms, said aliphatic carbocyclic ring, aromatic carbocyclic ring, aliphatic heterocyclic ring, and aromatic heterocyclic ring each being optionally substituted with J;

R^{14} and R^{15} are independently selected from the group consisting of H, alkyl having from 1 to 10 carbons, heteroaryl having from 1 to 10 carbons, alkanoyl having from

1 to 10 carbons, and aroyl, wherein said alkyl, heteroaryl, alkanoyl and aroyl groups are optionally substituted with J;

J is selected from the group consisting of halogen, $C(=O)OR^{16}$, $R^{16}OC(=O)$, $R^{16}OC(=O)NH$, OH, CN, NO_2, $NR^{16}R^{17}$, $N=C(R^{16})R^{17}$, $N=C(NR^{16}R^{17})_2$, SR^{16}, OR^{16}, phenyl, napththyl, heteroaryl, and a cycloalkyl group having from 3 to 8 carbons;

R^{16} and R^{17} are independently H, alkyl having from 1 to 10 carbons, aryl, or heteroaryl, wherein said alkyl, aryl and heteroaryl groups are optionally substituted with K; and

L is a phosphorus-containing enzyme reactive group.

2. The compound of claim 1 wherein:

R^1 is selected from the group consisting of benzyl, p-benzyloxybenzyl, $-(CH_2)_4-NHC(=O)-O-CH_2-C_6H_5$, $-(CH_2)_4-NHC(=O)-O-t-C_4H_9$, and $-(CH_2)_4-NHSO_2-C_6H_5$;

R_3, R_4, and R_5 are each H;

W^1 and W^2 together form $-C(=O)-$;

Y is H or CH_2F;

B is CO, O, S, SO_2 or a bond;

R^2 is $-C(=O)CH_3$, or $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl, dimethylamino, ethyl, 2-thienyl, 2-isoxazolyl, phenyl, *p*-methylphenyl, 4-N-methylimidazolyl, or 2-naphthyl;

G is tetrahydroisoquinolinyl, benzyl, 3-indolyl, phenyl, N-methylbenzylamino, p-benzyloxyphenyl, or 2-thienyl;

or Q and R^3 together form $-(CH_2)_3-$.

3. The compound of claim 1 wherein q is 0;B is a bond; G is benzyl or 2-thienyl; Y is H; R^1 is benzyl; and R^2 is $-S(=O)_2R^6$ wherein R^6 is methyl, phenyl, or 2-thienyl.

4. The compound of claim 1 wherein q is 1; G is tetrahydroisoquinolinyl, benzyl, 3-indolyl, phenyl, N-methylbenzylamino, p-benzyloxyphenyl; and R^2 is $-C(=O)CH_3$, or $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl,

dimethylamino, ethyl, 2-thienyl, 2-isoxazolyl, *p*-methylphenyl, 4-N-methylimidazolyl, or 2-naphthyl.

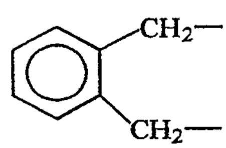
5. The compound of claim 4 wherein G is benzyl; and R^2 is $-C(=O)CH_3$, or $-S(=O)_2R^6$ wherein R^6 is methyl, p-fluorophenyl, dimethylamino, ethyl, 2-isoxazolyl, *p*-methylphenyl, 4-N-methylimidazolyl, or 2-naphthyl.

6. The compound of claim 5 wherein R^2 is $-S(=O)_2CH_3$.

7. The compound of claim 1 wherein q is 2; B is S; G is benzyl; Y is H; R^1 is benzyl; and R^2 is $-S(=O)_2CH_3$.

8. The compound of claim 1 wherein G is alkyl, benzyl, tetrahydroisoquinolyl, 3-indolyl, phenyl, N-methylbenzylamino, substituted benzyl, 2-thienyl or p-benzyloxyphenyl.

9. The compound of claim 1 wherein Q and R^3 taken together have a formula selected from the group consisting of $-(CH_2)_3-$, $-CH_2-CH(OSO_2C_6H_5)-CH_2-$, $-CH_2-CH(OSO_2C_6H_4CH_3)-CH_2-$, $-CH_2-CH(N_3)-CH_2-$, $-CH_2-CH(CN)-CH_2-$, $-CH_2-CH=CH-$, and



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10. The compound of claim 1 wherein B is selected from the group consisting of $-C(=O)-$, $-O-$, $-S-$, $-S(=O)_2-$, and a bond.

11. The compound of claim 1 wherein R^1 is selected from the group consisting of benzyl, substituted benzyl, a lysyl side chain, and a substituted lysyl side chain.

12. The compound of claim 1 wherein R^1 is selected from the group consisting of alkyl, benzyl, p-benzyloxybenzyl, 2-

pyridylmethyl, $-(CH_2)_4-NHC(=O)-O-CH_2-C_6H_5$, $-(CH_2)_4-NHC(=O)-O-t-C_4H_9$, and $-(CH_2)_4-NHSO_2-C_6H_5$.

13. The compound of claim 12 wherein said alkyl group is selected from the group consisting of ethyl, isobutyl, and *t*-butyl.

14. The compound of claim 1 wherein W^1 and W^2 are taken together to form -C(=O), and R^1 and Y together form $-(CH_2)_4-N(Pr)-$ where Pr is selected from the group consisting of H and *t*-butoxycarbonyl.

15. The compound of claim 1 wherein R^2 is selected from the group consisting of *t*-butyloxycarbonyl, $-S(=O)_2R^6$, and $-C(=O)CH_3$.

16. The compound of claim 15 wherein R^2 is-$S(=O)_2R^6$, said R^6 being selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

17. The compound of claim 16 wherein R^2 is selected from the group consisting of $-S(=O)_2CH_3$, $-S(=O)_2CH_2CH_3$, *p*-fluorophenylsulfonyl, 2-thienylsulfonyl, 2-isoxazolesulfonyl, phenylsulfonyl, *p*-methylphenylsulfonyl, 4-(N-methylimidazole)sulfonyl, and 2-naphthylsulfonyl.

18. The compound of claim 1 wherein Y is selected from the group consisting of H and CH_2F.

19. The compound of claim 1 wherein W^1 and W^2 taken together form -C(=O).

20. The compound of claim 1 wherein W^1 is OH and W^2 is SO_3Z^1 where Z^1 is Na.

21. The compound of claim 1 wherein W^1 is H and W^2 is OC(=O)NH-R^{26} where R^{26} is alkyl.

22. The compound of claim 1 wherein W^1 is OH and W^2 is aralkyl.

23. The compound of claim 1 wherein W^1 is OH and W^2 is aralkyloxy.

24. The compound of claim 1 wherein W^1 is OH and W^2 is aryloxy.

25. The compound of claim 1 wherein W^1 is OH and W^2 is heteroaryloxy.

26. The compound of claim 1 wherein W^1 is OH and W^2 is heteroaralkyloxy.

27. The compound of claim 1 wherein W^1 and W^2 are both alkoxy.

28. The compound of claim 1 wherein W^1 and W^2 taken together form a group selected from the group consiting of =NR^8, =N(→O)R^9, -S$(CH_2)_2$O-, and -N(R^{12})$(CH_2)_2$N(R^{12})-.

29. The compound of claim 11 wherein B is selected from the group consisting of -(C=O)-, -O-, a bond, SO_2, and -S-; Y is selected from the group consisting of H and CH_2F; R^1 is selected from the group consisting of benzyl, substituted benzyl, a lysyl side chain, and a substituted lysyl side chain; and R^2 is selected from the group consisting of *t*-butyloxycarbonyl, -C(=O)CH_3, and -S$(=O)_2R^6$.

30. The compound of claim 23 wherein R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

31. The compound of claim 1 wherein Q is benzyloxymethyl; R^1 is benzyl; R^2 is $-SO_2CH_3$; R_3, R_4, R_5 and Y are each H; and W^1 and W^2 together form -C(=O)-.

32. A composition for inhibiting a protease selected from the group consisting of serine proteases and cysteine proteases comprising a compound of claim 1.

33. A composition for inhibiting a protease selected from the group consisting of serine proteases and cysteine proteases comprising a compound of claim 1 in an enantiomerically enriched amount.

34. A composition of claim 33 wherein the enantiomerically enriched amount of the compound of claim 1 is an amount greater than about 75%.

35. A composition of claim 33 wherein the enantiomerically enriched amount of the compound of claim 1 is an amount greater than about 90%.

36. A composition of claim 33 wherein the enantiomerically enriched amount of the compound of claim 1 is about 100%.

37. A composition for inhibiting a protease selected from the group consisting of serine proteases and cysteine proteases consisting essentially of a compound of claim 1.

38. A method for inhibiting a protease comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory amount of a compound of claim 1.

39. A method for inhibiting a protease comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory

amount of a composition comprising a compound of claim 1 in an enantiomerically enriched amount.

40. A method of claim 38 wherein the enantiomerically enriched amount of the compound of claim 1 is an amount greater than about 75%.

41. A method of claim 38 wherein the enantiomerically enriched amount of the compound of claim 1 is an amount greater than about 90%.

42. A method of claim 38 wherein the enantiomerically enriched amount of the compound of claim 1 is about 100%.

43. A method for inhibiting a protease comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory amount of a composition consisting essentially of a compound of claim 1.

Figure 1

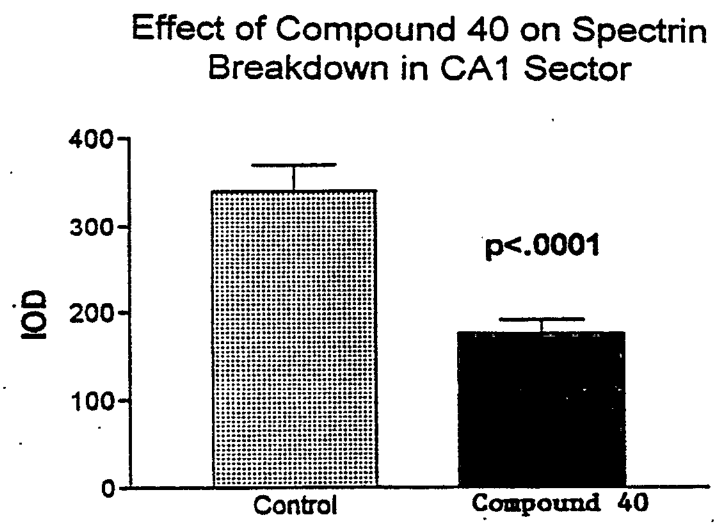


Figure 2

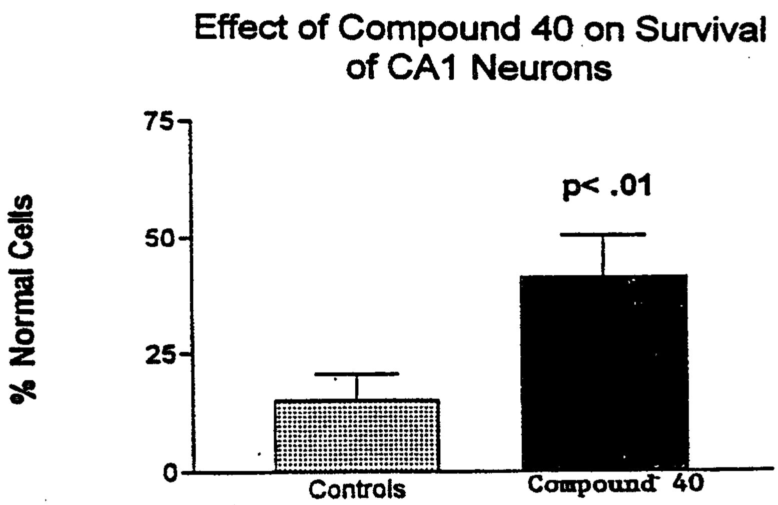
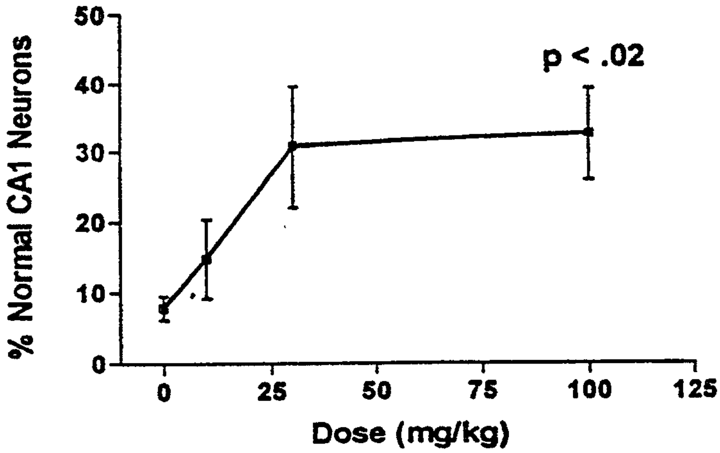


Figure 3


p < .02
% Normal CA1 Neurons
50
40
30
20
10
0
0
25
50
75
100
125
Dose (mg/kg)