ANTIPICORNAVIRAL COMPOUNDS, THEIR PREPARATION AND USE

CROSS-REFERENCE TO RELATED APPLICATION

This application is related to U.S. Provisional Application No. 60/083,828, filed April 30, 1998, in the name of Dragovich et al., the disclosure of which is incorporated by reference herein.

FIELD AND INDUSTRIAL APPLICABILITY OF THE INVENTION

The invention pertains to peptide-like and peptidomimetic compounds that advantageously inhibit the enzymatic activity of picornaviral 3C proteases, especially rhinovirus 3C proteases (RVPs), and that retard viral growth in cell culture. The invention also relates to the use of such compounds in pharmaceutical compositions and therapeutic treatments for rhinoviral infections. The invention further relates to processes for synthesizing such compounds and compounds useful in such syntheses.

BACKGROUND OF THE INVENTION

The picornaviruses are a family of tiny non-enveloped positive-stranded RNA-containing viruses that infect humans and other animals. These viruses include the human rhinoviruses, human polioviruses, human coxsackieviruses, human echoviruses, human and bovine enteroviruses, encephalomyocarditis viruses, meningitis virus, foot and mouth viruses, hepatitis A virus, and others. The human rhinoviruses are a major cause of the common cold. To date, there are no effective therapies on the market that cure the common cold, only treatments that relieve the symptoms.

Picornaviral infections may be treated by inhibiting the proteolytic 3C enzymes. These enzymes are required for the natural maturation of the picornaviruses. They are responsible for the autocatalytic cleavage of the genomic, large polyprotein into the essential viral proteins. Members of the 3C protease family are cysteine proteases, where the sulfhydryl group most often cleaves the glutamine-glycine amide bond. Inhibition of 3C proteases is believed to block proteolytic cleavage of the polyprotein, which in turn can retard the maturation and replication of the viruses by interfering with viral particle production. Therefore, inhibiting the processing of this cysteine protease with selective small molecules that are specifically recognized should represent an important and useful approach to treat and cure viral infections of this nature and, in particular, the common cold.

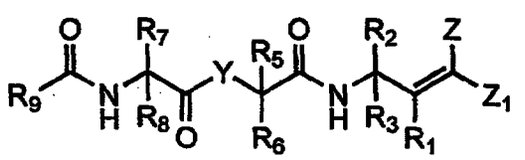
Some small-molecule inhibitors of the enzymatic activity of picornaviral 3C proteases (i.e., antipicornaviral compounds) have been recently discovered. See, for example: U.S. Patent Application No. 08/850,398, filed May 2, 1997, by Webber et al.; U.S. Patent Application No. 08/991,282, filed December 16, 1997, by Dragovich et al.; and U.S. Patent Application No. 08/991,739, filed December 16, 1997, by Webber et al. These U.S. patent applications, the disclosures of which are incorporated herein by reference, describe certain antipicornaviral compounds. There is still a desire to discover small-molecule compounds that are especially potent antipicornaviral agents.

SUMMARY OF THE INVENTION

Thus, an object of this invention is to discover small-molecule compounds that are especially potent antipicornaviral agents. A further object of the invention is to provide intermediates useful for the synthesis of said protease-inhibiting compounds and synthetic methods useful for such syntheses. A yet further object of the invention is to achieve pharmaceutical compositions that are highly effective for treating maladies mediated by inhibition of picornaviral 3C proteases, such as the common cold.

Such objects have been attained through the discovery of compounds of the invention, which are picornaviral 3C protease inhibitors displaying particularly strong antiviral activity. It has surprisingly been discovered that peptido and peptidomimetic compounds containing a five-membered heterocyclic group have high rhinoviral-protease-inhibiting activity. It has further been surprisingly found that the rhinoviral-protease-inhibiting activity of peptido and peptidomimetic compounds may be significantly enhanced by replacing a glutamine-like moiety found in some known rhinoviral-protease-inhibiting compounds with a side-chain comprising a gamma- or delta-lactam.

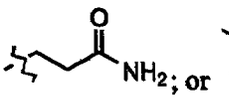
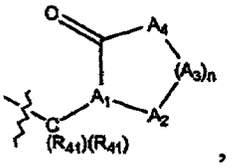
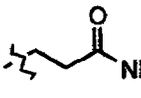
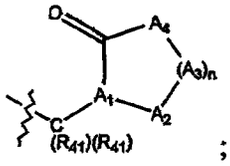
The inhibitors of the present invention are of the following general formula (I):



(I)

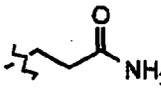
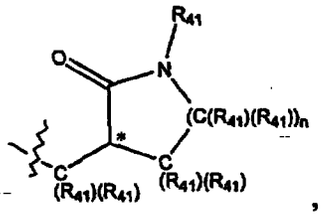
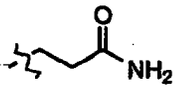
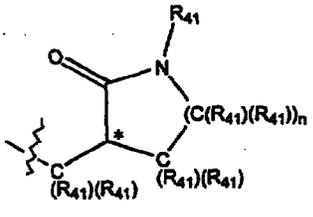
wherein:

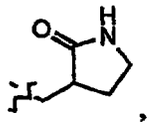
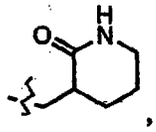
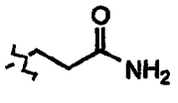
- Y is -N(R_y) -, -C(R_y)(R_y) -, or -O-, where each R_y is independently -H or lower alkyl;
- R_1 is -H, -F, -alkyl, -OH, -SH, or an O-alkyl group;

- R_2 and R_3 are each independently H;  ; or  , where n is an integer from 0 to 5, A_1 is CH or N, A_2 and each A_3 are independently selected from $C(R_{41})(R_{41})$, $N(R_{41})$, S, S(O), $S(O)_2$, and O, and A_4 is NH or NR_{41}, where each R_{41} is independently H or lower alkyl, provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, A_2, $(A_3)_n$, A_4 and C=O, and at least one of R_2 and R_3 is  or  ;
- R_5 and R_6 are each independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;
- R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$, where R_{17}, R_{18}, and R_{19} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, provided that at least one of R_7 and R_8 is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$;
- R_9 is a suitable organic moiety; and
- Z and Z_1 are each independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, -CN, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$, where R_{21}, R_{22}, R_{23}, and R_{24} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or where any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

- or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z_1 and R_1 are as defined above except for moieties that cannot form the cycloalkyl or heterocycloalkyl group;
- or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z_1 are as defined above except for moieties that cannot form the cycloalkyl or heterocycloalkyl group.

The invention also pertains to prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable solvates of compounds of the formula I.

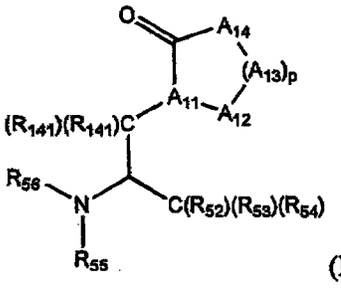
In preferred embodiments of the compounds of the formula I, R_2 and R_3 are each independently H; ; or , where n is an integer from 0 to 5, each R_{41} is independently H or lower alkyl, and the stereochemistry at the carbon denoted with an asterisk may be R or S; provided that at least one of R_2 and R_3 is  or . Preferably, R_9 is a five-membered heterocycle having one to three heteroatoms selected from O, N, and S.

In other preferred embodiments, the variables of formula I are as follows. Z and Z_1 are each independently selected from H, F, lower alkyl, $-CO_2R_{21}$, and $-C(O)NR_{21}R_{22}$, provided that Z and Z_1 are not both H, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group. At least one of R_2 or R_3 is , , or , and the other is H. R_5 and R_6 are each independently selected from H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, and a heteroaryl

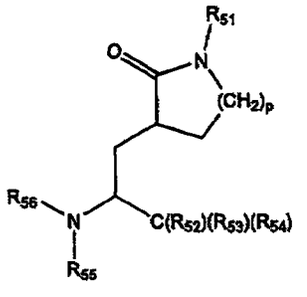
group, more preferably one of R_5 and R_6 is H and the other is alkyl or aryl (e.g., unsubstituted or substituted phenylmethyl). R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group; and more preferably one of R_7 and R_8 is H and the other is alkyl (e.g., 2-propyl, 2-methyl-2-propyl, or 2-methyl-1-propyl) or arylmethyl (e.g., unsubstituted or substituted phenylmethyl or naphthylmethyl). R_9 is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S, more preferably a five-membered heterocycle having at least one nitrogen heteroatom and at least one oxygen heteroatom (e.g., unsubstituted or substituted 1,2-oxazolyl (i.e., isoxazolyl), 1,3-oxazolyl (i.e., oxazolyl), or oxadiazolyl (1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, or 1,2,5-oxadiazolyl). When R_9 is oxadiazolyl, unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl are preferred. In especially preferred embodiments, R_9 is 3-isoxazolyl or 5-isoxazolyl, either unsubstituted or substituted with one or two methyl groups and/or halogens, with chlorine and fluorine being preferred halogen substituents.

In a preferred embodiment, the compounds, prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and solvates have an antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the H1-HeLa cell culture assay, and more preferably an antirhinoviral activity with an EC_{50} less than or equal to 10 μM in the H1-HeLa cell culture.

In another aspect, the invention is directed to intermediates of formula II, preferably of the formula II', which are useful in the synthesis of certain compounds:



(II)



(II')

wherein :

- p is an integer of from 0 to 5;
- A_{11} is CH or N, A_{12} and each A_{13} are independently selected from $C(R_{61})(R_{61})$, $N(R_{61})$, S, S(O), $S(O)_2$, and O, and A_{14} is NH or NR_{61}, where each R_{61} is independently H, alkyl, acyl, or aryl, provided that no more than two heteroatoms occur consecutively in the above-depicted ring in formula II formed by A_{11}, A_{12}, $(A_{13})_n$, A_{14} and C=O;
- each R_{141} is independently H or lower alkyl;

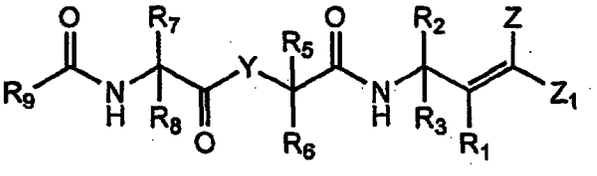
- R_{51} is H, alkyl, acyl, or aryl;
- R_{52}, R_{53}, and R_{54} are each independently selected from H, hydroxyl, alkyl, acyl, and aryl; or any two of R_{52}, R_{53}, and R_{54} together form =O or $=C(R_{57})(R_{58})$, where R_{57} and R_{58} are each independently selected from H, alkyl, $CO_2(C_1\text{-}C_6)$alkyl, $CO_2N(C_1\text{-}C_6)$alkyl, and CO_2(aryl); and
- R_{55} and R_{56} are each independently H or a suitable protecting group for nitrogen.

The invention is also directed to pharmaceutically acceptable salts of the compounds of formulae II and II'.

The invention also relates to pharmaceutical compositions containing a therapeutically effective amount of at least one compound of the formula I, or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate thereof. Additionally, the invention relates to methods of inhibiting picornaviral 3C protease by administering a therapeutically effective amount of at least one compound of the formula I, or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate thereof.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

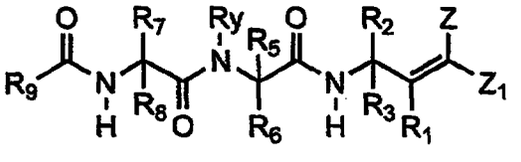
The present invention relates to compounds of the formula I:



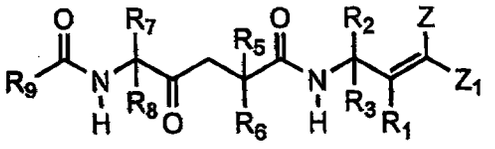
(I),

wherein Y, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, Z, and Z_1 are as defined above, and to pharmaceutically acceptable salts, prodrugs, active metabolites, and solvates thereof. Preferably, such compounds, pharmaceutically acceptable salts, prodrugs, active metabolites, and solvates have antipicornaviral activity, more preferably antirhinoviral activity, corresponding to an EC_{50} less than or equal to 100 μM in the H1-HeLa cell culture assay, more preferably corresponding to an EC_{50} less than or equal to 10 μM in the H1-HeLa cell culture assay.

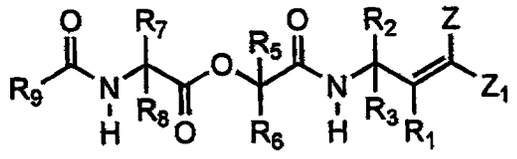
The present invention additionally relates to preferred compounds of the formulas I-A, I-B, and I-C:



(I-A)



(I-B)



(I-C)

wherein R_y (in formula I-A) is H or lower alkyl, and R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, Z, and Z_1 are as defined above, and to pharmaceutically acceptable salts, prodrugs, active metabolites, and solvates thereof.

The inventive compounds of formulas I-A, which are referred to herein as "peptide-like" compounds, I-B, which are referred to herein as "ketomethylene-type" compounds, and I-C, which are referred to herein as "depsipeptide" compounds, differ in their backbones, which may affect the specific biodistribution or other physical properties; nonetheless each possesses a strong rhinoviral-protease-inhibiting activity.

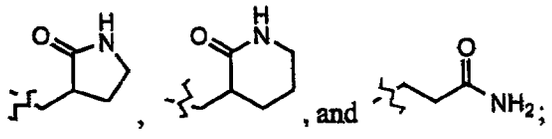
In preferred embodiments of compounds of formulas I-A, I-B, and I-C above:

R_1 is H, F, or an alkyl group;

R_y (in formula I-A) is H or methyl;

R_3, R_5, and R_8 are each H;

R_2 is selected from one of the following moieties:



R_6 is an alkyl group, which has as a preferred optional substituent an aryl group;

R_7 is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

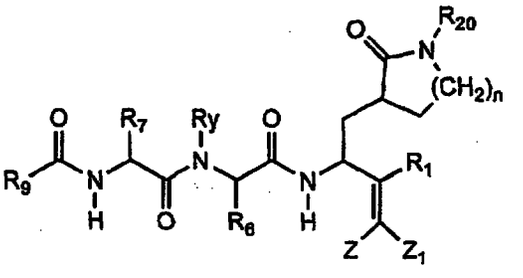
R_9 is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S, preferably where at least one of the heteroatoms is nitrogen, that is unsubstituted or substituted, where the optional substituents are preferably halogen or lower alkyl, and more preferably mono-chloro or -fluoro or a methyl group; and

Z and Z_1 are each independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, -CN, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$,

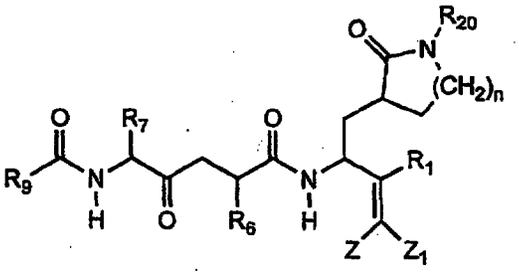
$-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$, where Z and Z_1 are not both H, and where R_{21}, R_{22}, R_{23}, and R_{24} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or where any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or Z and Z_1 (both as defined above), together with the atoms to which they are attached, form a heterocycloalkyl group.

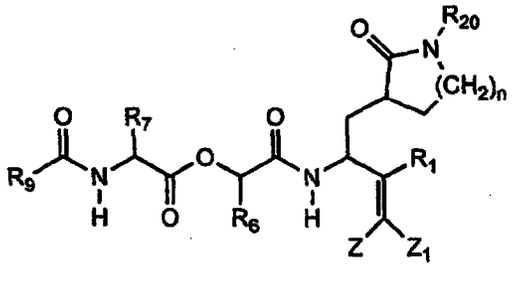
In preferred embodiments, the compounds of the invention are of the formulae I-A', I-B', and I-C':



(I-A')



(I-B')



(I-C')

wherein:

R_1, Z, and Z_1 are as defined above;

n is 1 or 2;

R_y (in formula I-A') is H or lower alkyl;

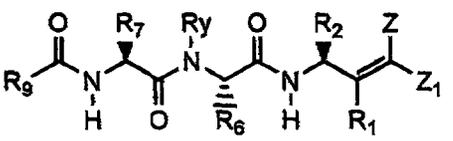
R_6 is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R_7 is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$, where R_{17}, R_{18}, and R_{19} are each independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or acyl;

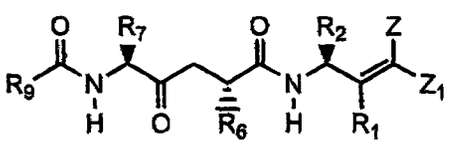
R_9 is a five-membered heterocycle having one to three heteroatoms selected from O, N, and S, that is unsubstituted or substituted, where the optional substituents are preferably one or two lower alkyl groups and/or halogens.

The invention also relates to prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and solvate of such compounds.

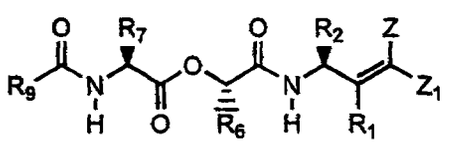
In preferred embodiments, the RVP-inhibiting agents of the invention are compounds of any of the stereospecific formulas I-A", I-B", and I-C":



(I-A")



(I-B")



(I-C")

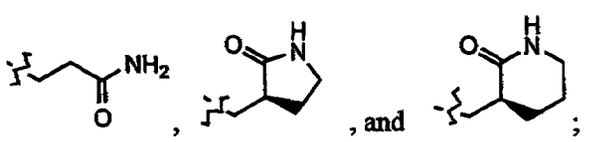
wherein R_y, R_1, R_2, R_6, R_7, R_9, Z, and Z_1 are as defined above, and pharmaceutically acceptable salts, prodrugs, active metabolites, and solvates thereof.

In preferred embodiments of compounds of the formula I-A", I-B", or I-C":

R_1 is H, F, or methyl;

R_y (in formula I-A') is H or methyl;

R_2 is selected from one of the following moieties:



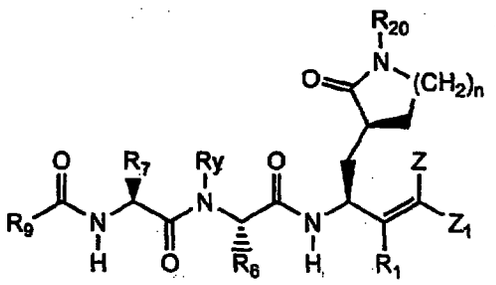
R_6 is arylmethyl or arylthiomethyl, where aryl is preferably an optionally substituted phenyl group;

R_7 is an alkyl group, more preferably selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, and arylmethyl, where the aryl group is preferably phenyl or naphthyl;

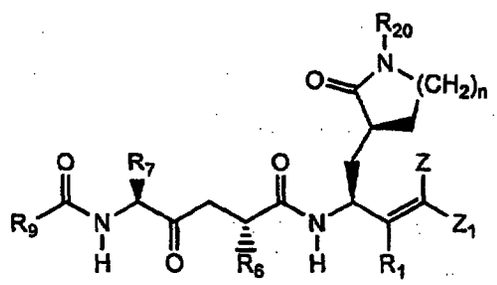
R_9 is isoxazolyl, oxazolyl, or oxadiazolyl, optionally substituted with one or two lower alkyl groups and/or halogens; and

Z is H, and Z_1 is $-CO_2R_{21}$, -CN, or $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are as defined above, or Z and Z_1 together form a cyclic ester or amide.

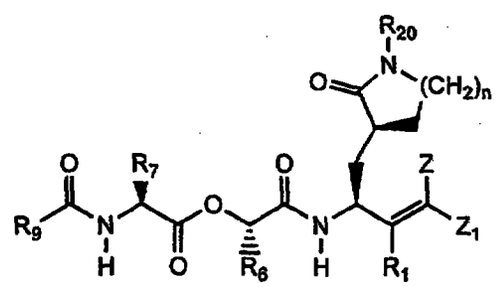
Even more preferably, the RVP-inhibiting agents of the invention are compounds of any of the formulas I-A''', I-B''', and I-C''':



(I-A''')



(I-B''')



(I-C''')

wherein n, R_y, R_1, R_{20}, R_6, R_7, R_9, Z, and Z_1 are as defined above, and pharmaceutically acceptable salts, prodrugs, active metabolites, and solvates thereof.

In preferred compounds of the formula (I-A'''), (I-B'''), or (I-C'''):

R_1 is H, F, or methyl;

R_y (in formula I-A') is H or methyl;

R_{20} is hydrogen;

R_6 is arylmethyl or arylthiomethyl, where aryl is preferably phenyl unsubstituted or substituted with halogen, lower alkyl, and/or lower alkoxy;

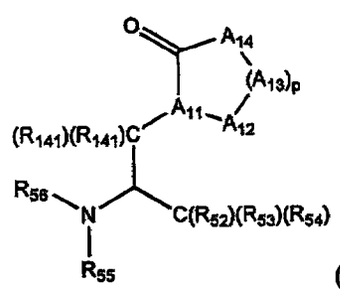
R_7 is an alkyl group, and more preferably is selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, and arylmethyl, where the aryl group is preferably phenyl or naphthyl;

R_9 is isoxazolyl, oxazolyl, or oxadiazolyl, each optionally substituted with one or two lower alkyl groups and/or halogens; and

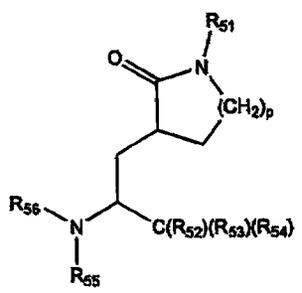
Z is H, and Z_1 is $-CO_2R_{21}$, -CN, or $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are as defined above, or Z and Z_1 together form a cyclic ester or amide.

In especially preferred compounds of the invention of the generic formula I (and subgeneric formulae), R_1 is H or F.

In another aspect, the invention is directed to intermediate compounds of the formulas II and II':



(II)

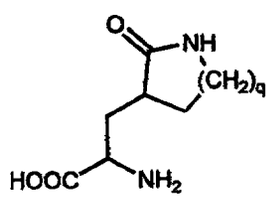


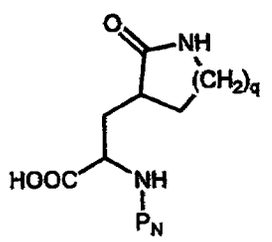
(II')

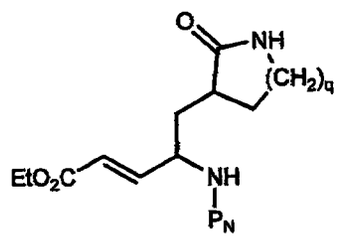
wherein the variables (p, A_{11}, A_{12}, A_{13}, A_{14}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, and R_{141}) are as defined above. These compounds are useful for synthesizing pharmaceutically useful compounds of the formula I.

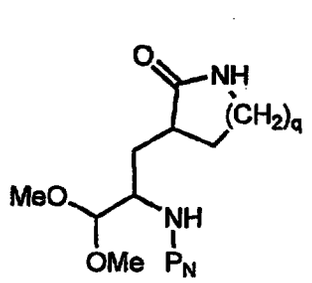
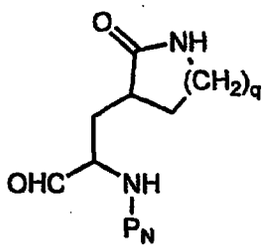
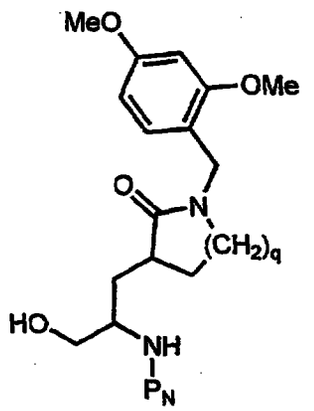
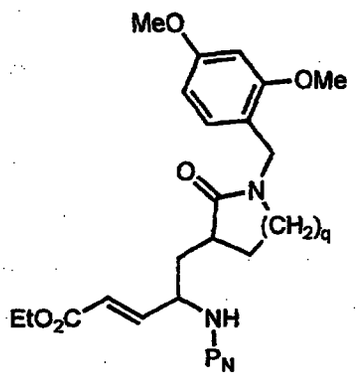
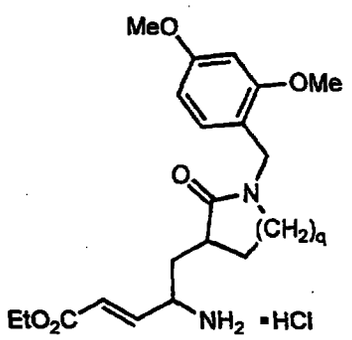
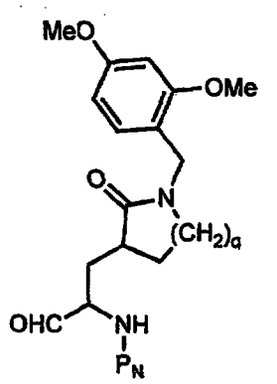
Preferred R_{55} and R_{56} groups are H and suitable protecting groups for nitrogen, for example, BOC (t-butyloxycarbonyl), CBZ (benzyloxycarbonyl), FMOC (fluorene-9-methyloxycarbonyl), other alkyloxycarbonyls (e.g. methyloxycarbonyl), and trityl (triphenylmethyl). Other suitable nitrogen-protecting groups may be readily selected by artisans (see, e.g., Greene and Wutz, *Protecting Groups in Chemical Synthesis* (2nd ed.), John Wiley & Sons, NY (1991)). Preferred groups for R_{52}, R_{53}, and R_{54} are H, alkoxy, hydroxy, and carbonyl.

Preferred formula-II compounds include the following, where P_N is a suitable protecting group for nitrogen and q is 1 or 2:

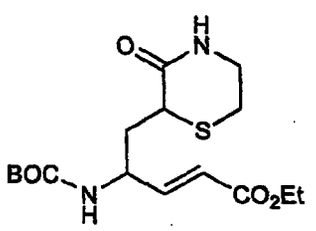
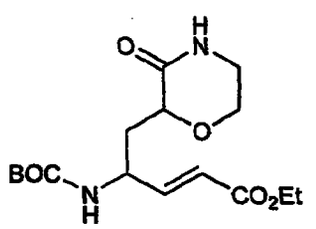
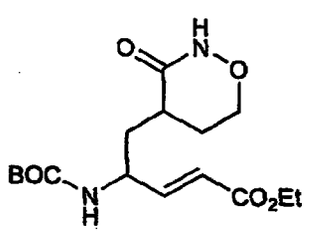




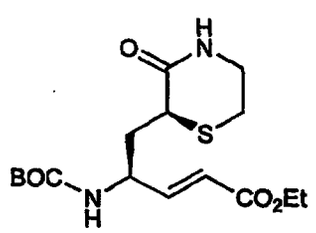
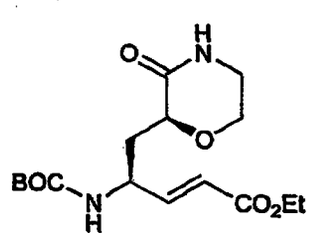
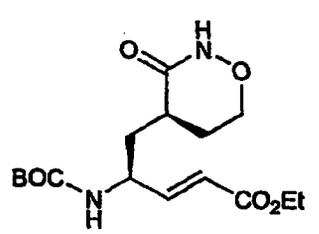


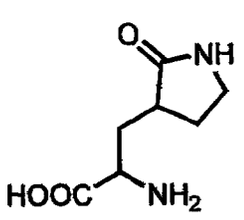
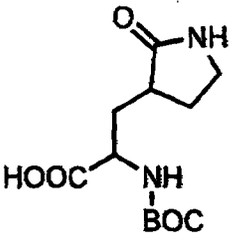
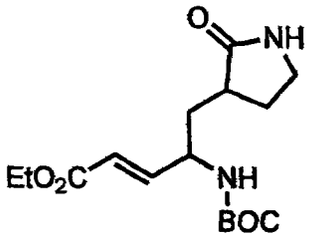
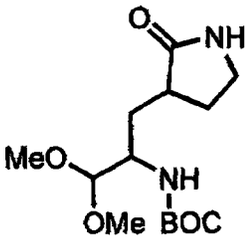
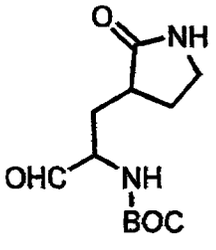
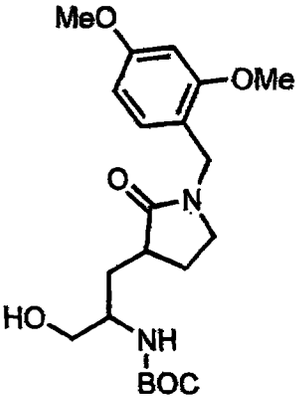
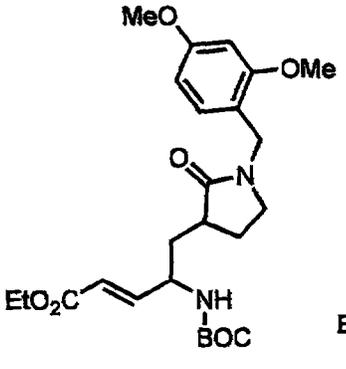
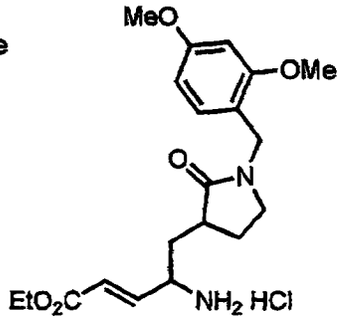
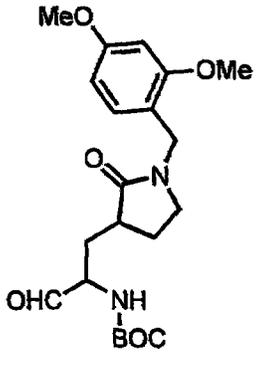
Other preferred intermediates include the following compounds, where BOC is t-butyloxycarbonyl:

Of these, the preferred stereoisomers are:

Especially preferred intermediates include the following compounds:

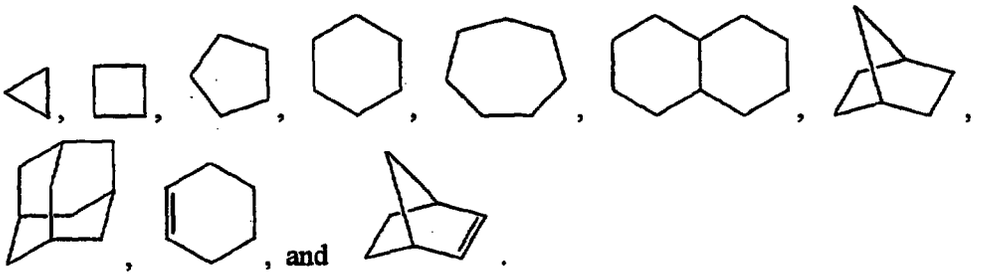
In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

Where chiral carbons are included in chemical structures, unless a particular orientation is depicted, both stereoisomeric forms are intended to be encompassed.

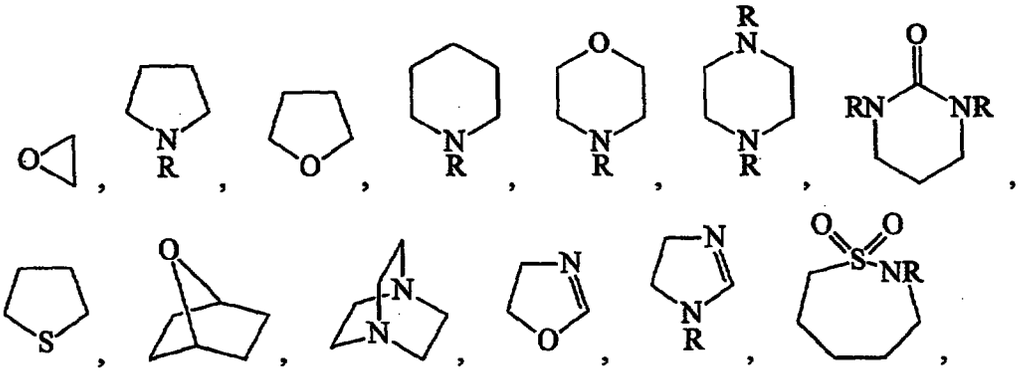
As used herein, the term "alkyl group" is intended to mean a straight- or branched-chain monovalent radical of saturated and/or unsaturated carbon atoms and hydrogen atoms, such as methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, pentenyl, butenyl, propenyl, ethynyl, butynyl, propynyl, pentynyl, hexynyl, and the like, which may be unsubstituted (i.e., containing only carbon and hydrogen) or substituted by one or more suitable

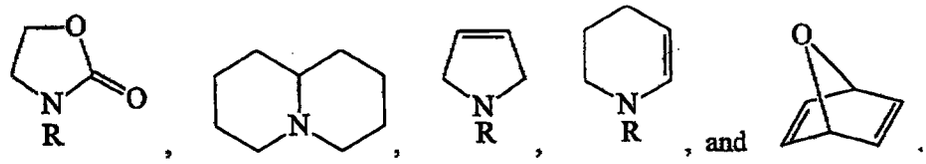
substituents as defined below (e.g., one or more halogens, such as F, Cl, Br, or I, with F and Cl being preferred). A "lower alkyl group" is intended to mean an alkyl group having from 1 to 4 carbon atoms in its chain.

A "cycloalkyl group" is intended to mean a non-aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon ring atoms, each of which may be saturated or unsaturated, and which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more heterocycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more substituents. Illustrative examples of cycloalkyl groups include the following moieties:

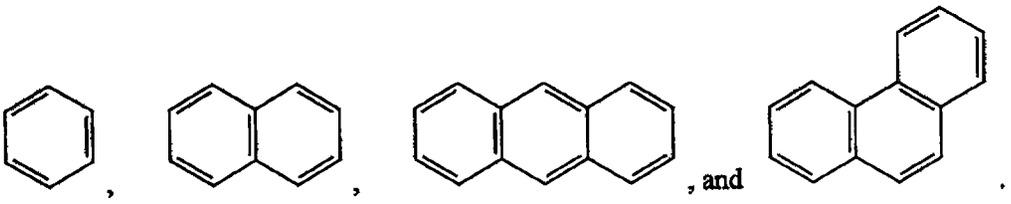


A "heterocycloalkyl group" is intended to mean a non-aromatic monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or unsaturated, containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, which includes 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, where the radical is unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heterocycloalkyl groups include the following moieties:

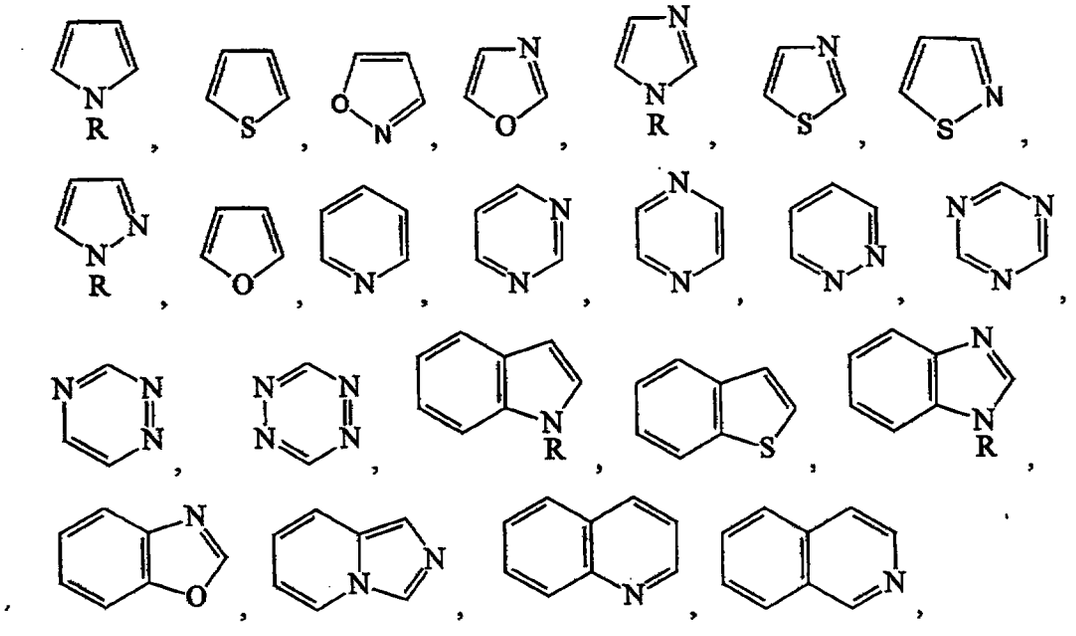


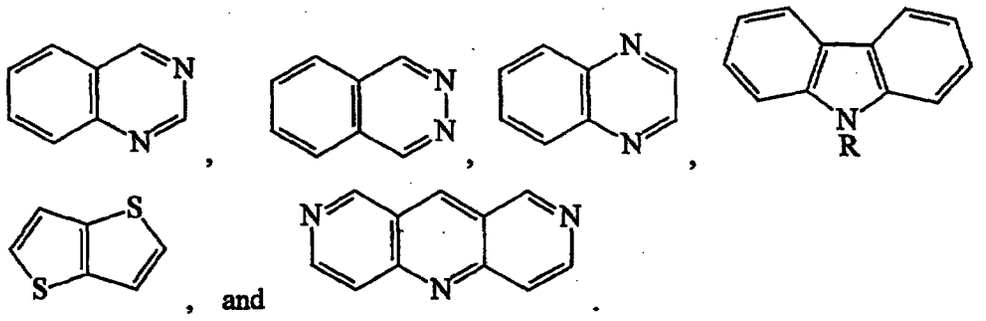


An "aryl group" is intended to mean an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 6, 10, 14, or 18 carbon ring atoms, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of aryl groups include the following moieties:



A "heteroaryl group" is intended to mean an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, including 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or aryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heteroaryl groups include the following moieties:





A "heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group (each of which, as defined above, are optionally substituted).

An "acyl group" is intended to mean a -C(O)-R radical, where R is a substituent as defined below.

A "thioacyl group" is intended to mean a -C(S)-R radical, where R is a substituent as defined below.

A "sulfonyl group" is intended to mean a $-SO_2R$ radical, where R is a substituent as defined below.

A "hydroxy group" is intended to mean the radical -OH.

An "amino group" is intended to mean the radical $-NH_2$.

An "alkylamino group" is intended to mean the radical $-NHR_a$, where R_a is an alkyl group.

A "dialkylamino group" is intended to mean the radical $-NR_aR_b$, where R_a and R_b are each independently an alkyl group.

An "alkoxy group" is intended to mean the radical $-OR_a$, where R_a is an alkyl group. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and the like.

An "alkoxycarbonyl group" is intended to mean the radical $-C(O)OR_a$, where R_a is an alkyl group.

An "alkylsulfonyl group" is intended to mean the radical $-SO_2R_a$, where R_a is an alkyl group.

An "alkylaminocarbonyl group" is intended to mean the radical $-C(O)NHR_a$, where R_a is an alkyl group.

A "dialkylaminocarbonyl group" is intended to mean the radical $-C(O)NR_aR_b$, where R_a and R_b are each independently an alkyl group.

A "mercapto group" is intended to mean the radical -SH.

An "alkylthio group" is intended to mean the radical $-SR_a$, where R_a is an alkyl group.

A "carboxy group" is intended to mean the radical -C(O)OH.

A "carbamoyl group" is intended to mean the radical -C(O)NH_2.

An "aryloxy group" is intended to mean the radical -OR_c, where R_c is an aryl group.

A "heteroaryloxy group" is intended to mean the radical -OR_d, where R_d is a heteroaryl group.

An "arylthio group" is intended to mean the radical -SR_c, where R_c is an aryl group.

A "heteroarylthio group" is intended to mean the radical -SR_d, where R_d is a heteroaryl group.

The term "suitable organic moiety" is intended to mean any organic moiety recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable organic moieties include, but are not limited to, hydroxy groups, alkyl groups, oxo groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, arylthio groups, heteroarylthio groups, and the like.

The term "substituent" or "suitable substituent" is intended to mean any suitable substituent that may be recognized or selected, such as through routine testing, by those skilled in the art. Illustrative examples of suitable substituents include hydroxy groups, halogens, oxo groups, alkyl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, aryloxy groups, heteroaryloxy groups, arylthio groups, heteroarylthio groups, and the like.

The term "optionally substituted" is intended to expressly indicate that the specified group is unsubstituted or substituted by one or more suitable substituents, unless the optional substituents are expressly specified, in which case the term indicates that the group is unsubstituted or substituted with the specified substituents. As defined above, various groups may be unsubstituted or substituted (i.e., they are optionally substituted) unless indicated otherwise herein (e.g., by indicating that the specified group is unsubstituted).

A "prodrug" is intended to mean a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active.

A "pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If an inventive compound is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid; hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid; and the like, or with an organic acid, such as acetic acid; maleic acid; succinic acid; mandelic acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; pyranosidyl acid, such as glucuronic acid or galacturonic acid; alpha-hydroxy acid, such as citric acid or tartaric acid; amino acid, such as aspartic acid or glutamic acid; aromatic acid, such as benzoic acid or cinnamic acid; sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid; or the like.

If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

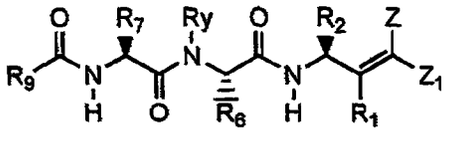
The inventive compounds may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates, and mixtures thereof are intended to be within the broad scope of the present invention. Preferably, however, the inventive compounds are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound comprising at least a sufficient activity. Preferably, an optically amount of a single enantiomer to yield a compound having the desired pharmacological pure compound of the invention comprises at least 90% of a single isomer (80% enantiomeric excess), more preferably at least 95% (90% e.e.), even more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

Preferably in the compounds of the formula I (or of any of the subgeneric formula), R_1 is H or F.

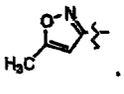
In the compounds of formula I, preferably R_9 is an unsubstituted or substituted isoxazolyl group, where the optional substituents are preferably one or two methyl groups and/or halogens.

Especially preferred embodiments of the invention are described below in reference to the following formula I-A'':

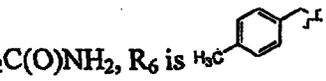
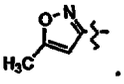


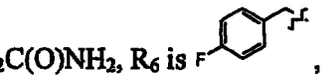
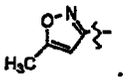
(I-A'')

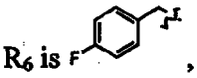
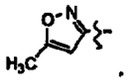
Preferred compounds of the present invention include peptido (peptide-like) Compounds **(A-1)** - **(A-8)** of the formula I-A'' above, wherein R_1 is H, Z is H, R_y is H, and R_2, R_6, R_7, Z_1, and R_9 are as respectively defined below:

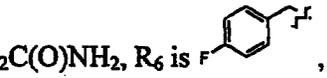
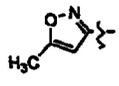
(A-1) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

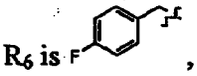
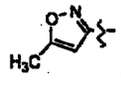
(A-2) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

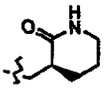
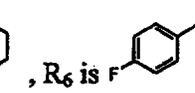
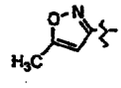
(A-3) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

(A-4) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

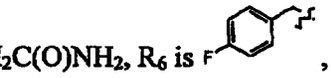
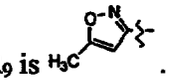
(A-5) R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

(A-6) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

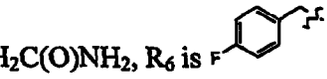
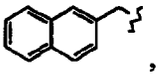
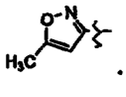
(A-7) R_2 is , R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

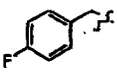
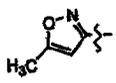
(A-8) R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

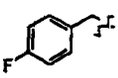
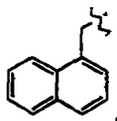
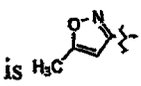
Preferred peptide-like compounds of the formula I-A"" further include Compounds (A-9) - (A-13) below, wherein R_1 is H, Z is H, Z_1 is $CO_2CH_2CH_3$, R_y is CH_3, and R_2, R_6, R_7, and R_9 are as respectively defined below:

(A-9) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , and R_9 is .

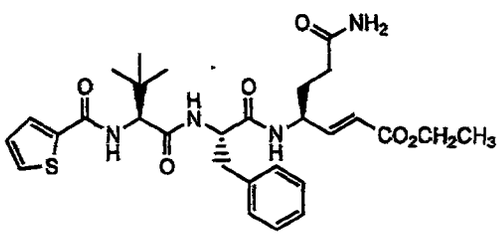
(A-10) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, and R_9 is .

(A-11) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , and R_9 is .

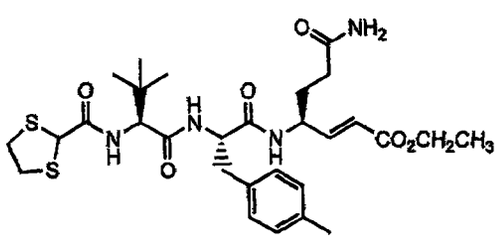
(A-12) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH_2CH(CH_3)_2$, and R_9 is .

(A-13) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , and R_9 is .

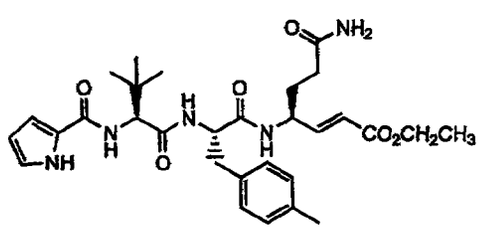
Other preferred peptide-like compounds include the following:



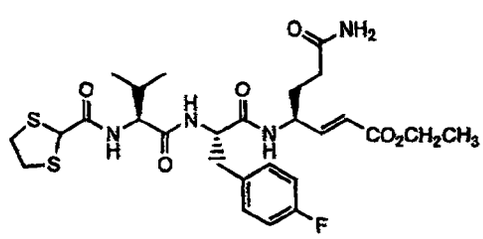
(A-14)



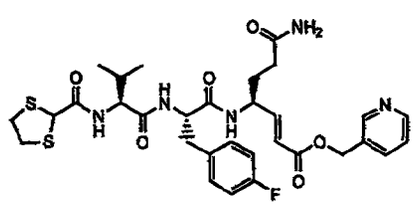
(A-15)



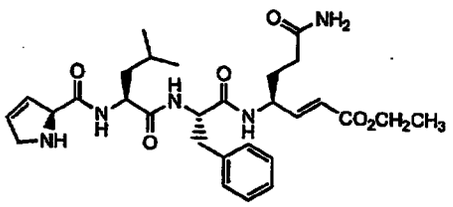
(A-16)



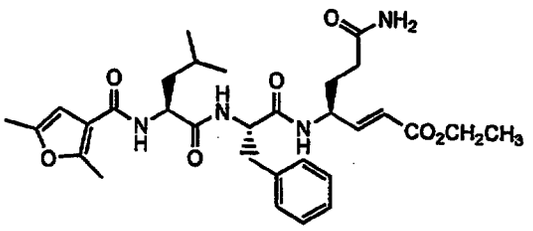
(A-17)



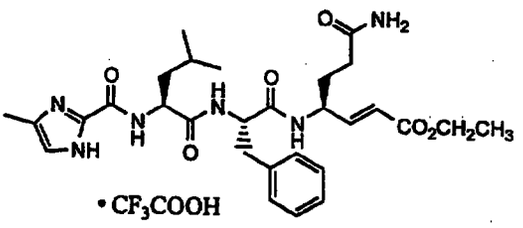
(A-18)



(A-19)

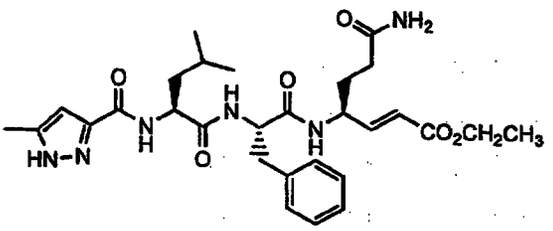


(A-20)

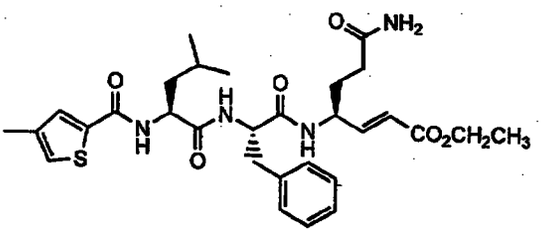


• CF_3COOH

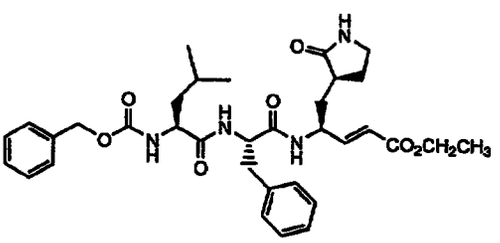
(A-21)



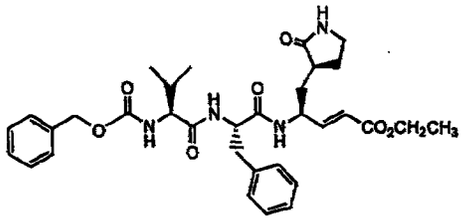
(A-22)



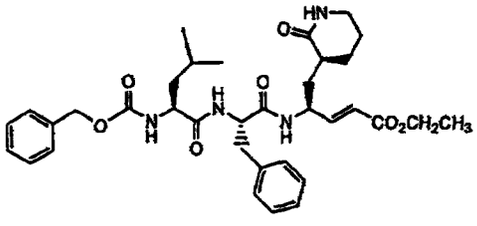
(A-23)



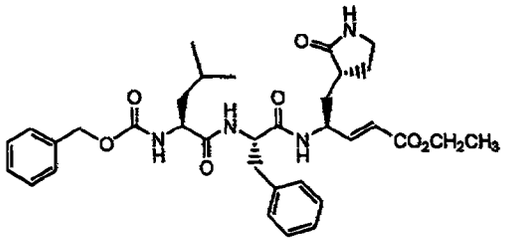
(A-24)



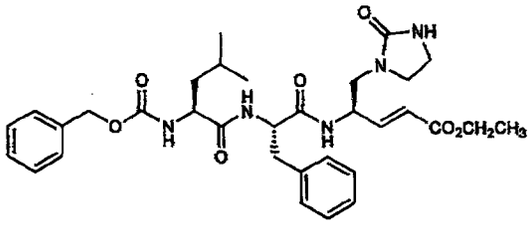
(A-25)



(A-26)

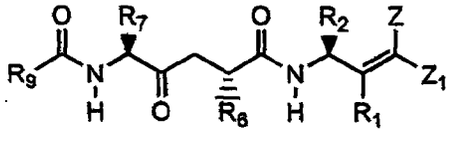


(A-27)

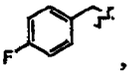


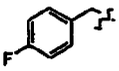
(A-28)

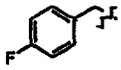
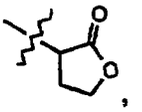
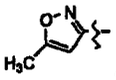
Preferred ketomethylene-type Compounds (B-1) - (B-4) of the invention are described below in reference to the following formula I-B'':

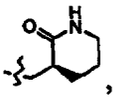
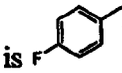


(I-B'')

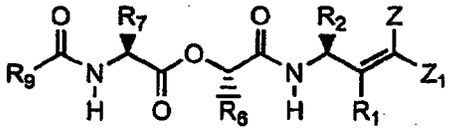
(B-1) R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

(B-2) R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

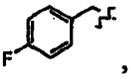
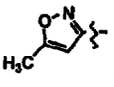
(B-3) R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z and Z_1 together are , where the carbonyl group is cis to the hydrogen corresponding to R_1 in formula I, and R_9 is .

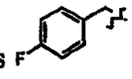
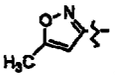
(B-4) R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

Preferred depsipeptide-type Compounds (C-1) and (C-2) of the invention are described below in reference to the following formula I-C'', where R_1 is H:



(I-C'')

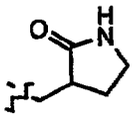
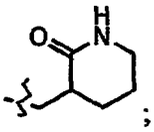
(C-1) Z is H, R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

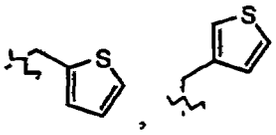
(C-2) Z is H, R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

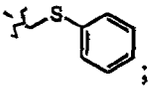
Additional compounds may be prepared in reference to formula I by selecting the variables from the following substituents:

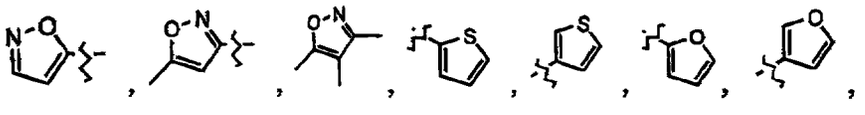
R_y = H or CH_3;

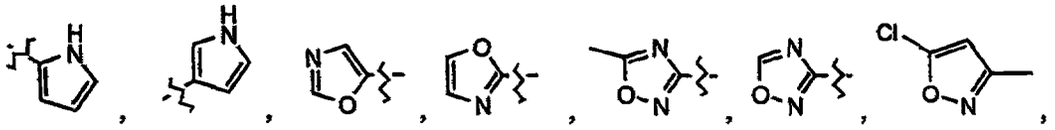
R_1 = H or CH_3;

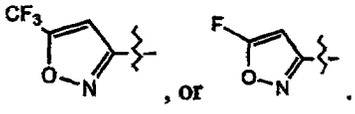
R_2 =  or ;

R_6 =  , or phenylmethyl (i.e., benzyl), where the aryl group is optionally substituted with one, two, or three substituents each independently selected from halogens, methoxy and methyl;

R_7 = 2-methyl-1-propyl, 2-propyl, 2-methyl-2-propyl, benzyl, or  ; and

R_9 =  ,

 ,

 , or .

The present invention is also directed to a method of inhibiting picornaviral 3C protease activity, comprising contacting the protease with an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. For example, picornaviral 3C protease activity may be inhibited in mammalian tissue by administering a compound of formula I or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. More preferably, the present method is directed at inhibiting rhinoviral protease activity.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, meningitis virus, and hepatitis A virus, and includes: (a) prophylactic treatment in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but not yet diagnosed as having it; (b) inhibiting the disease condition; and/or (c) alleviating, in whole or in part, the disease condition.

The activity of the inventive compounds as inhibitors of picornaviral 3C protease activity may be measured by any of the suitable methods known to those skilled in the art, including *in vivo* and *in vitro* assays. An example of a suitable assay for activity measurements is the antiviral H1-HeLa cell culture assay described herein.

Administration of the compounds of the formula I and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal. Intranasal delivery is especially preferred.

An inventive compound of formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof may be administered as a pharmaceutical composition in any pharmaceutical form recognizable to the skilled artisan as being suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use. In preferred embodiments, the inventive pharmaceutical compositions are delivered intranasally in the form of suspensions.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known or may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof), and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a

mammal, for example, a human patient, in need of treatment mediated by inhibition of picornaviral 3C protease activity, by any known or suitable method of administering the dose, including topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

A "therapeutically effective amount" is intended to mean the amount of an inventive compound that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus. The amount of a given compound of the invention that will be therapeutically effective will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, the identity of the mammal in need thereof, which amount may be routinely determined by artisans.

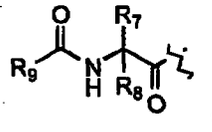
By way of illustration, a formulation for nasal delivery of the inventive compounds for treatment of rhinoviral infections can be prepared as follows, where all percentages are weight/weight and the suspension is prepared in purified water. A formula-I compound is micronized to a reduced particle size such that $D_{90} < 10$ μm. A suspension is prepared to contain a final concentration of from about 0.01% to about 2% of the active compound, preferably about from 0.2% to 2%. An appropriate preservative selected from those known in the art may be included, for example, benzalkonium chloride/EDTA, in appropriate final-concentration ranges, e.g., about 0.02%/0.01%. A suspending agent, such as mixture of microcrystalline cellulose (final concentration of about 1% - 1.5%, preferably about 1.2%) and sodium carboxymethylcellulose cellulose (final concentration of about 0.1% - 0.2%, preferably about 0.13%) may be included. A surfactant such as polysorbate 80 may be included in a final concentration of about from 0.05% to 0.2%, preferably about 0.1%. A tonicity modifier such as dextrose may be included to give a final concentration of about from 4% to 6%, preferably about 5%. The pH of the final solution is adjusted as appropriate to a physiological range, e.g., 4-6, using non-toxic acid and/or base, such as HCl and/or NaOH.

An exemplary formulation for nasal delivery of the inventive compound of Example 17 has the following composition, where all percentages are weight/weight and the suspension is prepared in purified water:

Active Compound	**(B-2)**	0.2 - 2 %
Preservative	Benzalkonium chloride/EDTA	0.02 % / 0.01 %
Suspending Agent	Microcrystalline cellulose/Na-carboxymethylcellulose	1.2 % / 0.13 %
Surfactant	Polysorbate 80	0.1 %
Tonicity Modifier	Dextrose	5%
pH Adjustment	NaOH/HCl	pH 4 - 6

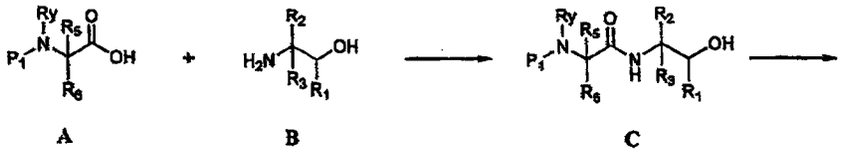
GENERAL SYNTHESES

The inventive compounds of formula (I) may be advantageously prepared by the methods of the present invention, including the general methods described below. In each of these general methods, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_y, Z, and Z_1 are as defined above, and R_4 is used (as a shorthand representation) to mean:

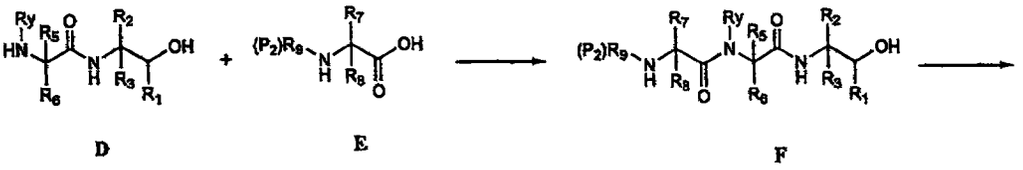


where R_7, R_8, and R_9 are as defined above.

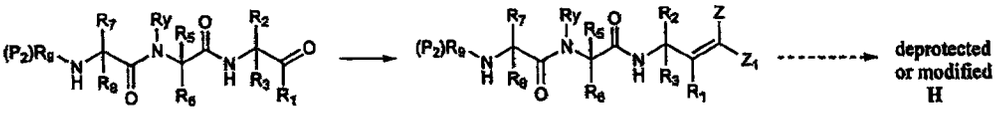
In General Method I, useful for synthesis of peptide-like compounds of formula I-A, an amino acid **A**, where P_1 is an appropriate protecting group for nitrogen, is subjected to an amide-forming reaction with amino alcohol (or salt thereof) **B** to produce amide **C**. Compound **C** is then deprotected to give free amine (or salt thereof) **D**. Amine **D** and amino acid **E**, which may incorporate either an R_4 group or a protecting group for nitrogen (P_2), are subjected to a bond-forming reaction generating compound **F**. Compound **F** is oxidized to intermediate **G**, which is then transformed into unsaturated product **H**. If protecting groups have been used on amino acid **E**, or on any R groups (R_1-R_9) and/or on R_y and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield deprotected or modified **H**.



A B C

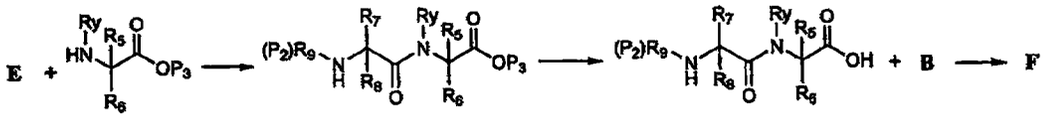


D E F



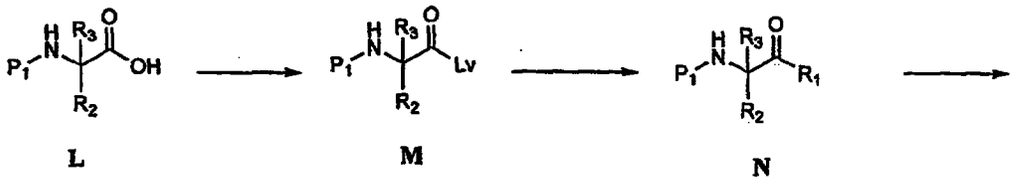
G H

An alternative method to prepare intermediate **F** is described as follows. Amino acid **E** and amino acid (or salt thereof) **I**, where P_3 is an appropriate protecting group for oxygen, are subjected to a bond-forming reaction to produce intermediate **J**. Molecule **J** is deprotected to yield free carboxylic acid **K**, which is subsequently subjected to an amide-forming reaction with amino alcohol (or salt thereof) **B** to generate intermediate **F**.

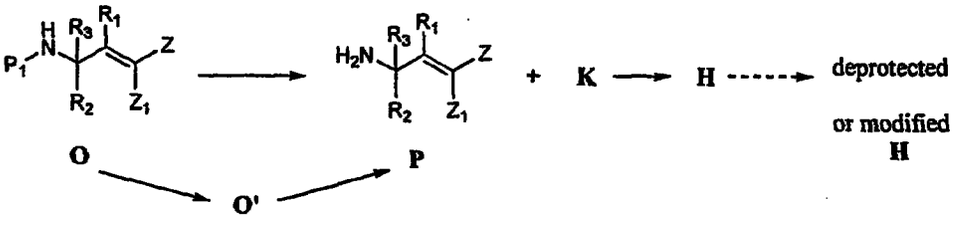


I J K

In General Method II, which is also useful for synthesizing peptide-like compounds of formula I-A, an amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative **M**, where "Lv" is a leaving group. Compound **M** is subjected to a reaction where Lv is replaced by R_1 to give derivative **N**. Derivative **N** is then transformed into unsaturated product **O**. Unsaturated compound **O** is deprotected to give free amine (or salt thereof) **P**, or modified at Z or Z_1 first to give **O'** and then deprotected to **P**. Intermediate **P** is subsequently subjected to an amide-forming reaction with carboxylic acid **K** to give final product **H**. If protecting groups have been used on any R group (R_1-R_9) and/or on R_y and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield deprotected or modified **H**.

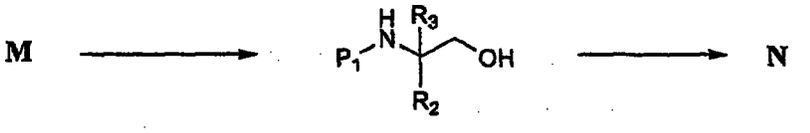


L M N



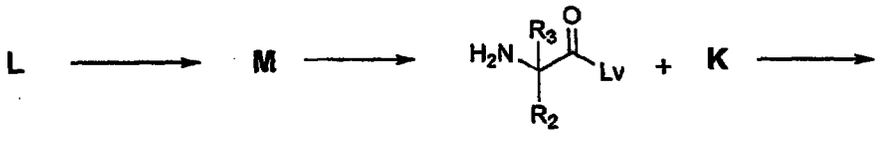
O O' P H deprotected or modified H

An alternative method to prepare intermediate N is described as follows. Compound M is subjected to a reaction where "Lv" is reduced to protected amino alcohol Q. Intermediate Q is subsequently oxidized to derivative N.

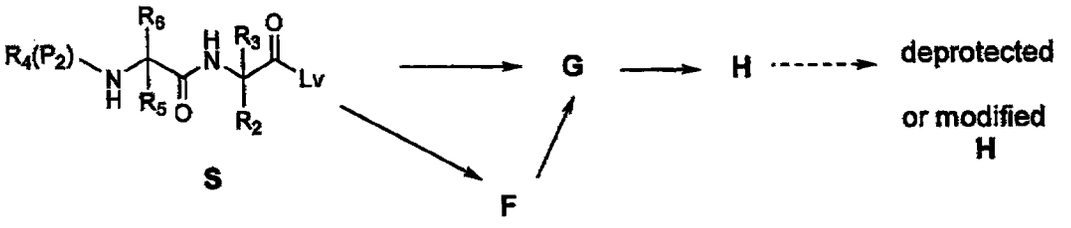


Q

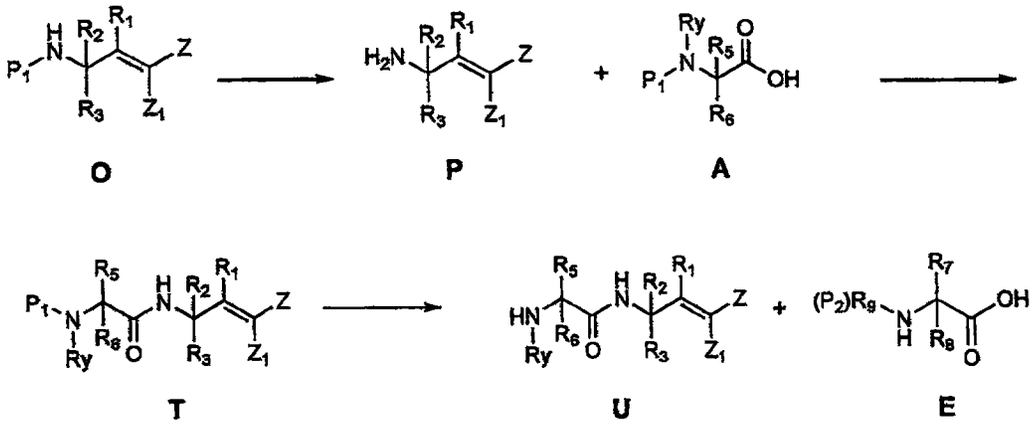
In General Method III, useful for synthesis of peptide-like compounds of formula I-A, an amino acid L, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative M, where "Lv" is a leaving group. Compound M is deprotected to give free amine (or salt thereof) R, which subsequently is subjected to an amide-forming reaction with carboxylic acid K to give intermediate S. Compound S is then either directly converted to carbonyl intermediate G, or successively reduced to alcohol F first, which is oxidized to G. Compound G is subjected to a reaction to yield the unsaturated final product H. If protecting groups have been used on any R groups (R_1-R9) and/or on R_y and/or on Z and/or Z_1, product H is deprotected and/or further modified to yield deprotected or modified H.



R

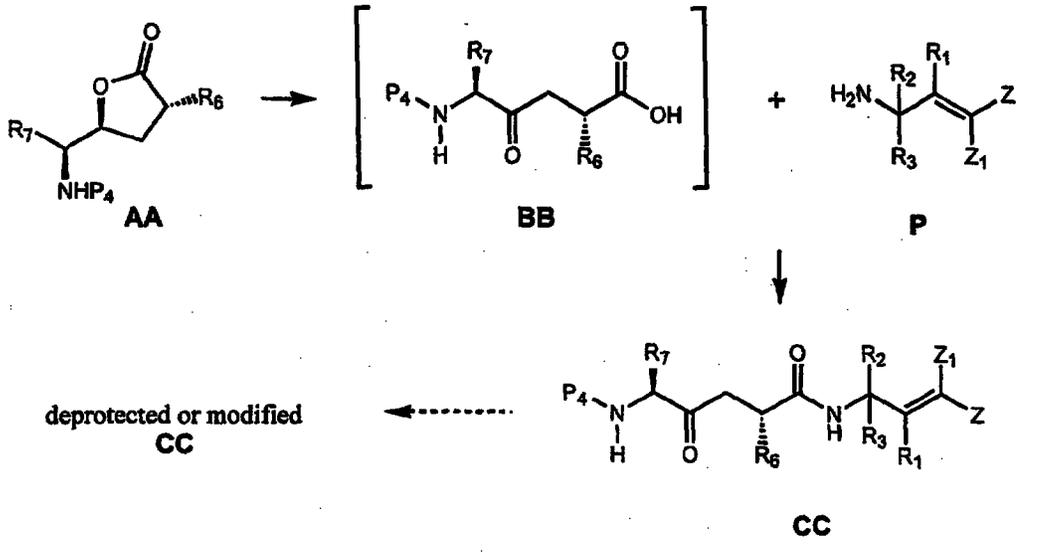


In General Method IV, useful for synthesis of peptide-like compounds of formula I-A, free amine (or salt thereof) **P**, prepared from intermediate **O** as described in General Method II, is converted to amide **T** by reaction with amino acid **A**, where P_1 is an appropriate protecting group for nitrogen. Compound **T** is further deprotected to free amine (or salt thereof) **U**, which is subsequently converted to **H** with amino acid **E**. If protecting groups have been used on any R groups (R_1-R9) and/or on R_y and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield deprotected or modified **H**.

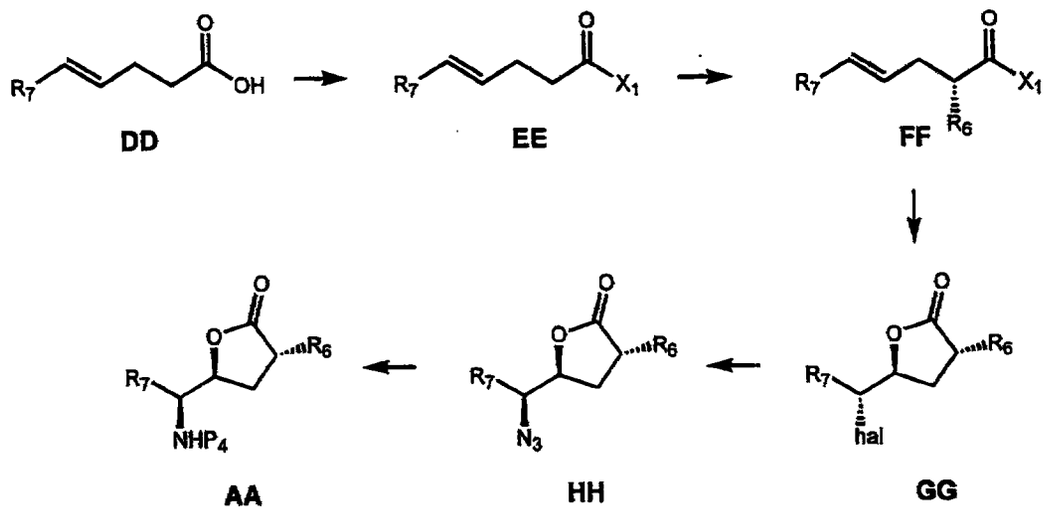


In General Method V, useful for synthesis of ketomethylene compounds of formula I-B, optically active lactone **AA**, where P_4 is an appropriate protecting group for nitrogen, and R_5 and R_8 are H (which may be prepared by the method described below and by various literature methods, including: (a) Herold et al., *J. Org. Chem.* **1989**, *54*, 1178; (b) Bradbury et al., *Tetrahedron Lett.* **1989**, *30*, 3845; (c) Bradbury et al., *J. Med. Chem.* **1990**, *33*, 2335; (d) Wuts et al., *J. Org. Chem.* **1992**, *57*, 6696; (e) Jones et al., *J. Org. Chem.* **1993**, *58*, 2286; (f) Pégorier et al., *Tetrahedron Lett.* **1995**, *36*, 2753; and (g) Dondoni et al., *J. Org. Chem.* **1995**, *60*, 7927) is transformed by a two-step procedure (basic hydrolysis and subsequent oxidation) into

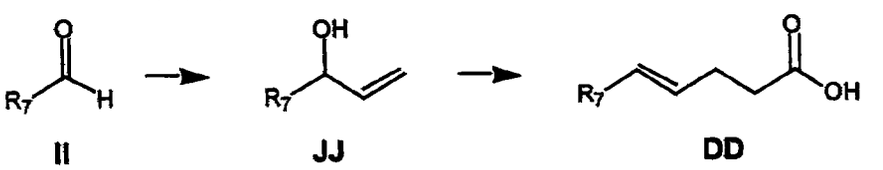
carboxylic acid **BB**. This material is not isolated, but is subjected to an amide-forming reaction with amine (or salt thereof) **P** to provide final product **CC**. The P_4 protecting group, along with any additional protecting groups that have been used on any R groups (R_1, R_2, R_3, R_6, and/or R_7) and/or on Z and/or on Z_1, is subsequently deprotected and/or further modified to yield deprotected or modified **CC**.



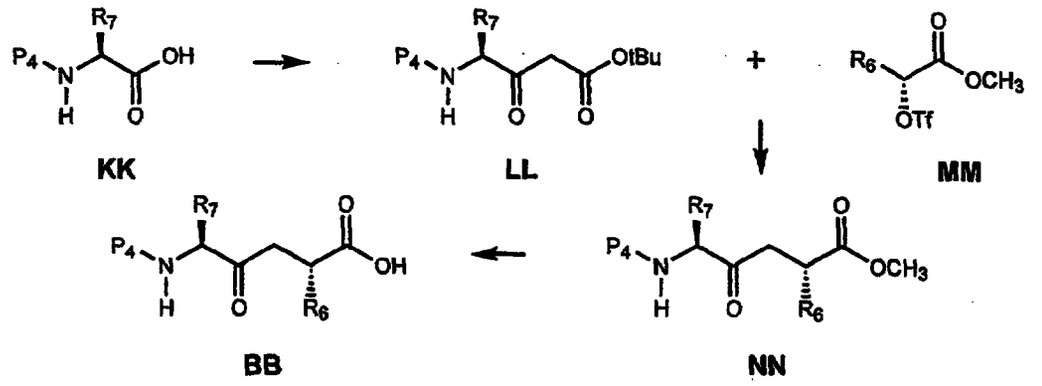
Lactone **AA** may be prepared in optically active form by the following General Method VI (see: Herold et al., *J. Org. Chem.* **1989**, *54*, 1178; Bradbury et al., *Tetrahedron Lett.* **1989**, *30*, 3845; and Bradbury et al., *J. Med. Chem.* **1990**, *33*, 2335). A γ,δ-unsaturated carboxylic acid **DD**, which incorporates R_7, is transformed into the corresponding acid chloride (not shown). This acid chloride is subjected to an amide-forming reaction with a chiral amine or a chiral oxazolidone to provide derivative **EE** (in which X_1 is a chiral amine or a chiral oxazolidone). Compound **EE** is subsequently deprotonated, and the resulting enolate is diastereoselectively alkylated with an electrophile corresponding to R_6 to provide compound **FF**, where R_5 is H. This material is then subjected to a halolactonization reaction to provide halo-lactone **GG**, in which R_5 and R_8 are H and "hal" is Br or I. Halo-lactone **GG** is subsequently transformed into azide **HH**, and this material is then converted into lactone **AA**, where P_4 is an appropriate protecting group for nitrogen.



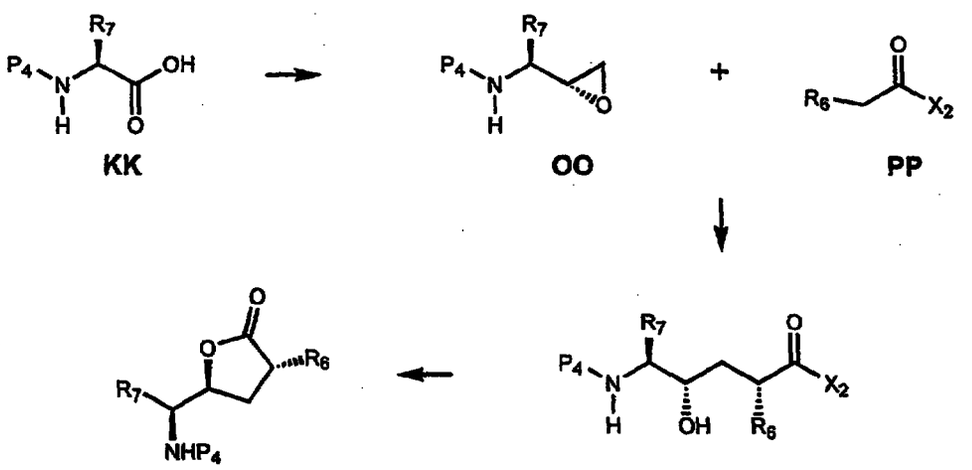
γ,δ-Unsaturated carboxylic acid **DD** may be prepared by the following General Method VII (see: Herold et al., *J. Org. Chem.* **1989**, *54*, 1178). An aldehyde **II**, which incorporates R7, is coupled with vinylmagnesium bromide to give alcohol **JJ**. Alcohol **JJ** is then transformed into γ,δ-unsaturated carboxylic acid **DD** by a three-step procedure as follows: (i) treatment with diethyl malonate and catalytic Ti(OEt)4 at 160°C for 1 hour, (ii) heating at 190°C for 4 hours, and (iii) hydrolysis with ethanolic KOH at reflux.



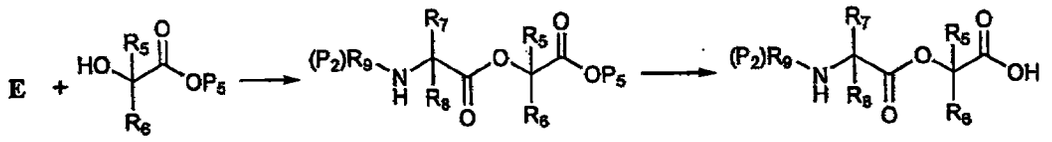
Carboxylic acid **BB** may also be prepared by General Method VIII (see Hoffman et al., *Tetrahedron*, **1997**, *53*, 7119). An amino acid **KK**, which incorporates R7 and where P4 is an appropriate protecting group for nitrogen, is transformed into β-ketoester **LL**. Compound **LL** is deprotonated and the resulting anion is condensed with triflate **MM**, which incorporates R6. The coupling product thus obtained is treated with trifluoroacetic acid to provide ketoester **NN**, and this material is subsequently hydrolyzed to afford carboxylic acid **BB**. If basic hydrolysis results in epimerization, ketoester **NN** can be transesterified (allyl alcohol, Ti(O*i*-Pr)4) and subsequently deprotected under neutral conditions (Pd(PPh3)4, morpholine) to give carboxylic acid **BB**. Triflate **MM**, in turn, may be prepared from the corresponding alcohol by treatment with trifluoromethanesulfonic anhydride and 2,6-lutidine.



Lactone **AA** may also be prepared by General Method IX (see: Askin et al., *J. Org. Chem.* **1992**, *57*, 2771; and McWilliams et al., *J. Am. Chem. Soc.* **1996**, *118*, 11970). An amino acid **KK**, which incorporates R_7 and where P_4 is an appropriate protecting group for nitrogen, is transformed into epoxide **OO** (single diastereomer) by the method described in Luly et al., *J. Org. Chem.* **1987**, *52*, 1487. Epoxide **OO** is condensed with the anion derived from compound **PP**, which incorporates R_6 and in which X_2 is a chiral auxiliary (including (1*S*,2*R*)-1-aminoindan-2-ol acetonide) to afford coupling product **QQ**. This material is subsequently cyclized under acidic conditions to provide lactone **AA**. Compound **PP** may be prepared from the corresponding carboxylic acid (not shown) by the method outlined in Askin et al., *J. Org. Chem.* **1992**, *57*, 2771.



General Method X, useful in preparation of depsipeptide compounds of the formula I-C, illustrates a method to prepare intermediate **TT**. Amino acid **E** and alcohol **RR**, where P_5 is an appropriate protecting group for oxygen, are subjected to an ester bond-forming reaction to produce intermediate **SS**. Molecule **SS** is deprotected to yield free carboxylic acid **TT**, which may be utilized in lieu of carboxylic acid **K** in any of the general methods described above.

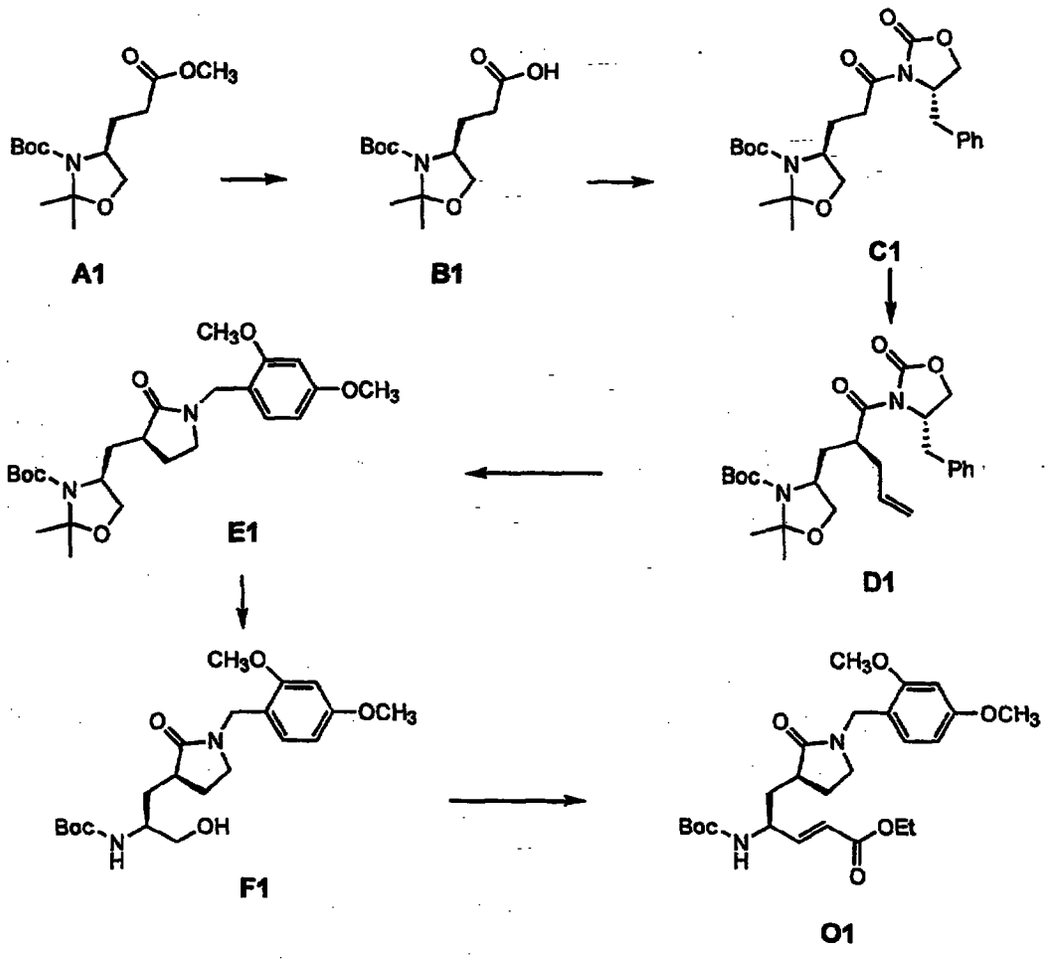


RR SS TT

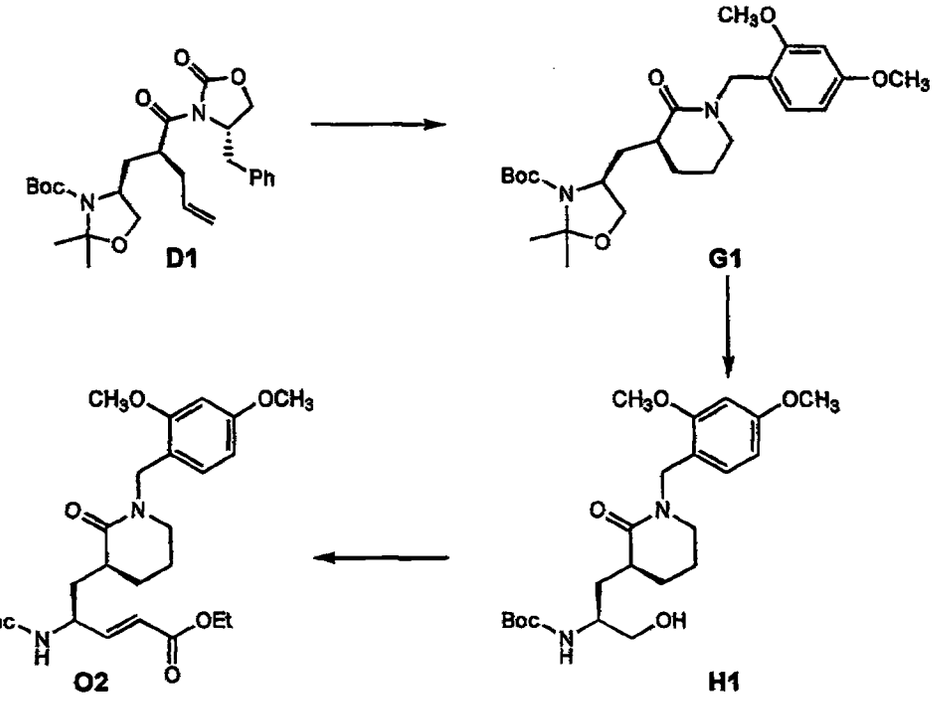
SPECIFIC SYNTHESES

The following specific methods may also be used to prepare various compounds according to the invention.

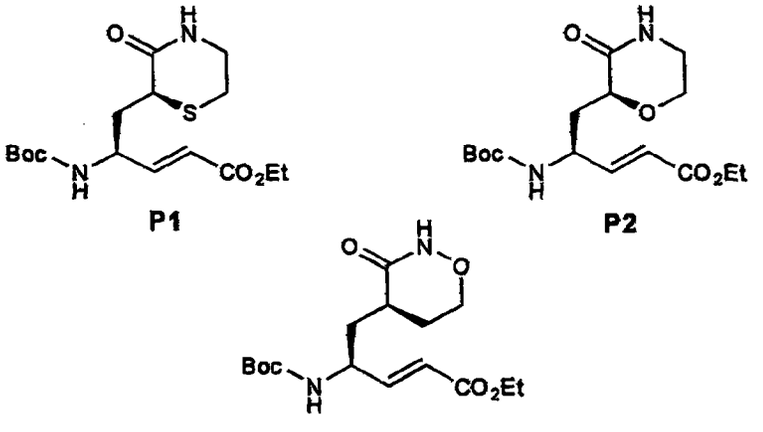
Specific Method I describes the preparation of specific intermediate **O1**, which may be utilized as intermediate **O** in the general methods described above. Thus, ester **A1** (prepared as described in Chida et al., *J. Chem. Soc., Chem. Commun.* **1992**, 1064) is hydrolyzed to give acid **B1**, which, in turn, is transformed into oxazolidinone **C1**. Compound **C1** is subsequently deprotonated, and the resulting enolate is diastereoselectively alkylated to give allyl intermediate **D1**. This entity is oxidized via ozonolysis, and the resulting aldehyde (not shown) is subjected to a reductive amination reaction producing lactam **E1**. Acid-catalyzed methanolysis of **E1** then affords alcohol **F1**. This intermediate is oxidized via the method of Swern (or other suitable oxidation conditions) to the resulting aldehyde (not shown), which is subsequently subjected to an olefin-forming reaction to provide specific intermediate **O1**.



Specific Method II describes the preparation of specific intermediate **O2**, which may be utilized as intermediate **O** in the general methods described above. Allyl intermediate **D1** is subjected to a hydroboration/oxidation sequence to afford a primary alcohol (not shown). This entity is oxidized via the method of Swern (or other suitable oxidation conditions), and the resulting aldehyde (not shown) is subjected to a reductive-amination reaction, producing lactam **G1**. Acid-catalyzed methanolysis of **G1** then affords alcohol **H1**. This intermediate is oxidized via the method of Swern (or other suitable oxidation conditions) to the resulting aldehyde (not shown), which is subsequently subjected to an olefin-forming reaction to provide specific intermediate **O2**.

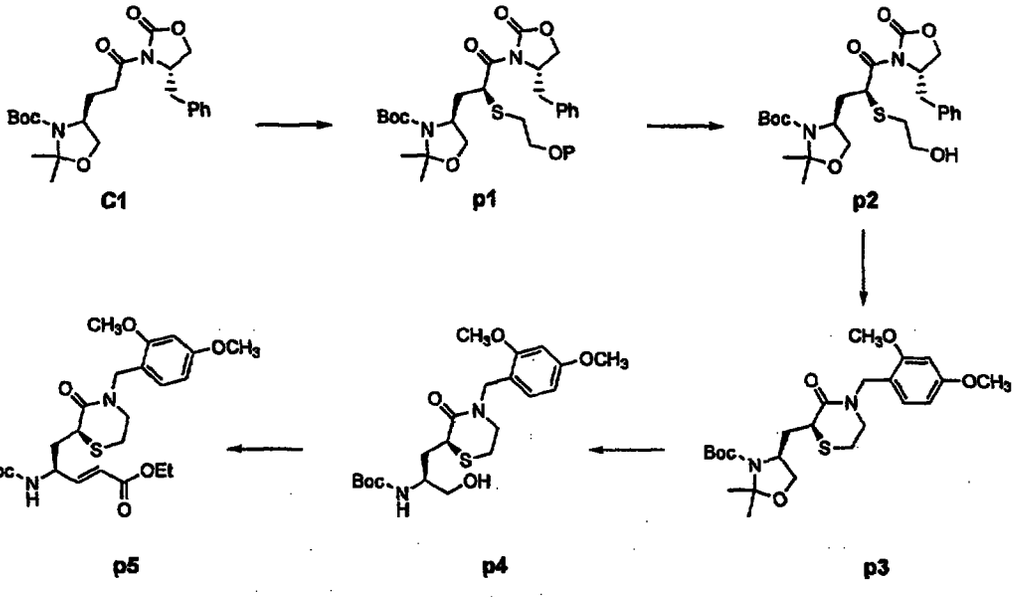


The following intermediates **P1**, **P2**, and **P3** may be used in the above general methods in place of intermediate **O**, to vary the substituent group in the R_2 position.

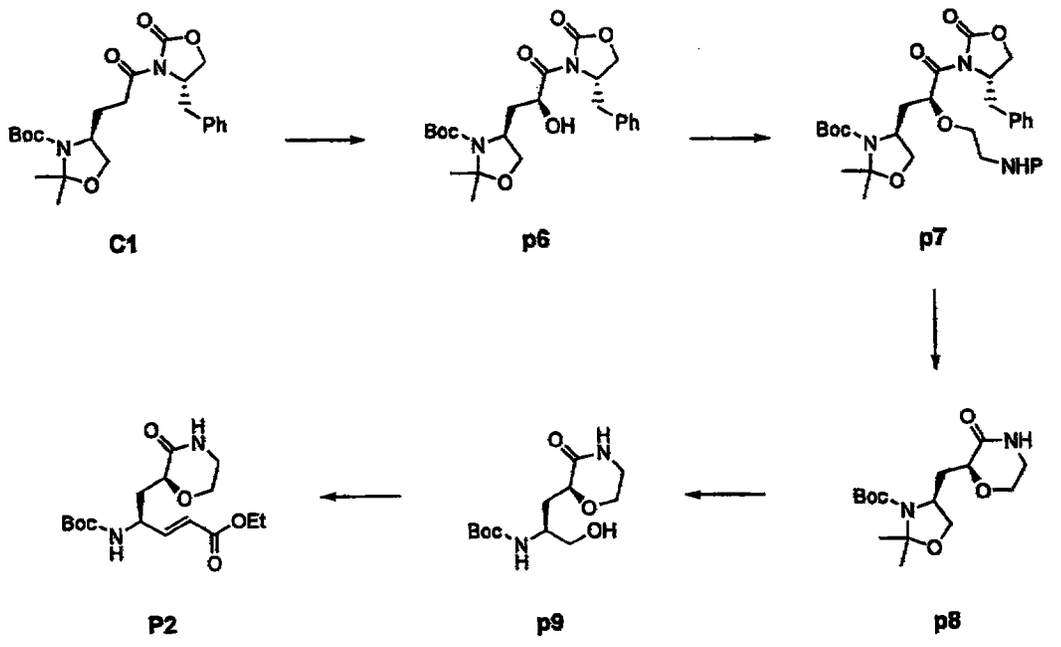


A synthesis of intermediate **P1** is described below. Intermediate **C1** (described above) is deprotonated, and the resulting enolate is trapped with an appropriate disulfide (symmetrical or mixed) to give sulfide **p1** (P is a suitable protecting group for oxygen). The oxygen-protecting group is then removed to give alcohol **p2**. This intermediate is oxidized via the method of Swern (or using other suitable oxidation conditions), and the resulting aldehyde (not shown) is subjected to a reductive amination reaction to give lactam **p3**. Acid-catalyzed methanolysis of **p3** then affords alcohol **p4**. This intermediate is oxidized via the method of

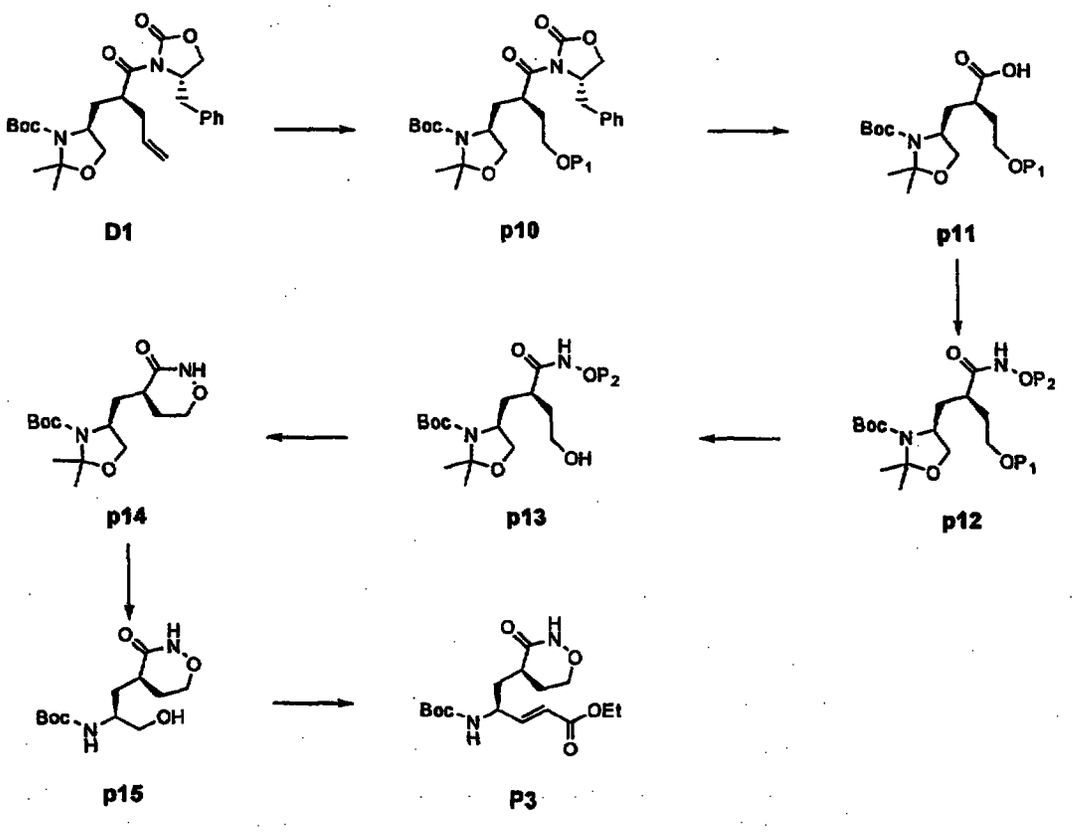
Swern (or using other suitable oxidation conditions) to the resulting aldehyde (also not shown), which is subsequently subjected to an olefin-forming reaction to provide intermediate **p5**. This compound may be utilized in place of intermediate **O** in the above general synthetic methods; alternatively, the lactam-protecting group may be removed to give intermediate **P1**.



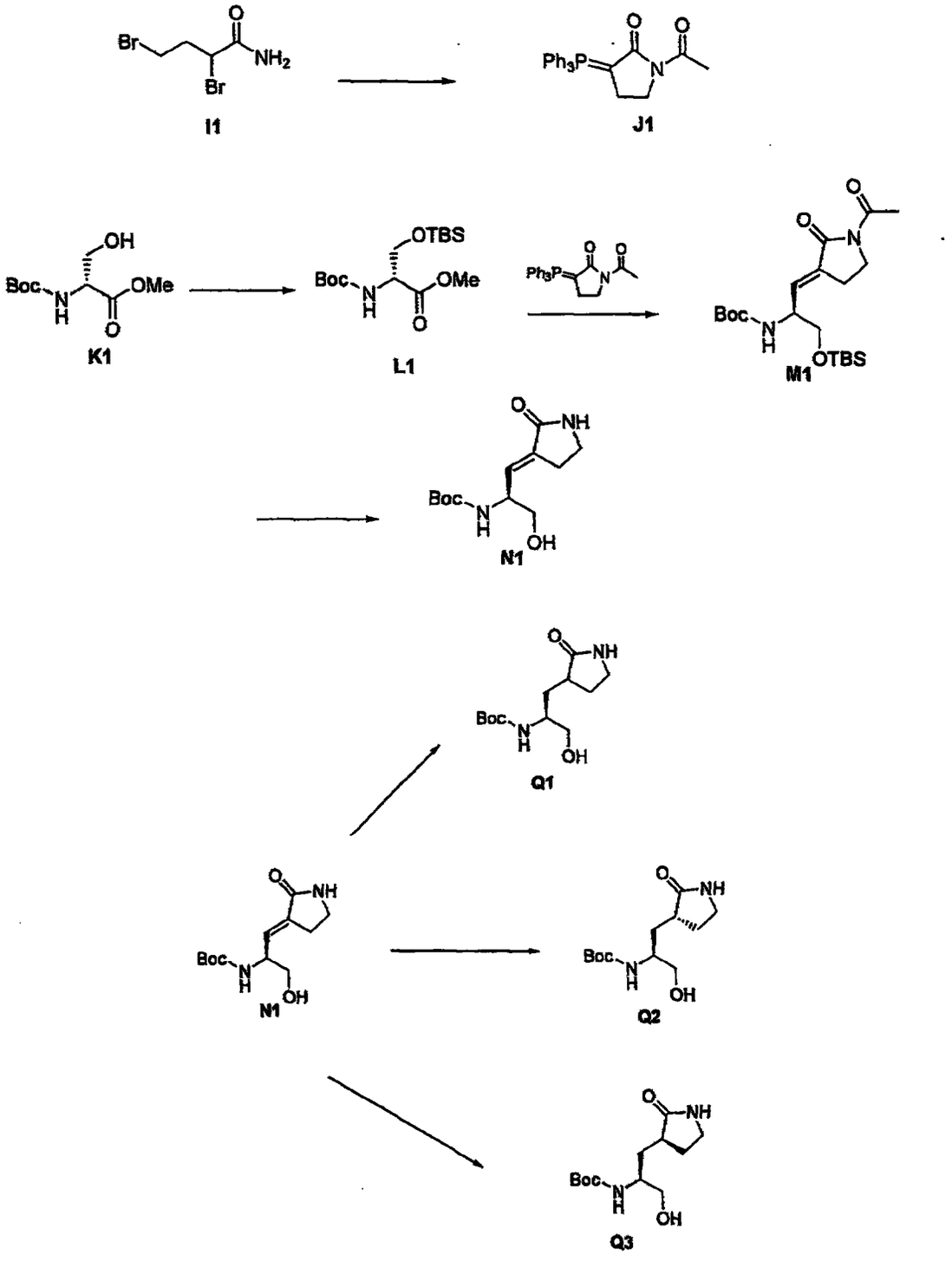
To synthesize intermediate **P2**, intermediate **C1** is deprotonated, and the resulting enolate is trapped with an appropriate source of electrophilic oxygen (e.g., an oxaziridine) to give alcohol **p6**. This intermediate is alkylated with a suitably functionalized alkyl halide or triflate to give ether **p7** (P is an appropriate protecting group for nitrogen). The nitrogen-protecting group is then removed, and the resulting amine (not shown) is subjected to cyclization conditions to give lactam **p8**. Acid-catalyzed methanolysis of **p8** then affords alcohol **p9**. This intermediate is oxidized via the method of Swern (or using other suitable oxidation conditions) to the resulting aldehyde (also not shown), which is subsequently subjected to an olefin-forming reaction to provide intermediate **P2**.



A synthesis of specific intermediate **P3** is now described. Intermediate **D1** (described above) is ozonized, and the resulting aldehyde (not shown) is reduced to the corresponding alcohol (also not shown). This intermediate is then protected to afford compound **p10** (P_1 is an appropriate protecting group for oxygen). The imide functionality present on **p10** is hydrolyzed to carboxylic acid **p11**, and this intermediate is coupled with a suitably protected hydroxylamine derivative to give amide **p12** (P_2 is an appropriate protecting group for oxygen that is stable to conditions which will remove P_1). The P_1 protecting group is then removed, and the resulting alcohol (**p13**) is transformed into an appropriate leaving group (halide or triflate, not shown). The P_2 protecting group is then removed, and the resulting hydroxamic acid is cyclized to give intermediate **p14**. Acid-catalyzed methanolysis of **p14** then affords alcohol **p15**. This intermediate is oxidized via the method of Swern (or using other suitable oxidation conditions) to the resulting aldehyde (not shown), which is subsequently subjected to an olefin-forming reaction to provide intermediate **P3**.



Specific Method III describes the preparation of intermediates **Q1**, **Q2**, and **Q3**, which may be utilized in the general methods described above. The known compound **I1** is transformed into the literature molecule **J1** by a modification of a published procedure (Ikuta et al., *J. Med. Chem.* **1987**, vol. 30, p. 1995). Independently, the amino acid ester **K1** is protected to afford silyl ether **L1**. The ether is reduced with DIBAL (or using other suitable reduction conditions), and the resulting aldehyde (not shown) is subjected to an olefin-forming reaction with intermediate **J1**, producing **M1**. Silyl deprotection of **M1** then affords alcohol **N1**. This intermediate is subjected to a variety of hydrogenation conditions to provide intermediates **Q1**, **Q2**, and **Q3**. These intermediates may be transformed into intermediates analogous to intermediate **O1** (see Specific Method I above) by oxidation and subsequent olefination.



The artisan will recognize that various compounds of the invention may be made by following the above-described general and specific methods as well as teachings in the art, including the references cited herein, the disclosures of which are hereby incorporated by reference. Additionally, the artisan may prepare various compounds of the invention according

to the example described below or through routine modifications to the syntheses described herein.

EXAMPLES

Examples of various preferred compounds of formula I are set forth below. The structures of the compounds of the following examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis, mass spectrometry, thin layer chromatography, melting-point determination, and boiling-point determination. Where there is any discrepancy between the given structural formula shown for a compound and its chemical name provided, the structural formula applies.

Proton magnetic resonance (^{1}H NMR) spectra were determined using a Varian UNITY*plus* 300 spectrometer operating at a field strength of 300 megahertz (MHz). Chemical shifts are reported in parts per million (ppm, δ) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced to residual protic solvent signals as follows: $CHCl_3$ = 7.26 ppm; DMSO = 2.49 ppm; C_6HD_5 = 7.15 ppm. Peak multiplicities are designated as follows: s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; br = broad resonance; and m = multiplet. Coupling constants are given in Hertz. Infrared absorption (IR) spectra were obtained using a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc. (Norcross, GA) and gave results for the elements stated within ±0.4% of the theoretical values. Flash column chromatography was performed using Silica gel 60 (Merck Art 9385). Analytical thin layer chromatography (TLC) was performed using precoated sheets of Silica 60 F_{254} (Merck Art 5719). Melting points (abbreviated as mp) were determined on a Mel-Temp apparatus and are uncorrected. All reactions were performed in septum-sealed flasks under a slight positive pressure of argon, unless otherwise noted. All commercial reagents were used as received from their respective suppliers with the following exceptions: tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl prior to use; dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use; anhydrous lithium chloride was prepared by heating at 110°C under vacuum overnight.

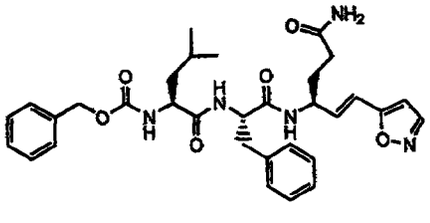
The following abbreviations are used herein: Et_2O refers to diethyl ether; DMF refers to *N,N*-dimethylformamide; DMSO refers to dimethylsulfoxide; and MTBE refers to *tert*-butyl methyl ether. Other abbreviations include: CH_3OH (methanol), EtOH (ethanol), EtOAc (ethyl acetate), DME (ethylene glycol dimethyl ether), Ac (acetyl), Me (methyl), Ph (phenyl), Tr

(triphenylmethyl), Cbz (benzyloxycarbonyl), Boc (*tert*-butoxycarbonyl), TFA (trifluoroacetic acid), DIEA (*N,N*-diisopropylethylamine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), HOBt (1-hydroxybenzotriazole hydrate), PyBOP (benzotriazole1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride), DCC (dicyclohexylcarbodiimide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), DMAP (4-dimethylaminopyridine), Gln (glutamine), Leu (leucine), Phe (phenylalanine), Val (valine), His (histidine), 1-Naphth (1-naphthlyalanine), 2-Naphth (2-naphthylalanine), α-t-Butyl-Gly (tert-butyl glycine), (*S*)-Pyrrol-Ala ((2*S*,3'*S*)-2-amino-3-(2'-oxopyrrolidin-3'-yl)-propionic acid), and (*S*)-Piper-Ala ((2*S*,3'*S*)-2-amino-3-(2'-oxo-piperidin-3'-yl)-propionic acid). Additionally, "L" represents naturally occurring amino acids.

A simplified naming system employing amino acid abbreviations is used to identify some intermediates and final products. When naming compounds, italicized amino acid abbreviations represent modifications at the C-terminus of that residue where the following apply: (1) acrylic acid esters are reported as "E" (trans) propenoates; (2) substituted 3-methylene-dihydrofuran-2-ones are reported as "E" (trans) 2-(α-vinyl-γ-butyrolactones); and (3) 5-vinylisoxazoles are reported as "E" (trans) propenisoxazoles. In addition, the terminology "$AA_1\Psi[COCH_2]$-AA_2" indicates that, for any peptide sequence, two amino acids (AA_1 and AA_2) usually linked by an amide bond are replaced by a ketomethlyene dipeptide isostere moiety. The terminology "AA_1-NCH_3-AA_2" indicates that, for any peptide sequence, the amide bond that usually connects the two amino acids (AA_1 and AA_2) is replaced by an *N*-methyl amide linkage. The terminology "AA_1-O-AA_2" indicates that, for any peptide sequence, the amide bond that usually connects the two amino acids (AA_1 and AA_2) is replaced by an ester linkage.

Examples of embodiments in accordance with the invention are described below.

Example 1 - Preparation of Comparison Compound #1: 5-(3'-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-Propene)-isoxazole



(Comparison Compound #1)

Preparation of Intermediate Cbz-L-(Tr-Gln)-OMe

Cbz-L-(Tr-Gln) (0.26 g, 0.50 mmol, 1 equiv.) was added to a solution of acetyl chloride (0.25 mL, 3.52 mmol, 7.0 equiv.) in CH_3OH (5 mL), and stirring was continued at 23°C for 1 h (hour). The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4 and was concentrated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to afford Cbz-L-(Tr-Gln)-OMe (0.23 g, 84% yield) as a white solid: mp = 139-140°C; IR (cm^{-1}) 1742, 1207; ^1H NMR (DMSO-d_6) δ 1.16 (t, 1H, J = 7.0), 1.77 (m, 1H), 1.97 (m, 1H), 3.61 (s, 3H), 4.99 (m, 1H), 5.03 (s, 2H), 7.02-7.55 (m, 20H), 7.69 (d, 1H, J = 7.7), 8.59 (s, 1H); Anal. ($C_{33}H_{32}N_2O_5$) C, H, N.

Preparation of Intermediate Cbz-L-(Tr-Glutaminol)

Lithium chloride (0.24 g, 5.66 mmol, 2.0 equiv.) was added to a solution of Cbz-L-(Tr-Gln)-OMe (1.50 g, 2.79 mmol, 1 equiv.) in 2:1 THF:EtOH (30 mL), and the mixture was stirred at 23°C until all solids had dissolved (10 minutes). Sodium borohydride (0.21 g, 5.55 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred overnight at 23°C. The solvents were removed under reduced pressure, the residue was taken up in water (50 mL), and the pH was adjusted to 2-3 with 10% HCl. The product was extracted with EtOAc (50 mL), and the organic layer was washed with water (50 mL) and brine (50 mL) before drying over $MgSO_4$. The organic layer was concentrated, and the residue was purified by flash column chromatography (gradient elution, 20→50% EtOAc in benzene) to give Cbz-L-(Tr-glutaminol) (1.02 g, 72% yield) as a white glassy solid: mp = 66-70°C; IR (cm^{-1}) 3318, 1699, 1510, 1240; ^1H NMR (DMSO-d_6) δ 1.40 (m, 1H), 1.72 (m, 1H), 2.26 (m, 2H), 3.17-3.50 (m, 3H), 4.64 (t, 1H, J = 5.0), 5.00 (s, 2H), 7.00-7.40 (m, 20H), 6.96 (d, 1H, J = 8.5), 8.54 (s, 1H); Anal. ($C_{32}H_{32}N_2O_4$) C, H, N.

Preparation of Intermediate L-(Tr-Glutaminol)

A suspension of Cbz-L-(Tr-glutaminol) (1.93 g, 3.79 mmol) in CH_3OH (25 mL) and Pd/C (10%, 0.19 g) was stirred under a hydrogen atmosphere (balloon) for 4 hours, then was filtered through a layer of Celite. The filtrate was concentrated under reduced pressure to give L-(Tr-glutaminol) as a white amorphous solid (1.38 g, 98% yield): mp = 191-193°C; IR (cm^{-}

1]) 3255 (br), 1642, 1527; ^{1}H NMR (DMSO-d_6) δ 1.29 (m, 1H), 1.53 (m, 1H), 2.29 (m, 2H), 3.08 (m, 1H), 3.18 (m, 2H), 3.38 (s, br, 2H), 4.43 (s, br, 1H), 7.14-7.28 (m, 15H), 8.62 (s, 1H).

Preparation of Intermediate Cbz-L-Leu-L-Phe-L-(Tr-Glutaminol)

Carbonyldiimidazole (0.17 g, 1.05 mmol, 1.0 equiv.) was added to a solution of Cbz-L-Leu-L-Phe-OH (0.41 g, 1.0 mmol, 0.95 equiv.) in THF (10 mL), and the reaction mixture was stirred at 23°C for 1 hour. L-(Tr-Glutaminol) (0.39 g, 1.05 mmol, 1 equiv.) was then added, and the resulting solution was stirred overnight. The volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography (gradient elution, 2→4% CH_3OH in $CHCl_3$) to give Cbz-L-Leu-L-Phe-L-(Tr-glutaminol) (0.47 g, 62% yield) as a white amorphous solid: mp = 92-95°C; IR (cm^{-1}) 3302, 1657, 1520, 1238; ^{1}H NMR (DMSO-d_6) δ 0.79 (t, 6H, J = 7.0), 1.30 (m, 2H), 1.44 (m, 2H), 1.75 (m, 1H), 2.22 (m, 2H), 2.82 (m, 1H), 2.97 (m, 1H), 3.14 (m, 1H), 3.25 (m, 1H), 3.63 (m, 1H), 3.95 (m, 1H), 4.48 (m, 1H), 4.65 (t, 1H, J = 5.0), 4.96 (d, 1H, J = 13.0), 5.02 (d, 1H, J = 13.0), 7.07-7.33 (m, 25H), 7.42 (d, 1H, J = 8.0), 7.66 (d, 1H, J = 8.5), 7.86 (d, 1H, J = 8.0), 8.52 (s, 1H); Anal. ($C_{47}H_{52}N_4O_6 \cdot 0.5H_2O$) C, H, N.

Preparation of Intermediate Cbz-L-Leu-L-Phe-L-(Tr-Gln)-H

o-Iodoxybenzoic acid (0.63 g, 2.25 mmol, 3.0 equiv.) was added to a solution of Cbz-L-Leu-L-Phe-L-(Tr-glutaminol) (0.58 g, 0.75 mmol, 1 equiv.) in DMSO (7.5 mL) at 23°C. After stirring for 2 hours, the DMSO was removed under reduced pressure. The residue was twice diluted with CH_2Cl_2, and the solvent evaporated to remove any remaining DMSO. The residue was diluted with EtOAc (30 mL) and filtered, and the filtrate was washed with 5% $Na_2S_2O_3$/5% $NaHCO_3$ solution (30 mL), water (30 mL), and brine (30 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give Cbz-L-Leu-L-Phe-L-(Tr-Gln)-H (0.53 g, 92% yield) as a white glassy solid, which was used immediately without further purification: ^{1}H NMR (DMSO-d_6) δ 0.79 (m, 6H), 1.00-1.98 (m, 5H), 2.27 (m, 2H), 2.84 (m, 1H), 3.02 (m, 1H), 3.98 (m, 2H), 4.58 (m, 1H), 4.99 (s, 2H), 7.14-7.32 (m, 25H), 7.39 (d, 1H, J = 8.1), 7.97 (d, 1H, J = 8.5), 8.38 (d, 1H, J = 8.0), 8.60 (s, 1H), 9.20 (s, 1H).

Preparation of Intermediate 5-{3'-(Cbz-L-Leu-L-Phe-L-(Tr-*Gln*))-E-Propene}-Isoxazole

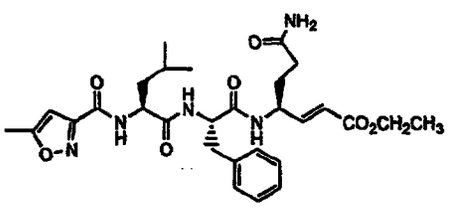
A solution of $KN((CH_3)_3Si)_2$ (0.95 mL of a 0.5 M solution in THF, 0.477 mmol, 1.0 equiv.) was added to a suspension of isoxazol-5-ylmethyl-triphenylphosphonium bromide (0.222 g, 0.525 mmol, 1.1 equiv) in THF (20 mL) at 0°C, and the reaction was stirred at 0°C for 30 minutes. A solution of Cbz-L-Leu-L-Phe-L-(Tr-Gln)-H (0.366 g, 0.477 mmol, 1 equiv.)

in THF (10 mL) was added, and the reaction mixture was then stirred overnight at 23°C. The solvent was removed *in vacuo*, and the residue was diluted with EtOAc (30 mL), washed with water (30 mL), and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash silica gel chromatography (gradient elution, 0→1% CH_3OH in $CHCl_3$) to give 5-{3'-(Cbz-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propene}-isoxazole (0.307 g, 70% yield) as an amorphous solid: IR (cm^{-1}) 3423, 1678, 1568, 1265, 1043, 711; ^1H NMR (DMSO-d_6) δ 0.77-0.81 (m, 6H), 1.21-1.36 (m, 2H), 1.40-1.55 (m, 1H), 1.60-1.80 (m, 2H), 2.34-2.45 (m, 2H), 2.82-2.87 (m, 1H), 2.91-3.04 (m, 1H), 3.95-4.00 (m, 1H), 4.41-4.50 (m, 1H), 4.53-4.60 (m, 1H), 4.99 (q, 2H, J = 6.0), 6.19 (d, 1H, J = 15.0), 6.36 (dd, 1H, J = 15.0, 6.0), 6.46 (s, 1H), 7.15-7.33 (m, 20H), 7.42 (d, 1H, J = 9.0), 7.56-7.63 (m, 5H), 7.96 (d, 1H, J = 9.0), 8.08 (d, 1H, J = 9.0), 8.51 (s, 1H), 8.58 (s, 1H); HRMS calcd. for $C_{51}H_{53}N_5O_6$+Cs 964.3050 (M+Cs), found 964.3018.

Preparation of Product: 5-(3'-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-Propene)-Isoxazole

Trifluoroacetic acid (1 mL) was added to a solution of 5-{3'-(Cbz-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propene}-isoxazole (0.214 g, 0.257 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred at 23°C overnight. The solvent was removed *in vacuo* and the residue purified by flash silica gel chromatography (gradient elution, 0→1% CH_3OH in $CHCl_3$) to give 5-(3'-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-propene)-isoxazole as a white solid (0.054 g, 36% yield): ^1H NMR (DMSO-d_6) δ 0.77-0.83 (m, 6H), 1.26-1.46 (m, 2H), 1.47-1.62 (m, 1H), 1.69-1.79 (m, 2H), 2.04-2.29 (m, 2H), 2.83-2.88 (m, 1H), 2.97-3.10 (m, 1H), 3.99-4.12 (m, 1H), 4.37-4.43 (m, 1H), 4.48-4.57 (m, 1H), 5.01 (q, 2H, J = 6.0), 6.20 (d, 1H, J = 15.0), 6.36 (dd, 1H, J = 15.0, 6.0), 6.45 (d, 1H, J = 3.0), 6.75 (s, 1H), 7.14-7.29 (m, 6H), 7.31-7.40 (m, 5H), 7.45 (d, 1H, J = 9.0), 8.04 (d, 1H, J = 9.0), 8.07 (d, 1H, J = 9.0), 8.51 (d, 1H, J = 3.0); Anal. ($C_{32}H_{39}N_5O_6$) C, H, N.

Example 2 - Preparation of Compound A-1: Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-Propenoate



(A-1)

Preparation of Intermediate Boc-L-(Tr-Gln)-N(OMe)Me

Isobutyl chloroformate (4.77 mL, 36.8 mmol, 1.0 equiv.) was added to a solution of Boc-L-(Tr-Gln)-OH (18.7 g, 36.7 mmol, 1 equiv.) and 4-methylmorpholine (8.08 mL, 73.5 mmol, 2.0 equiv.) in CH_2Cl_2 (250 mL) at 0°C. The reaction mixture was stirred at 0°C for 20 min. (minutes), then *N,O*-dimethylhydroxylamine hydrochloride (3.60 g, 36.7 mmol, 1.0 equiv.) was added. The resulting solution was stirred at 0°C for 20 min. and at 23°C for 2 hours (h), and then was partitioned between water (150 mL) and CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (gradient elution, 40→20% hexanes in EtOAc) provided Boc-L-(Tr-Gln)-N(OMe)Me (16.1 g, 82% yield) as a white foam: IR (cm^{-1}) 3411, 3329, 3062, 1701, 1659; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.63-1.77 (m, 1H), 2.06-2.17 (m, 1H), 2.29-2.43 (m, 2H), 3.17 (s, 3H), 3.64 (s, 3H), 4.73 (s, br, 1H), 5.38-5.41 (m, 1H), 7.20-7.31 (m, 15H); Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

Preparation of Intermediate Boc-L-(Tr-Gln)-H

Diisobutylaluminum hydride (50.5 mL of a 1.5 M solution in toluene, 75.8 mmol, 2.5 equiv.) was added to a solution of Boc-L-(Tr-Gln)-N(OMe)Me (16.1 g, 30.3 mmol, 1 equiv.) in THF at -78°C, and the reaction mixture was stirred at -78°C for 4 hours. Methanol (4 mL) and 1.0 M HCl (10 mL) were added sequentially, and the mixture was warmed to 23°C. The resulting suspension was diluted with Et_2O (150 mL), and was washed with 1.0 M HCl (3 x 100 mL), half-saturated $NaHCO_3$ (100 mL), and water (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude Boc-L-(Tr-Gln)-H (13.8 g, 97% yield) as a white solid: mp = 114-116°C; IR (cm^{-1}) 3313, 1697, 1494; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.65-1.75 (m, 1H), 2.17-2.23 (m, 1H), 2.31-2.54 (m, 2H), 4.11 (s, br, 1H), 5.38-5.40 (m, 1H), 7.11 (s, 1H), 7.16-7.36 (m, 15H), 9.45 (s, 1H).

Preparation of Intermediate Ethyl-3-(Boc-L-(Tr-*Gln*))-E-Propenoate

Sodium bis(trimethylsilyl)amide (22.9 mL of a 1.0 M solution in THF, 22.9 mmol, 1.0 equiv.) was added to a solution of triethyl phosphonoacetate (5.59 g, 22.9 mmol, 1.0 equiv.) in THF (200 mL) at -78°C, and the resulting solution was stirred for 20 minutes at that temperature. Crude Boc-L-(Tr-Gln)-H (10.8 g, 22.9 mmol, 1 equiv.) in THF (50 mL) was added via cannula, and the reaction mixture was stirred for 2 hours at -78°C, warmed to 0°C for 10 minutes, and then partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were

concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) provided ethyl-3-[Boc-L-(Tr-*Gln*)]-E-propenoate (10.9 g, 88% yield) as a white foam: IR (cm^{-1}) 3321, 1710; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2), 1.42 (s, 9H), 1.70-1.78 (m, 1H), 1.80-1.96 (m, 1H), 2.35 (t, 2H, J = 7.0), 4.18 (q, 2H, J = 7.2), 4.29 (s, br, 1H), 4.82-4.84 (m, 1H), 5.88 (dd, 1H, J = 15.7, 1.6), 6.79 (dd, 1H, J = 15.7, 5.3), 6.92 (s, 1H), 7.19-7.34 (m, 15H); Anal. ($C_{33}H_{38}N_2O_5$) C, H, N.

Preparation of Intermediate Ethyl-3-(Boc-L-Phe-L-(Tr-*Gln*))-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 15 mL), was added to a solution of ethyl-3-(Boc-L-(Tr-*Gln*))-E-propenoate (3.26 g, 6.01 mmol, 1 equiv.) in the same solvent (15 mL) at 23°C. After 2 h, the volatiles were removed under reduced pressure to afford ethyl-3-(H_2N-L-(Tr-*Gln*))-E-propenoate•HCl. This material was dissolved in CH_2Cl_2 (60 mL) and Boc-L-Phe-OH (1.59 g, 6.01 mmol, 1.0 equiv.), HOBt (1.22 g, 9.02 mmol, 1.5 equiv.), 4-methylmorpholine (1.98 mL, 18.03 mmol, 3 equiv.), and EDC (1.73 g, 9.02 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was stirred at 23°C overnight, and then was partitioned between water (100 mL) and CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue was purified by flash column chromatography (40% EtOAc in hexane) to afford ethyl-3-(Boc-L-Phe-L-(Tr-*Gln*))-E-propenoate (3.55 g, 85%) as white foam: IR (cm^{-1}) 3306, 1706, 1661; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2), 1.38 (s, 9H), 1.65-1.76 (m, 1H), 1.87-1.99 (m, 1H), 2.25-2.27 (m, 2H), 2.94-3.01 (m, 2H), 4.14-4.26 (m, 3H), 4.48-4.53 (m, 1H), 4.95 (s, br, 1H), 5.64 (d, 1H, J = 15.8), 6.29 (d, 1H, J = 8.1), 6.64 (dd, 1H, J = 15.8, 5.4), 6.80 (s, br, 1H), 7.14-7.32 (m, 20H); Anal. ($C_{42}H_{47}N_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-(Boc-L-Leu-L-Phe-L-(Tr-*Gln*))-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 15 mL) was added to a solution of ethyl-3-(Boc-L-Phe-L-(Tr-*Gln*))-E-propenoate (6.40 g, 9.28 mmol, 1 equiv.) in the same solvent (15 mL) at 23°C. After 2 hours, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), and Boc-L-Leu-OH (2.58 g, 11.1 mmol, 1.2 equiv.), HOBt (1.88 g, 13.9 mmol, 1.5 equiv.), 4-methylmorpholine (3.06 mL, 27.8 mmol, 3 equiv.), and EDC (2.67 g, 13.92 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was stirred at 23°C overnight, and then was partitioned between water (100 mL) and CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to afford ethyl-3-(Boc-L-

Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate (6.46 g, 87% yield) as white foam: IR (cm^{-1}) 3284, 1651, 1515; ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, J = 6.0), 0.89 (d, 3H, J = 6.0), 1.29 (t, 3H, J = 7.2), 1.34 (s, 9H), 1.38-1.60 (m, 3H), 1.62-1.89 (m, 1H), 1.95-1.97 (m, 1H), 2.28-2.30 (m, 2H), 3.06-3.08 (m, 2H), 3.92-3.94 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.48-4.51 (m, 2H), 4.67 (m, 1H), 5.66 (d, 1H, J = 15.9), 6.51-6.57 (m, 2H), 6.69 (dd, 1H, J = 15.6, 5.1), 7.10-7.33 (m, 21H); Anal. ($C_{48}H_{58}N_4O_7 \cdot 0.33H_2O$) C, H, N.

Preparation of Intermediate Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-Propenoate

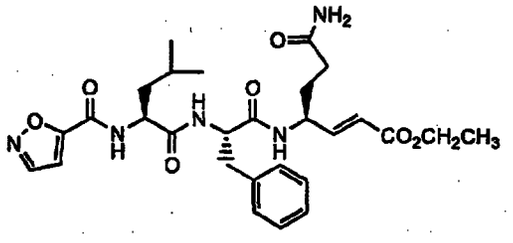
A solution of HCl in 1,4-dioxane (4.0 M, 3 mL), was added to a solution of ethyl-3-(Boc-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate (0.216 g, 0.27 mmol, 1 equiv.) in the same solvent (3 mL) at 23°C. After 2 hours, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), cooled to 0°C, and triethylamine (0.112 mL, 0.81 mmol, 3.0 equiv.) and 5-methylisoxazole-3-carbonyl chloride (0.058 g, 0.40 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was stirred at 0°C for 30 minutes, and then was partitioned between water (50 mL) and CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to afford ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate (0.199 g, 91% yield) as a white foam: IR (cm^{-1}) 3286, 1650, 1541; ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, J = 5.4), 0.89 (d, 3H, J = 5.7), 1.28 (t, 3H, J = 7.2), 1.43-1.59 (m, 2H), 1.67-1.75 (m, 1H), 1.95-1.99 (m, 2H), 2.28 (t, 2H, J = 7.2), 2.41 (s, 3H), 2.97-3.04 (m, 1H), 3.06-3.13 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.31-4.33 (m, 1H), 4.48-4.52 (m, 2H), 5.72 (d, 1H, J = 15.9), 6.19 (s, 1H), 6.41 (d, 1H, J = 7.5), 6.59 (d, 1H, J = 8.1), 6.71 (dd, 1H, J = 15.3, 6.0), 6.95 (d, 1H, J = 6.6), 7.09-7.21 (m, 21H); Anal. ($C_{48}H_{53}N_5O_7 \cdot H_2O$) C, H, N.

Preparation of Product Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-Propenoate

Triisopropylsilane (0.077 mL, 0.376 mmol, 1.8 equiv.) and trifluoroacetic acid (3 mL) were added sequentially to a solution of ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate (0.185 g, 0.21 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) at 23°C, producing a bright yellow solution. The reaction mixture was stirred for 30 minutes at 23°C, during which time it became colorless. The volatiles were removed under reduced pressure, and the resulting white solid was triturated with Et_2O (10 mL), filtered, and air-dried to give

ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-propenoate (0.87 g, 81% yield) as white solid: mp = 223-225°C; IR (cm^{-1}) 3298, 1662, 1544, 1457, 1278; ^1H NMR (DMSO-d_6) δ 0.81 (d, 3H, J = 6.0), 0.85 (d, 3H, J = 6.3), 1.23 (t, 3H, J = 6.9), 1.38-1.42 (m, 1H), 1.48-1.77 (m, 4H), 2.04 (t, 2H, J = 7.2), 2.46 (s, 3H), 2.78-2.86 (m, 1H), 2.93-3.00 (m, 1H), 4.11 (q, 2H, J = 7.2), 4.36-4.54 (m, 3H), 5.63 (d, 1H, J = 15.6), 6.56 (s, 1H), 6.68 (dd, 1H, J = 15.9, 5.4), 6.76 (s, br, 1H), 7.19 (m, 6H), 8.09 (d, 1H, J = 8.1), 8.14 (d, 1H, J = 7.8), 8.58 (d, 1H, J = 7.5); Anal. ($C_{29}H_{39}N_5O_7$) C, H, N.

Example 3 - Preparation of Compound A-2: Ethyl-3-((Isoxazole-5'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-Propenoate



(A-2)

Preparation of Intermediate Ethyl-3-((Isoxazole-5'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-Propenoate

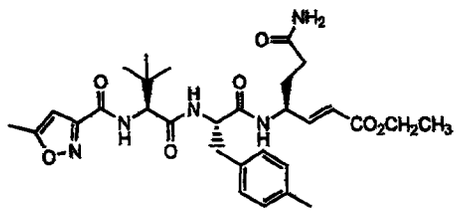
This compound was prepared from ethyl-3-(Boc-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate and isoxazole-5-carbonyl chloride using the procedure described above (Example 2) for the preparation of ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate: IR (cm^{-1}) 3282, 1643, 1530; ^1H NMR ($CDCl_3$) δ 0.87 (t, 6H, J = 6.6), 1.29 (t, 3H, J = 7.2), 1.49-1.64 (m, 3H), 1.69-1.80 (m, 1H), 1.90-1.96 (m, 1H), 2.30 (t, 2H, J = 7.2), 2.92-2.96 (m, 1H), 3.02-3.09 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.42-4.48 (m, 3H), 5.69 (d, 1H, J = 15.3), 6.65 (s, br, 1H), 6.66 (dd, 1H, J = 15.9, 5.4), 6.76-6.79 (m, 2H), 7.00-7.31 (m, 22H), 8.24 (s, 1H); Anal. ($C_{47}H_{51}N_5O_7 \cdot 0.75\ H_2O$) C, H, N.

Preparation of Ethyl-3-((Isoxazole-5'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-Propenoate

The title compound was prepared from ethyl-3-((isoxazole-5'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate using a procedure analogous to that described above (Example 2) for the preparation of ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*)-E-propenoate: mp = 217-220°C; IR (cm^{-1}) 3302, 1655, 1541; ^1H NMR (DMSO-d_6) δ 0.81 (d, 3H, J = 6.0), 0.86 (d, 3H, J = 6.0), 1.21 (t, 3H, J = 7.2), 1.42-1.75 (m, 5H), 2.04 (t, 2H, J = 7.2), 2.78-2.87 (m, 1H), 2.94-3.01 (m, 1H), 4.11 (q, 2H, J = 7.2), 4.37 (m, 1H), 4.41-4.52 (m, 2H), 5.64 (d, 1H, J = 15.6), 6.68 (dd, 1H, J = 15.9, 5.4), 6.76 (s, br, 1H), 7.12-7.19 (m, 7H),

8.02 (d, 1H, J = 8.1), 8.20 (d, 1H, J = 8.1), 8.74 (d, 1H, J = 1.8), 8.94 (d, 1H, J = 7.8); Anal. ($C_{28}H_{37}N_5O_7$) C, H, N.

Example 4 - Preparation of Compound A-3: Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-*Gln*)-E-Propenoate



(A-3)

Preparation of Intermediate Ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-Propenoate

Ethyl-3-(H_2N-L-(Tr-*Gln*))-E-propenoate•HCl (prepared as described in Example 2 above, 1.37 g, 3.10 mmol) was dissolved in DMF (10 mL) at 23°C. Diisopropylethylamine (1.08 mL, 6.20 mmol) was added, followed by Boc-L-(4-Me-Phe)-OH (0.87 g 3.10 mmol). The reaction was cooled to 0°C. HATU (1.18 g, 3.10 mmol) was added, and the reaction allowed to warm to room temperature. The DMF was removed *in vacuo*. The residue was dissolved in EtOAc (30 mL), and the organic phase was washed sequentially with 10% HCl solution (25 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL). The solvent was dried ($MgSO_4$) and filtered, and the residue purified by flash column chromatography (gradient elution, 0→0.75% CH_3OH in $CHCl_3$) to give ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (1.48 g, 68% yield) as a white amorphous solid: IR (cm^{-1}) 1713, 1655, 1491, 1175; ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.0), 1.30 (s, 9H), 1.62-1.66 (m, 2H), 2.23 (s, 3H), 2.32 (m, 2H), 2.72 (m, 1H), 2.84 (m, 1H), 4.07-4.09 (m, 1H), 4.10 (q, 2H, J = 7.0), 4.38 (m, 1H), 5.64 (d, 1H, J = 15.5), 6.72 (dd, 1H, J = 15.5, 5.5), 6.88 (d, 1H, J = 8.0), 7.04 (d, 2H, J = 7.7), 7.10 (d, 2H, J = 7.7), 7.14-7.28 (m, 15H), 8.02 (d, 1H, J = 8.0), 8.53 (s, 1H); Anal. ($C_{43}H_{49}N_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-(Boc-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-Propenoate

Ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (1.45 g, 2.06 mmol) was dissolved in 1,4-dioxane (27 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 14 mL) was added. The reaction was stirred at room temperature for 4 hours. The solvent was removed by evaporation, and the residue taken up in EtOAc (50 mL). The organic phase was washed with saturated $NaHCO_3$ solution (50 mL) and then brine (50 mL), dried ($MgSO_4$), and the solvent

removed under reduced pressure to give 1.23 g of an off-white amorphous solid. This material was coupled with Boc-L-α-(t-Butyl-Gly)-OH using the procedure described for the synthesis of ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate above to afford ethyl-3-(Boc-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (49% yield) as a white amorphous solid: IR (cm^{-1}) 1655, 1507, 1248, 1171; ^1H NMR (DMSO-*d6*) δ 0.81 (s, 9H), 1.21 (t, 3H, *J* = 7.0), 1.37 (s, 9H), 1.52-1.70 (m, 2H), 2.22 (s, 3H), 2.26-2.28 (m, 2H), 2.73-2.91 (m, 2H), 3.86 (d, 1H, *J* = 9.6), 4.05-4.14 (m, 2H), 4.31-4.36 (m, 1H), 4.47-4.55 (m, 1H), 5.54 (d, 1H, *J* = 15.4), 6.37 (d, 1H, *J* = 9.6), 6.65 (dd, 1H, *J* = 15.8, 5.5), 7.01 (d, 2H, *J* = 8.1), 7.07 (d, 2H, *J* = 7.7), 7.11-7.32 (m, 15H), 8.03 (d, 1H, *J* = 8.1), 8.10 (d, 1H, *J* = 7.7), 8.49 (s, 1H); Anal. ($C_{49}H_{60}N_4O_7 \cdot 0.4H_2O$) C, H, N.

Preparation of Intermediate Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-Propenoate

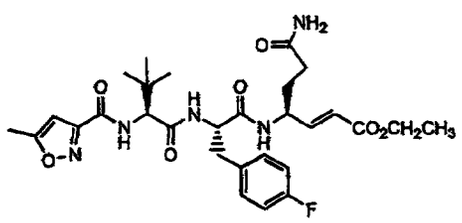
Ethyl-3-(Boc-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate was deprotected using the procedure described for the deprotection of ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate above, and the resulting amine (0.22 g, 0.30 mmol) was dissolved in CH_2Cl_2 (3 mL). Pyridine (0.025 mL, 0.32 mmol) was added, and the reaction was cooled to 0°C. 5-Methylisoxazole-3-carbonyl chloride (0.046 g, 0.32 mmol) was added. The reaction was allowed to warm to room temperature, and was stirred for one hour. The solvent was removed *in vacuo*, and the residue subjected to flash column chromatography (gradient elution, 0→1% CH_3OH in CH_2Cl_2) to afford ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (0.19 g, 77% yield) as a white amorphous solid: IR (cm^{-1}) 1651, 1518; ^1H NMR (DMSO-*d6*) δ 0.88 (s, 9H), 1.20 (t, 3H, *J* = 7.0), 1.55-1.67 (m, 2H), 2.14 (s, 3H), 2.18-2.28 (m, 2H), 2.45 (s, 3H), 2.70-2.77 (m, 1H), 2.86-2.93 (m, 1H), 4.07-4.14 (m, 2H), 4.46 (d, 1H, *J* = 9.6), 4.50-4.55 (m, 1H), 5.54 (d, 1H, *J* = 15.8), 6.59 (s, 1H), 6.65 (dd, 1H, *J* = 15.8, 5.5, 15.8), 6.95 (d, 2H, *J* = 8.1), 7.05 (d, 2H, *J* = 8.1), 7.13-7.28 (m, 15H), 7.60 (d, 1H, *J* = 9.6), 8.13 (d, 1H, *J* = 8.1), 8.41 (d, 1H, *J* = 8.1), 8.51 (s, 1H); Anal. ($C_{49}H_{55}N_5O_7$) C, H, N.

Preparation of Product Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-*Gln*)-E-Propenoate

Ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (0.17 g, 0.20 mmol) was dissolved in CH_2Cl_2 (4 mL) at 23°C. Trifluoroacetic acid (0.4 mL) was added, and the reaction was stirred at room temperature for

six hours. The solvents were removed *in vacuo*, and the residue was subjected to flash column chromatography (gradient elution, 0→2% CH_3OH in CH_2Cl_2) to afford ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-*Gln*)-E-propenoate (0.085 g, 73% yield) as a white amorphous solid: IR (cm^{-1}) 1661, 1541, 1206; ^1H NMR (DMSO-d_6) δ 0.88 (s, 9H), 1.21 (t, 3H, J = 7.0), 1.60-1.73 (m, 2H), 2.01-2.06 (m, 2H), 2.14 (s, 3H), 2.50 (s, 3H), 2.70-2.77 (m, 1H), 2.86-2.93 (m, 1H), 4.07-4.14 (m, 2H), 4.34-4.37 (m, 1H), 4.45 (d, 1H, J = 9.6), 4.50-4.55 (m, 1H), 5.57 (d, 1H, J = 15.8), 6.60 (s, 1H), 6.66 (dd, 1H, J = 15.8, 5.5), 6.75 (s, br, 1H), 6.96 (d, 2H, J = 8.1), 7.06 (d, 2H, J = 7.7), 7.17 (s, br, 1H), 7.65 (d, 1H, J = 9.6), 8.14 (d, 1H, J = 8.1), 8.40 (d, 1H, J = 7.7); Anal. ($C_{30}H_{41}N_5O_7$•0.5TFA•0.5H_2O) C, H, N.

Example 5 - Preparation of Compound A-4: Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-α -(t-Butyl-Gly)-L-(4-F-Phe)-L-*Gln*)-E-Propenoate



(A-4)

Preparation of Intermediate Ethyl-3-(Boc-L-(4-F-Phe)-L-(Tr-*Gln*))-E-Propenoate

Boc-L-(4-F-Phe)-OH (1.41 g, 5.0 mmol) was dissolved in THF (50 mL). Ethyl-3-(H_2N-L-(Tr-*Gln*))-E-propenoate•HCl (prepared as described in Example 2 above, 1.0 g, 5.0 mmol) was added, followed by Et_3N (0.70 mL, 5.0 mmol). Carbonyldiimidazole (0.81 g, 5.0 mmol) was added, and the reaction was stirred at room temperature for 20 hours. The solvent was removed *in vacuo*, and the residue subjected to flash column chromatography (gradient elution, 0→1% CH_3OH in CH_2Cl_2) to afford ethyl-3-(Boc-L-(4-F-Phe)-L-(Tr-*Gln*))-E-propenoate (1.13 g, 32% yield) as a white amorphous solid: IR (cm^{-1}) 1712, 1666, 1510, 1169; ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.0), 1.29 (s, 9H), 1.61-1.70 (m, 2H), 2.27-2.34 (m, 2H), 2.74-2.78 (m, 1H), 2.86-2.90 (m, 1H), 4.06-4.13 (m, 3H), 4.36-4.40 (m, 1H), 5.58 (d, 1H, J = 15.6), 6.71 (dd, 1H, J = 15.6, 5.5), 6.98 (d, 1H, J = 8.1), 7.03-7.09 (m, 2H), 7.14-7.28 (m, 17H), 8.06 (d, 1H, J = 8.1), 8.53 (s, 1H); LRMS (M+Na) 730.

Preparation of Intermediate Ethyl-3-(Boc-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*))-E-Propenoate

Ethyl-3-(Boc-L-(4-F-Phe)-L-(Tr-*Gln*))-E-propenoate was deprotected and coupled with Boc-L-α-(t-Butyl-Gly)-OH using the procedures described above to prepare ethyl-3-(Boc-

L–α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate, to provide ethyl-3-(Boc-L–α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*))-E-propenoate (54% yield) as a white amorphous solid: IR (cm^{-1}) 1720, 1651, 1506, 1168; ^1H NMR (DMSO-d_6) δ 0.80 (s, 9H), 1.20 (t, 3H, J = 7.0), 1.36 (s, 9H), 1.53-1.67 (m, 2H), 2.23-2.28 (m, 2H), 2.79-2.94 (m, 2H), 3.85 (d, 1H, J = 9.9), 4.09 (q, 2H, J = 7.0), 4.31-4.35 (m, 1H), 4.53-4.55 (m, 1H), 5.46 (d, 1H, J = 15.8), 6.36 (d, 1H, J = 9.2), 6.64 (dd, 1H, J = 15.8, 5.5), 6.97-7.03 (m, 2H), 7.13-7.28 (m, 17H), 8.08 (d, 1H, J = 8.1), 8.14 (d, 1H, J = 8.1), 8.49 (s, 1H); Anal. ($C_{48}H_{57}N_4O_7F$) C, H, N.

Preparation of Intermediate Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L–α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*))-E-Propenoate

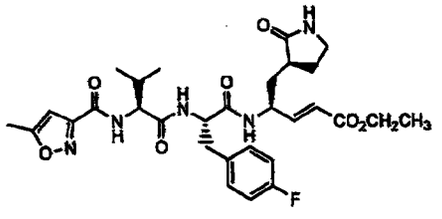
Ethyl-3-(Boc-L–α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*))-E-propenoate was deprotected and coupled with 5-methylisoxazole-3-carbonyl chloride using the procedures described above to prepare ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L–α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate to afford ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L–α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*))-E-propenoate (74% yield) as a white amorphous solid: IR (cm^{-1}) 1659, 1535, 1510; ^1H NMR (DMSO-d_6) δ 0.88 (s, 9H), 1.20 (t, 3H, J = 7.4), 1.52-1.67 (m, 2H), 2.23-2.28 (m, 2H), 2.45 (s, 3H), 2.75-2.82 (m, 1H), 2.89-2.96 (m, 1H), 4.09 (q, 2H, J = 7.0), 4.32-4.36 (m, 1H), 4.45 (d, 1H, J = 9.6), 4.50-4.55 (m, 1H), 5.44 (d, 1H, J = 15.6), 6.58 (s, 1H), 6.63 (dd, 1H, J = 15.6, 5.5, 15.6), 6.93-6.99 (m, 2H), 7.13-7.28 (m, 17H), 7.64 (d, 1H, J = 9.6), 8.16 (d, 1H, J = 8.5), 8.46 (d, 1H, J = 8.1), 8.51 (s, 1H); Anal. ($C_{48}H_{52}N_5O_7F$) C, H, N.

Preparation of Ethyl-3-((5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-*Gln*)-E-Propenoate

Ethyl-3-[(5'-methylisoxazole-3'-carbonyl)-L–α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(Tr-*Gln*)]-E-propenoate was deprotected using a procedure analogous to that described above for the preparation of ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-Me-Phe)-L-*Gln*)-E-propenoate to provide ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-*Gln*)-E-propenoate (80% yield) as a white amorphous solid: IR (cm^{-1}) 1653, 1543, 1223; ^1H NMR (DMSO-d_6) δ 0.88 (s, 9H), 1.21 (t, 3H, J = 7.0), 1.59-1.75 (m, 2H), 2.01-2.06 (m, 2H), 2.46 (s, 3H), 2.75-2.82 (m, 1H), 2.89-2.96 (m, 1H), 4.09 (q, 2H, J = 7.0), 4.33-4.36 (m, 1H), 4.44 (d, 1H, J = 9.6), 4.50-4.58 (m, 1H), 5.47 (d, 1H, J = 15.8), 6.59 (s, 1H), 6.64 (dd, 1H, J = 15.8, 5.5), 6.75 (s, br, 1H), 6.94-7.00 (m, 2H), 7.16 (s, br, 1H), 7.18-7.23

(m, 2H), 7.69 (d, 1H, J = 9.6), 8.16 (d, 1H, J = 8.1), 8.44 (d, 1H, J = 8.1); Anal. ($C_{29}H_{38}N_5O_7F$) C, H, N.

Example 6 - Preparation of Compound A-5: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-((*S*)-*Pyrrol-Ala*)}-E-Propenoate



(A-5)

Preparation of Intermediate (4*S*)-4-(2'-Carboxyethyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

Sodium hydroxide (27 mL of a 4.0 M solution in H_2O, 108 mmol, 3.0 equiv.) was added to a solution of (4*S*)-4-(2-methoxycarbonylethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (prepared as described in Chida et al., *J. Chem. Soc., Chem. Commun.* **1992**, 1064) (10.5 g, 36.5 mmol, 1 equiv.) in CH_3OH (150 mL), and the resulting cloudy reaction mixture was stirred at 23°C for 3.5 h. The mixture was concentrated under reduced pressure to ~30 mL volume, and then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over $MgSO_4$ and were gravity filtered. The filtrate was concentrated under reduced pressure and the residue dried under vacuum, to afford (4*S*)-4-(2'-carboxyethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (10.0 g, 100% crude yield). This material was used without further purification: ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 1.49 (s), 1.57 (s), 1.60 (s), 1.84-2.05 (m), 2.39-2.41 (m), 3.71-3.74 (m), 3.91-4.05 (m).

Preparation of Intermediate (4*S*,4''*S*)-4-{3'-(4''-Benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

Triethylamine (8.87 mL, 63.6 mmol, 3.0 equiv.) and pivaloyl chloride (2.61 mL, 21.2 mmol, 1.0 equiv.) were added sequentially to a solution of (4*S*)-4-(2'-carboxyethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (5.80 g, 21.2 mmol, 1 equiv.) in THF (450 mL) at 0°C. The cloudy reaction mixture was stirred at 0°C for 3.5 h, then lithium chloride (0.988 g, 23.3 mmol, 1.1 equiv.) and (*S*)-(-)-4-benzyl-2-oxazolidinone (3.57 g, 20.1 mmol, 0.95 equiv.) were added sequentially. After warming to 23°C and stirring for 19 h, the reaction mixture was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were washed with half-saturated Na_2CO_3 (150 mL), dried over

$MgSO_4$, and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% EtOAc in hexanes) to give (4*S*,4''*S*)-4-{3'-(4''-benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7.17 g, 83%) as a colorless oil: IR (cm^{-1}) 2978, 1783, 1694; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 1.49 (s), 1.59 (s), 1.63 (s), 2.01-2.10 (m), 2.76 (dd, *J* = 13.5, 9.8), 2.82-3.13 (m), 3.30-3.41 (m), 3.76-3.82 (m), 3.90 (s, br), 3.97 (dd, *J* = 9.0, 5.6), 4.10-4.19 (m), 4.63-4.71 (m), 7.22-7.36 (m); Anal. ($C_{23}H_{32}N_2O_6$) C, H, N.

Preparation of Intermediate (2'*S*,4*S*,4''*S*)-4-{2'-(4''-Benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

A solution of (4*S*,4''*S*)-4-{3'-(4''-benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7.17 g, 16.6 mmol, 1 equiv.) in THF (50 mL) was added to a solution of sodium bis(trimethylsilyl)amide (16.6 mL of a 1.0 M solution in THF, 16.6 mmol, 1.0 equiv.) in the same solvent (150 mL) at -78°C. The reaction mixture was stirred for 20 min. at -78°C, and then allyl iodide (4.55 mL, 49.8 mmol, 3.0 equiv.) was added. After stirring an additional 3 h at -78°C, the reaction mixture was maintained at -45°C for 2 h, and then was partitioned between a 2:1 mixture of half-saturated NH_4Cl and 5% $Na_2S_2O_3$ (300 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 200 mL). The combined organic layers were washed with H_2O (200 mL), dried over $MgSO_4$, and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (15% EtOAc in hexanes) to provide (2'*S*,4*S*,4''*S*)-4-{2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4.29 g, 55%) as a colorless oil: IR (cm^{-1}) 2978, 1780, 1695; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 1.45 (s), 1.49 (s), 1.68-1.80 (m), 2.13-2.47 (m), 2.49-2.67 (m), 3.32 (dd, J = 13.4, 3.1), 3.69-3.97 (m), 4.11-4.21 (m), 4.66-4.74 (m), 5.06-5.13 (m), 5.74-5.88 (m), 7.20-7.36 (m); Anal. ($C_{26}H_{36}N_2O_6$) C, H, N.

Preparation of Intermediate (1*S*,3*S*)-{3-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylpropyl}-carbamic Acid *tert*-Butyl Ester

Ozone was bubbled through a solution of (2'*S*,4*S*,4''*S*)-4-(2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4.29 g, 9.08 mmol, 1 equiv.) in CH_2Cl_2 (200 mL) and CH_3OH (0.735 mL, 18.1 mmol, 2.0 equiv.) at -78°C until a blue color persisted. The reaction mixture was then purged with

argon until it became colorless. Methyl sulfide (6.67 mL, 90.8 mmol, 10 equiv.) was added, the mixture was stirred at -78°C for 3.5 h, and was maintained at 0°C for an additional 1 h. After partitioning the reaction mixture between H_2O (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 200 mL), the combined organic layers were dried over $MgSO_4$ and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was immediately utilized without further purification.

The above residue was dissolved in a 2:1 mixture of THF and EtOH (240 mL) at 23°C, and 2,4-dimethoxybenzylamine hydrochloride (7.40 g, 36.3 mmol, 4.0 equiv.), sodium acetate (2.98 g, 36.2 mmol, 4.0 equiv.), and sodium cyanoborohydride (1.14 g, 18.1 mmol, 2.0 equiv.) were added sequentially. The resulting suspension was stirred for 18 h at 23°C, and then was partitioned between 0.5 M HCl (400 mL) and EtOAc (2 x 200 mL). The combined organic layers were washed with half-saturated $NaHCO_3$ (300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a short silica gel column (eluting with 50% EtOAc in hexanes) to give (3'*S*,4*S*)-4-{1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-ylmethyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester contaminated with (*S*)-(-)-4-benzyl-2-oxazolidinone.

This material was dissolved in CH_3OH (100 mL), and $TsOH \cdot H_2O$ (0.345 g, 1.81 mmol, 0.20 equiv.) was added. The reaction mixture was heated to 50°C, and was maintained at that temperature for 2.5 h. After cooling to 23°C, the reaction mixture was concentrated under reduced pressure to ~20 mL volume and was partitioned between half-saturated $NaHCO_3$ (150 mL) and a 9:1 mixture of CH_2Cl_2 and CH_3OH (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography (3% CH_3OH in CH_2Cl_2) afforded (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester (1.62 g, 44%) as a foam: IR (cm^{-1}) 3328, 1669; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.50-1.75 (m, 2H), 1.90-2.00 (m, 1H), 2.17-2.27 (m, 1H), 2.52-2.62 (m, 1H), 3.14-3.24 (m, 2H), 3.51-3.65 (m, 3H), 3.70-3.78 (m, 1H), 3.80 (s, 6H), 4.35 (d, 1H, J = 14.3), 4.48 (d, 1H, J = 14.3), 5.51-5.54 (m, 1H), 6.42-6.46 (m, 2H), 7.09-7.12 (m, 1H); Anal. ($C_{21}H_{32}N_2O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*])-E-Propenoate

DMSO (0.270 mL, 3.80 mmol, 3 equiv. was added dropwise to a -78°C solution of oxalyl chloride (0.166 mL, 1.90 mmol, 1.5 equiv.) in CH_2Cl_2 (14 mL). The reaction mixture was stirred 20 min., then a solution of (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester (0.518 g, 1.27 mmol, 1 equiv.) in CH_2Cl_2 (13 mL) was added via cannula along the side of the reaction vessel. After stirring 20 min., triethylamine (1.06 mL, 7.60 mmol, 6 equiv.) was added dropwise, and the reaction mixture was stirred for 1.5 h. Acetic acid (0.479 mL, 8.37 mmol, 6.6 equiv.) was added, and the reaction mixture was warmed to 0°C for 5 min., then diluted with MTBE (200 mL) and washed with water, saturated $NaHCO_3$, and brine (25 mL each). The organic phase was dried over Na_2SO_4 and concentrated to provide the crude aldehyde as a foam (0.516 g, quant.), which was used without further purification.

Sodium bis(trimethylsilyl)amide (1.23 mL of a 1.0 M solution in THF, 1.23 mmol, 1 equiv.) was added to a solution of triethyl phosphonoacetate (0.244 mL, 1.23 mmol, 1 equiv.) in THF (15 mL) at -78°C, and the resulting solution was stirred for 20 min. at that temperature. The crude aldehyde (prepared above, 0.500 g, 1.23 mmol, 1 equiv.) in THF (13 mL) was added via cannula along the side of the reaction vessel, and the reaction mixture was stirred for 45 min. at -78°C, warmed to 0°C for 7 min., and partitioned between 0.5 M HCl (20 mL) and MTBE (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and were concentrated. Purification of the residue by flash column chromatography (60% EtOAc in hexanes) provided ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (0.356 g, 61%) as a white foam: R_f= 0.43 (60% EtOAc in hexanes); IR (cm^{-1}) 3307, 1708, 1678; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.2), 1.43 (s, 9H), 1.52-1.70 (m, 2H), 1.98-2.09 (m, 1H), 2.21-2.34 (m, 1H), 2.48-2.59 (m, 1H), 3.16-3.24 (m, 2H), 3.80 (s, 6H), 4.18 (q, 2H, *J* = 7.2), 4.27-4.40 (m, 1H), 4.41 (s, 2H), 5.40 (d, 1H, *J* = 8.1), 5.95 (dd, 1H, *J* = 15.6, 1.6), 6.41-6.48 (m, 2H), 6.86 (dd, 1H, *J* = 15.6, 5.3), 7.08-7.13 (m, 1H); Anal. ($C_{25}H_{36}N_2O_7 \cdot 0.25H_2O$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-(4-F-Phe)-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

This material was prepared from ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate and Boc-L-(4-F-Phe)-OH using a procedure similar to that described for

the preparation of ethyl-3-(Boc-L-(4-Me-Phe)-L-(Tr-*Gln*))-E-propenoate (Example 4) above: R_f= 0.34 (60% EtOAc in hexanes); IR (cm^{-1}) 3258, 1705, 1666; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.2), 1.45 (s, 9H), 1.51-1.66 (m, 2H), 1.78-1.90 (m, 1H), 2.06-2.23 (m, 2H), 2.99 (dd, 1H, *J* = 13.7, 6.2), 3.11 (dd, 1H, *J* = 13.7, 5.3), 3.17-3.23 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.18 (q, 2H, *J* = 7.2), 4.35 (s, 2H), 4.38-4.51 (m, 2H), 5.29-5.37 (m, 1H), 5.76 (d, 1H, *J* = 15.8), 6.43-6.47 (m, 2H), 6.72 (dd, 1H, *J* = 15.8, 5.3), 6.83-6.91 (m, 2H), 7.09-7.17 (m, 3H), 7.92 (br, 1H); Anal. ($C_{34}H_{44}FN_3O_8$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-Val-L-(4-F-Phe)-L-[(*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*]}-E-Propenoate

This compound was prepared from ethyl-3-{Boc-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate and Boc-L-Val-OH using a similar procedure to that described above for the preparation of ethyl-3-(Boc-L-Phe-L-(Tr-*Gln*))-E-propenoate (Example 2): R_f= 0.24 (60% EtOAc in hexanes); IR (cm^{-1}) 3284, 1713, 1678 br, 1643; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = 6.8), 0.97 (d, 3H, *J* = 6.8), 1.28 (t, 3H, *J* = 7.2), 1.45 (s, 9H), 1.50-1.62 (m, 2H), 1.66-1.82 (m, 1H), 1.90-2.02 (m, 1H), 2.08-2.21 (m, 2H), 2.94 (dd, 1H, *J* = 13.5, 5.8), 3.17-3.27 (m, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.97-4.05 (m, 1H), 4.17 (q, 2H, *J* = 7.2), 4.27 (d, 1H, *J* = 14.3), 4.29-4.38 (m, 1H), 4.40 (d, 1H, *J* = 14.3), 4.86-4.93 (m, 1H), 5.10 (d, 1H, *J* = 8.7), 5.76 (dd, 1H, *J* = 15.6, 1.2), 6.45-6.52 (m, 2H), 6.70 (dd, 1H, *J* = 15.6, 5.4), 6.79-6.88 (m, 3H), 7.12-7.22 (m, 3H), 8.30 (d, 1H, *J* = 5.9); Anal. ($C_{39}H_{53}FN_4O_9$) C, H, N.

Preparation of Intermediate Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

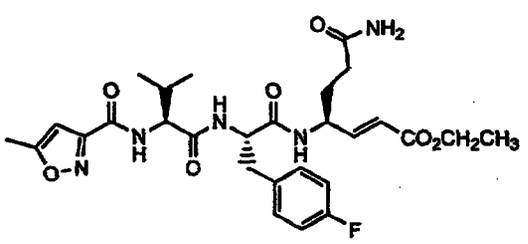
This compound was prepared from ethyl-3-{Boc-L-Val-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate and isoxazole-5-carbonyl chloride using the procedure described above (Example 2) for the preparation of ethyl-3-((5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*))-E-propenoate: R_f= 0.36 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3284, 1717, 1650; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3H, *J* = 6.8), 1.01 (d, 3H, *J* = 6.8), 1.28 (t, 3H, *J* = 7.2), 1.51-1.64 (m, 2H), 1.72-1.84 (m, 1H), 1.95-2.05 (m, 1H), 2.11-2.33 (m, 2H), 2.48 (s, 3H), 2.98 (dd, 1H, *J* = 13.7, 5.6), 3.16-3.24 (m, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.17 (q, 2H, *J* = 7.2), 4.23 (d, 1H, *J* = 14.3), 4.31-4.42 (m, 1H), 4.40 (d, 1H, *J* = 14.3), 4.44-4.50 (m, 1H), 4.88-4.96 (m, 1H), 5.79 (dd, 1H, *J* = 15.6, 1.4), 6.43-6.49 (m, 3H), 6.71 (dd, 1H, *J* = 15.6,

5.3), 6.80-6.88 (m, 2H), 6.94 (d, 1H, J = 9.3), 7.11-7.17 (m, 3H), 7.29 (d, 1H, J = 8.7), 8.33 (d, 1H, J = 6.2); Anal. ($C_{39}H_{48}FN_5O_9 \cdot 0.5H_2O$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-Propenoate

A suspension of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-(*(N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (0.263 g, 0.351 mmol, 1 equiv.), water (2 drops), and DDQ (0.104 g, 0.458 mmol, 1.3 equiv.) was refluxed for 9 h and then allowed to cool to room temperature over 8 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with a 2:1 mixture of saturated $NaHCO_3$ and 1 N NaOH (20 mL). The organic phase was dried over $MgSO_4$ and evaporated. Purification of the residue by flash column chromatography (gradient elution 2→3% CH_3OH in CH_2Cl_2) gave ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-(*(S)-pyrrol-Ala*)}-E-propenoate (0.117 g, 56%) as a white solid: mp = 219-220°C; R_f = 0.23 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3401 br, 3295, 1655 br; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.8), 0.97 (d, 3H, J = 6.5), 1.29 (t, 3H, J = 7.2), 1.54-1.65 (m, 1H), 1.72-1.91 (m, 2H), 2.07-2.26 (m, 2H), 2.28-2.39 (m, 1H), 2.49 (d, 3H, J = 0.9), 3.01 (dd, 1H, J = 13.8, 6.1), 3.12 (dd, 1H, J = 13.8, 6.4), 3.26-3.38 (m, 2H), 4.18 (q, 2H, J = 7.2), 4.34 (dd, 1H, J = 8.7, 7.2), 4.43-4.54 (m, 1H), 4.90 (dt, 1H, J = 9.0, 6.2), 5.76 (dd, 1H, J = 15.6, 1.6), 6.00 (s, 1H), 6.42 (q, 1H, J = 0.9), 6.72 (dd, 1H, J = 15.6, 5.4), 6.86-6.94 (m, 2H), 7.01 (d, 1H, J = 9.0), 7.11-7.18 (m, 2H), 7.21 (d, 1H, J = 8.7), 7.76 (d, 1H, J = 7.2); Anal. ($C_{30}H_{38}FN_5O_7$) C, H, N.

Example 7 - Preparation of Compound A-6: Ethyl-3-[(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-*Gln*]-E-Propenoate



(A-6)

Preparation of Intermediate Ethyl-3-{Boc-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-Propenoate

This compound was prepared from ethyl-3-(Boc-L-(Tr-*Gln*))-E-propenoate and Boc-L-(4-F)-Phe-OH using a procedure like that described above (Example 2) for the preparation of ethyl-3-(Boc-L-Phe-L-(Tr-*Gln*))-E-propenoate: IR (cm^{-1}) 3328, 1707, 1506, 1168; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2), 1.37 (s, 9H), 1.66-1.78 (m, 1H), 1.88-1.98 (m, 1H), 2.32 (t, 2H,

J = 6.6), 2.85-2.92 (m, 1H), 2.97-3.04 (m, 1H), 4.18 (q, 2H, J = 7.2), 4.52 (m, 1H), 4.96 (m, 1H), 5.60 (d, 1H, J = 15.6), 6.56 (d, 1H, J = 8.1), 6.66 (dd, 1H, J = 15.6, 5.1), 6.80 (s, br, 1H), 6.92-6.98 (m, 2H), 7.08-7.12 (m, 2H), 7.17-7.23 (m, 6H), 7.24-7.33 (m, 10H); Anal. ($C_{42}H_{46}FN_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-Val-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-Propenoate

This compound was prepared from ethyl-3-{Boc-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-propenoate and Boc-L-Val-OH in the manner described above (Example 2) for the preparation of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate: IR (cm^{-1}) 3319, 1657, 1511, 1172; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6.9), 0.87 (d, 3H, J = 6.9), 1.29 (t, 3H, J = 7.2), 1.37 (s, 9H), 1.69-1.79 (m, 1H), 1.93-2.06 (m, 2H), 2.33 (t, 2H, J = 7.2), 2.97-3.04 (m, 1H), 3.73-3.77 (m, 1H), 4.18 (q, 2H, J = 7.2), 4.42-4.54 (m, 2H), 4.80 (d, 1H, J = 6.9), 5.61 (dd, 1H, J = 15.6, 1.5), 6.44 (d, 1H, J = 7.8), 6.69 (dd, 1H, J = 15.9, 5.4), 6.71 (s, br, 1H), 6.92-6.98 (m, 2H), 7.07-7.13 (m, 2H), 7.18-7.31 (m, 16H), 8.02 (s, 1H); Anal. ($C_{47}H_{55}FN_4O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-Propenoate

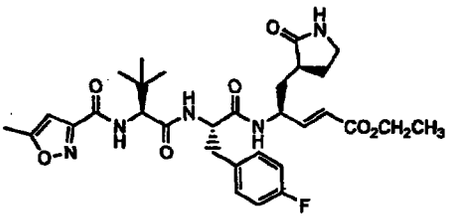
This compound was prepared from ethyl-3-{Boc-L-Val-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-propenoate and 5-methylisoxazole-3-carbonyl chloride in a manner like that described above (Example 2) for the preparation of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate: IR (cm^{-1}) 3319, 1657, 1511, 1172; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.9), 0.89 (d, 3H, J = 6.9), 1.30 (t, 3H, J = 7.2), 1.68-1.80 (m, 1H), 1.95-2.06 (m, 1H), 2.08-2.17 (m, 1H), 2.34 (t, 2H, J = 7.2), 2.44 (s, 3H), 2.87-2.94 (m, 1H), 3.01-3.08 (m, 1H), 4.18 (q, 2H, J = 7.2), 4.48-4.56 (m, 2H), 5.68 (dd, 1H, J = 15.6, 1.8), 6.23 (s, 1H), 6.39 (d, 1H, J = 7.8), 6.70 (dd, 1H, J = 15.9, 5.4), 6.84-6.90 (m, 3H), 7.04-7.08 (m, 4H), 7.17-7.30 (m, 16H); Anal. ($C_{47}H_{50}N_5O_7$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F)-Phe-L-*Gln*}-E-Propenoate

Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F)-Phe-L-(Tr-*Gln*)}-E-propenoate was deprotected using the procedure described above (Example 2) for the preparation of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate: IR (cm^{-1}) 3284, 1652, 1542; ^1H NMR (DMSO-d_6) δ 0.76 (d, 3H, J = 6.9), 0.79 (d, 3H, J = 6.9), 1.20 (t, 3H, J = 7.2), 1.57-1.76 (m, 2H), 1.96-2.06 (3H), 2.46 (s, 3H), 2.75-2.83 (m, 1H), 2.89-2.96 (m, 1H), 4.09 (q, 2H, J = 7.2), 4.13-4.25 (m, 1H), 4.35 (m, 1H), 4.49-4.56 (m, 1H),

5.53 (d, 1H, J = 15.6), 6.57 (s, 1H), 6.66 (dd, 1H, J = 15.6, 5.4), 6.75 (s, br, 1H), 6.97-7.03 (m, 2H), 7.17-7.24 (m, 3H), 8.15 (d, 1H, J = 7.8), 8.24 (d, 1H, J = 8.7), 8.32 (d, 1H, J = 8.1); Anal. ($C_{28}H_{36}N_5O_7$) C, H, N.

Example 8 - Preparation of Compound A-7: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-Propenoate



(A-7)

Preparation of Intermediate Boc-L-(4-F-Phe)-Obn

DCC (0.765 g, 3.71 mmol, 1.05 equiv.), benzyl alcohol (0.347 mL, 3.35 mmol, 0.95 equiv.) and DMAP (0.022 g, 0.18 mmol, 0.05 equiv.) were added sequentially to a solution of Boc-L-(4-F-Phe)-OH (1.0 g, 3.53 mmol, 1 equiv.) in CH_2Cl_2 (15 mL). After stirring 18 h, the precipitate was removed by filtration, and the filtrate was diluted with MTBE (75 mL), washed with 10% $KHSO_4$ and brine (10 mL each), dried over Na_2SO_4 and evaporated. Purification of the residue by flash column chromatography (12% EtOAc in hexanes) gave Boc-L-(4-F-Phe)-OBn (0.992 g, 79%) as a white solid. ^1H NMR spectral data matches literature (see Jackson et al., *J. Org. Chem.* **1992**, vol. 57, 3397).

Preparation of Intermediate Boc-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-OBn

Boc-L-(4-F-Phe)-OBn (2.0 g, 5.36 mmol, 1 equiv.) was stirred for 1 h in a mixture of CH_2Cl_2 (20 mL) and TFA (10 mL), then more TFA (10 mL) was added and the reaction solution was stirred an additional hour. The volatiles were evaporated and the residue was dissolved in DMF (30 mL). Boc-L-α-(t-butyl-Gly)-OH (1.24 g, 5.36 mmol, 1 equiv.) was added, and the solution was cooled to 0°C. *N,N*-diisopropylethylamine (2.80 mL, 16.1 mmol, 3 equiv.) and HATU (2.04 g, 5.37 mmol, 1 equiv.) were added sequentially. After stirring 20 min., the reaction mixture was allowed to warm to room temperature over 1 h, then diluted with MTBE (500 mL) and washed with 5% $KHSO_4$ (100 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried and evaporated. Purification of the residue by flash column chromatography (20% EtOAc in hexanes) gave Boc-L-α-(t-butyl-Gly)-L-(4-F-Phe)-OBn (2.04 g, 78%) as a white foam: R_f = 0.49 (25% EtOAc in hexanes); IR (cm^{-1}) 3307, 1737, 1655 br; ^1H NMR ($CDCl_3$) δ 0.94 (s, 9H), 1.45 (s, 9H), 3.04 (dd, 1H, J = 14.2, 5.8),

3.11 (dd, 1H, J = 14.2, 6.1), 3.79 (d, 1H, J = 9.3), 4.88 (dt, 1H, J = 7.8, 5.8), 5.08 (d, 1H, J = 12.0), 5.16-5.23 (m, 1H), 5.19 (d, 1H, J = 12.0), 6.08 (d, 1H, J = 7.8), 6.83-6.97 (m, 4H), 7.28-7.40 (m, 5H); Anal. ($C_{27}H_{35}FN_2O_5$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 8 mL) was added to a solution of ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (0.309 g, 0.648 mmol, 1 equiv.) in 1,4-dioxane (8 mL). After stirring for 1.5 h, the volatiles were evaporated to give the crude amine salt as a foam.

Palladium on carbon (10%, 200 mg) was added to a solution of Boc-L-α-(t-butyl-Gly)-L-(4-F-Phe)-OBn (2.04 g, 4.19 mmol) in EtOAc (200 mL). The atmosphere was replaced with hydrogen via balloon. After stirring 3 h, the atmosphere was replaced with argon, and the reaction mixture was filtered through #3 and #5 Whatman filter papers. The filtrate was evaporated to give a white foam.

This foam was combined with the crude amine salt (prepared above) in DMF (5 mL) and cooled to 0°C. *N,N*-diisopropylethylamine (0.339 mL, 1.95 mmol, 3 equiv.) and HATU (0.247 g, 0.650 mmol, 1 equiv.) were added sequentially. After stirring 20 min., the reaction mixture was allowed to warm to room temperature over 1 h, then diluted with MTBE (100 mL) and washed with 5% $KHSO_4$, saturated $NaHCO_3$ and brine (15 mL each). The organic phase was dried and evaporated. Purification of the residue by flash column chromatography (60% EtOAc in hexanes) gave ethyl-3-{Boc-L-α-(t-butyl-Gly)-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (0.364 g, 74%) as a white foam: R_f = 0.34 (60% EtOAc in hexanes); IR (cm^{-1}) 3284, 1713, 1655; ^1H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.28 (t, 3H, J = 7.2), 1.46 (s, 9H), 1.50-1.63 (m, 2H), 1.68-1.81 (m, 1H), 1.85-1.99 (m, 1H), 2.09-2.20 (m, 1H), 2.94 (dd, 1H, J = 13.5, 5.4), 3.15-3.26 (m, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.97 (d, 1H, J = 9.3), 4.17 (q, 2H, J = 7.2), 4.27-4.38 (m, 1H), 4.29 (d, 1H, J = 14.3), 4.42 (d, 1H, J = 14.3), 4.84-4.92 (m, 1H), 5.22 (d, 1H, J = 9.6), 5.74 (dd, 1H, J = 15.6, 1.6), 6.45-6.53 (m, 2H), 6.69 (dd, 1H, J = 15.6, 5.4), 6.76-6.87 (m, 3H), 7.10-7.28 (m, 3H), 8.26 (d, 1H, J = 5.9); Anal. ($C_{40}H_{55}FN_4O_9$) C, H, N.

Preparation of Intermediate Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

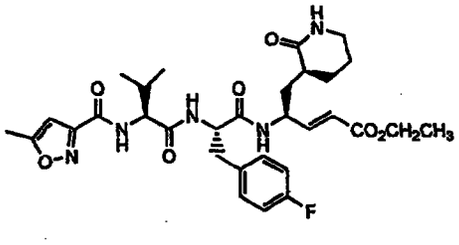
This compound was prepared from ethyl-3-{Boc-L-α-(t-butyl-Gly)-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate and isoxazole-5-carbonyl chloride using

the procedure described above (Example 2) for the preparation of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate: R_f = 0.60 (10% CH_3OH in $CHCl_3$); IR (cm^{-1}) 3295, 1713, 1666, 1643; ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.29 (t, 3H, *J* = 7.2), 1.51-1.64 (m, 2H), 1.71-1.83 (m, 1H), 1.96-2.07 (m, 1H), 2.11-2.21 (m, 1H), 2.49 (s, 3H), 2.99 (dd, 1H, *J* = 13.7, 5.9), 3.13-3.26 (m, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.18 (q, 2H, *J* = 7.2), 4.23-4.48 (m, 4H), 4.85-4.93 (m, 1H), 5.76 (dd, 1H, *J* = 15.6, 1.4), 6.40-6.52 (m, 3H), 6.71 (dd, 1H, *J* = 15.6, 5.3), 6.79-6.88 (m, 2H), 6.92 (d, 1H, *J* = 9.0), 7.09-7.22 (m, 3H), 7.37 (d, 1H, *J* = 9.0), 8.27 (d, 1H, *J* = 6.2); Anal. ($C_{40}H_{50}FN_5O_9 \cdot 0.25H_2O$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-Propenoate

This compound was prepared from ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-α-(t-Butyl-Gly)-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate using a procedure as described above (Example 6) for the preparation of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-((*S*)-*Pyrrol-Ala*)}-E-propenoate: R_f = 0.30 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3307 br, 1684, 1660; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.29 (t, 3H, *J* = 7.2), 1.51-1.61 (m, 1H), 1.75-1.97 (m, 2H), 2.14-2.25 (m, 1H), 2.28-2.40 (m, 1H), 2.50 (s, 3H), 3.03 (d, 2H, *J* = 6.5), 3.27-3.42 (m, 2H), 4.18 (q, 2H, *J* = 7.2), 4.36 (d, 1H, *J* = 9.8), 4.52-4.63 (m, 1H), 4.86-4.95 (m, 1H), 5.71 (dd, 1H, *J* = 15.6, 1.4), 6.44 (s, 1H), 6.57-6.64 (m, 1H), 6.73 (dd, 1H, *J* = 15.6, 5.3), 6.83-6.91 (m, 2H), 7.09-7.15 (m, 2H), 7.28-7.36 (m, 2H), 7.59 (d, 1H, *J* = 8.1); Anal. ($C_{31}H_{40}FN_5O_7$) C, H, N.

Example 9 - Preparation of Compound A-8: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-(*(S)-Piper-Ala*)}-E-Propenoate



(A-8)

Preparation of Intermediate (2'*S*,4*S*,4''*S*)-4-{2'-(4''-Benzyl-2''-oxo-oxazolidine-3''-carbonyl)-5'-hydroxypentyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

A solution of borane-tetrahydrofuran complex (0.96 mL of a 1.0 M solution in THF, 0.96 mmol, 1 equiv.) was added to a 0°C solution of (2'*S*,4*S*,4''*S*)-4-{2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl

ester (prepared as described in Example 6, 0.455 g, 0.963 mmol, 1 equiv.) in THF (3 mL). After stirring 30 min., water (3 mL) and sodium perborate tetrahydrate (0.148 g, 0.962 mmol, 1 equiv.) were added, and the ice bath was removed. After an additional hour, the reaction mixture was diluted with MTBE (125 mL), washed with water (15 mL) and brine (2 x 15 mL), dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography (50% EtOAc in hexanes) provided (2'*S*,4*S*,4''*S*)-4-{2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-5'-hydroxypentyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (0.339 g, 72%) as a colorless glass: R_f = 0.41 (50% EtOAc in hexanes); IR (cm^{-1}) 3486, 1780, 1693; ^1H NMR ($CDCl_3$) δ 1.42-1.85 (m, 21H), 2.13-2.24 (m, 1H), 2.70 (dd, 1H, *J* = 13.1, 10.0), 3.29-3.38 (m, 1H), 3.61-4.22 (m, 8H), 4.63-4.76 (m, 1H), 7.19-7.38 (m, 5H); Anal. ($C_{26}H_{38}N_2O_7 \cdot 0.5H_2O$) C, H, N.

Preparation of Intermediate (1*S*,3'*S*)-{2-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-piperidin-3'-yl)-1-hydroxymethylethyl}-carbamic Acid *tert*-Butyl Ester

(2'*S*,4*S*,4''*S*)-4-{2'-(4''-Benzyl-2''-oxo-oxazolidine-3''-carbonyl)-5'-hydroxypentyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3.88 g, 7.92 mmol, 1 equiv.) was dissolved in Et_3N (3.97 mL, 28.51 mmol, 3.6 equiv.). The mixture was cooled to -12°C, and a solution of sulfur trioxide-pyridine complex (5.04 g, 31.67 mmol, 4 equiv.) in DMSO (150 mL) was added at a rate to maintain the temperature between 8-17°C. The solution was stirred at 23°C for 3 h. The reaction mixture was cooled in an ice water bath and quenched by the addition of H_2O (150 mL). The resulting solution was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with 5% citric acid (100 mL), brine (100 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was dried under vacuum to give a white foam (3.53 g).

To a solution of this material (3.53 g, 7.22 mmol, 1 equiv.) in a 2:1 mixture of THF and EtOH (120 mL) was added 2,4-dimethoxybenzylamine hydrochloride (5.88 g, 28.89 mmol, 4 equiv.), NaOAc (2.37 g, 28.89 mmol, 4 equiv.), and $NaBH_3CN$ (0.908 g, 14.45 mmol, 2 equiv.). The reaction mixture was stirred overnight (20 h) and then diluted with MTBE (200 mL). The organic layer was washed with 10% $KHSO_4$ (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), and dried over Na_2SO_4, and concentrated to give a pale yellow foam.

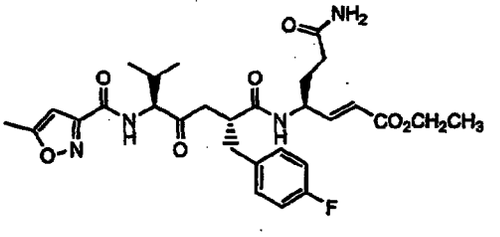
To a solution of this foam (3.34 g, 7.22 mmol, 1 equiv.) in CH_3OH (50 mL) was added *p*-toluenesulfonic acid (0.275 g, 1.44 mmol, 0.2 equiv.). The reaction mixture was stirred at

50°C for 2.5 h and then was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with saturated $NaHCO_3$ (100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (3% CH_3OH in CH_2Cl_2) to give (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-piperidin-3'-yl)-1-hydroxymethyl-ethyl}-carbamic acid *tert*-butyl ester as a white foam (1.33 g, 44% over three steps): ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 1.71-1.85 (m, 2H), 1.92-1.98 (m, 2H), 2.40-2.48 (m, 1H), 2.71-2.78 (m, 1H), 3.19-3.32 (m, 2H), 3.45-3.69 (m, 4H), 4.11-4.20 (m, 2H), 4.68 (m, 1H), 5.47 (m, 1H), 6.44 (s, 1H), 7.20-7.33 (m, 2H).

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-*((S)-Piper-Ala)*}-E-Propenoate

(1*S*,3'*S*)-{2-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-piperidin-3'-yl)-1-hydroxy-methylethyl}-carbamic acid *tert*-butyl ester was converted to the product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-*((S)-Piper-Ala)*}-E-propenoate in a manner analogous to the conversion of (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-piperidin-3'-yl]-1-hydroxymethylethyl)-carbamic acid *tert*-butyl ester to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-*((S)-Pyrrol-Ala)*}-E-propenoate described in Example 6 above: R_f = 0.24 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3284 br, 1713, 1655, 1637 br; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J* = 6.8), 0.98 (d, 3H, *J* = 6.8), 1.29 (t, 3H, *J* = 7.2), 1.43-1.56 (m, 2H), 1.66-1.78 (m, 1H), 1.83-2.05 (m, 4H), 2.16-2.28 (m, 1H), 2.49 (s, 3H), 3.00 (dd, 1H, *J* = 13.7, 6.2), 3.13 (dd, 1H, *J* = 13.7, 5.9), 3.21-3.37 (m, 2H), 4.18 (q, 2H, *J* = 7.2), 4.36-4.45 (m, 2H), 4.80-4.88 (m, 1H), 5.76 (dd, 1H, *J* = 15.6, 1.6), 5.96 (s, 1H), 6.43 (s, 1H), 6.70 (dd, 1H, *J* = 15.6, 5.3), 6.81 (d, 1H, *J* = 8.7), 6.86-6.98 (m, 2H), 7.09-7.19 (m, 2H), 7.22-7.29 (m, 1H), 8.07 (d, 1H, *J* = 6.5).

Example 10 - Preparation of Compound B-1: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(B-1)

Preparation of Intermediate trans-6-Methyl-hept-4-enoic Acid.

A solution of isobutyraldehyde (9.59 g, 133 mmol, 1 equiv.) in THF (50 mL) was added dropwise via addition funnel to a solution of vinylmagnesium bromide (133 mL of a 1.0 M solution in THF, 133 mmol, 1.0 equiv.) in THF (300 mL) at 0°C. Upon completion of the addition, the reaction mixture was stirred for 30 min. at 0°C, and then ethyl malonyl chloride (17.0 mL, 133 mmol, 1.0 equiv.) was added. After stirring for 1 h at 0°C, the reaction mixture was partitioned between saturated NH_4Cl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by filtration through silica gel (eluting with 5% EtOAc in hexanes) afforded the intermediate malonate ester (11.5 g, 40% yield). This material was not characterized, but was combined (neat) with $Ti(OEt)_4$ (1.13 mL, 5.39 mmol, 0.10 equiv.) and was heated to 190°C for 4 h, and then was cooled to 60°C. EtOH (50 mL) and 6.0 M KOH (50 mL) were added sequentially, and the brown reaction mixture was refluxed for 4 h. After cooling to 23°C, the reaction mixture was filtered through a medium frit, and the filtrate was partitioned between water (150 mL) and Et_2O (2 x 150 mL). The aqueous layer was then acidified to pH = 2 (as indicated by pH paper) with concentrated HCl and was extracted with a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue was distilled at reduced pressure to afford trans-6-methyl-hept-4-enoic acid (3.58 g, 47%) as a colorless liquid: bp 107-112°C (1 Torr); IR (cm^{-1}) 2960, 1711; ^1H NMR ($CDCl_3$) δ 0.96 (d, 6H, J = 6.5), 2.18-2.45 (m, 5H), 5.31-5.50 (m, 2H); Anal. ($C_8H_{14}O_2$) C, H.

Preparation of Intermediate trans-6-Methyl-hept-4-enoic Acid (2*R*-hydroxy-1*R*-methyl-2-phenyl-ethyl)-methyl Amide.

Oxalyl chloride (2.25 mL, 25.8 mmol, 1.05 equiv.) was added to a solution of trans-6-methyl-hept-4-enoic acid (3.50 g, 24.6 mmol, 1 equiv.) and *N,N*-dimethylformamide (0.03 mL, 0.39 mmol, 0.016 equiv.) in benzene (60 mL) at 23°C. The reaction mixture was stirred at 23°C for 2 h, and then was concentrated under reduced pressure. The resulting oil was dissolved in THF (20 mL) and was added via cannula to a solution of (1*R*,2*R*)-(-)-pseudoephedrine (3.87 g, 23.4 mmol, 1 equiv.) and triethylamine (3.92 mL, 28.1 mmol, 1.2 equiv.) in THF (150 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min., then was partitioned between half-saturated NH_4Cl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue purified by flash column

chromatography (gradient elution 40→50% EtOAc in hexanes) to afford trans-6-methyl-hept-4-enoic acid (2*R*-hydroxy-1*R*-methyl-2-phenyl-ethyl)-methyl amide (6.31 g, 93%) as a viscous oil: R_f = 0.35 (50% EtOAc in hexanes); IR (cm^{-1}) 3382, 1622; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.96 (d, *J* = 6.8), 0.97 (d, *J* = 6.5), 1.11 (d, *J* = 6.9), 2.18-2.59 (m), 2.82 (s), 2.92 (s), 3.99-4.04 (m), 4.32-4.42 (m), 4.44-4.49 (m), 4.55-4.62 (m), 5.32-5.49 (m), 7.24-7.42 (m); Anal. ($C_{18}H_{27}NO_2$) C, H, N.

Preparation of Intermediate trans-6-Methyl-2*S*-(4-fluorobenzyl)-hept-4-enoic Acid (2*R*-Hydroxy-1*R*-methyl-2-phenylethyl)methyl Amide.

n-Butyllithium (32.5 mL of a 1.6 M solution in hexanes, 52.0 mmol, 3.1 equiv.) was added to a suspension of anhydrous lithium chloride (7.18 g, 169 mmol, 10 equiv.) and diisopropylamine (7.80 mL, 55.7 mmol, 3.3 equiv.) in THF (250 mL) at -78°C. The reaction mixture was stirred for 30 min. at -78°C, was maintained at 0°C for 5 min., and subsequently cooled again to -78°C. trans-6-Methyl-hept-4-enoic acid (2*R*-hydroxy-1*R*-methyl-2-phenyl-ethyl)-methyl amide (4.91 g, 17.0 mmol, 1 equiv) in THF (50 mL) was added via cannula, and the resulting solution was stirred at -78°C for 1.75 h, maintained at 0°C for 20 min., stirred at 23°C for 5 min., and then was cooled again to 0°C. A solution of 4-fluorobenzyl bromide (6.34 mL, 50.9 mmol, 3 equiv.) in THF (15 mL) was added and the reaction mixture was stirred at 0°C for 30 min., which was then partitioned between half-saturated NH_4Cl (230 mL) and a 1:1 mixture of EtOAc and hexanes (200 mL, 2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution 20→40% EtOAc in hexanes) provided trans-6-methyl-2*S*-(4-fluorobenzyl)-hept-4-enoic acid (2*R*-hydroxy-1*R*-methyl-2-phenylethyl)methyl amide (6.33 g, 94%) as a viscous oil: R_f = 0.38 (40% EtOAc in hexanes); IR (cm^{-1}) 3378, 1614; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.85-0.95 (m), 0.96 (d, *J* = 6.8), 2.10-2.32 (m), 2.34-2.46 (m), 2.58 (s), 2.67-2.79 (m), 2.82-2.94 (m), 3.00-3.18 (m), 3.94 (br), 4.37-4.52 (m), 5.24-5.42 (m), 5.44-5.56 (m), 6.89-7.01 (m), 7.08-7.14 (m), 7.19-7.38 (m); Anal. ($C_{25}H_{32}FNO_2$) C, H, N.

Preparation of Intermediate 5*S*-(1*R*-Bromo-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one.

N-Bromosuccinimide (2.93 g, 16.5 mmol, 1.05 equiv.) was added in small portions over 10 minutes to a solution of trans-6-methyl-2*S*-(4-fluorobenzyl)-hept-4-enoic acid (2*R*-hydroxy-1*R*-methyl-2-phenylethyl)methyl amide (6.24 g, 15.7 mmol, 1 equiv.) and glacial acetic acid (4.49 mL, 78.4 mmol, 5 equiv.) in a 4:1 mixture of THF and H_2O (165 mL) at 0°C. The

resulting yellow solution was stirred for 15 min. at 0°C, and then was warmed to 23°C and subsequently refluxed for 45 min. After cooling to 23°C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 200 mL, 100 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Flash chromatographic purification of the residue (gradient elution 4→10% EtOAc in hexanes) gave 5*S*-(1*R*-bromo-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one (4.14 g, 80%) as a pale yellow oil (containing approximately 5-10% unidentified impurities by ^1H NMR): R_f= 0.56 (25% EtOAc in hexanes); IR (cm^{-1}) 1772; ^1H NMR ($CDCl_3$, major isomer) δ 0.94 (d, 3H, *J* = 6.5), 1.00 (d, 3H, *J* = 6.8), 2.05-2.35 (m, 3H), 2.83 (dd, 1H, *J* = 13.6, 8.4), 2.92-3.03 (m, 1H), 3.11 (dd, 1H, *J* = 13.6, 4.7), 3.90 (dd, 1H, *J* = 9.0, 3.7), 4.33-4.40 (m, 1H), 6.98-7.06 (m, 2H), 7.14-7.20 (m, 2H); Anal. ($C_{15}H_{18}BrFO_2$) C, H.

Preparation of Intermediate 5*S*-(1*S*-Azido-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one.

A suspension of sodium azide (1.90 g, 29.2 mmol, 2.5 equiv.) and 5*S*-(1*R*-bromo-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one (3.85 g, 11.7 mmol, 1 equiv.) in *N,N*-dimethylformamide (40 mL) was heated at 50°C for 67 hours. The reaction mixture was cooled to 23°C and was partitioned between half-saturated NaCl (200 mL) and a 1:1:1 mixture of EtOAc, hexanes and acetone (2 x 200 mL, 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue purified by flash column chromatography (gradient elution 9→17% EtOAc in hexanes) to give 5*S*-(1*S*-azido-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one (2.10 g, 62%) as a white solid (containing approximately 5-10% unidentified impurities by ^1H NMR): mp 91-96°C; R_f= 0.44 (25% EtOAc in hexanes); IR (cm^{-1}) 2097, 1772; ^1H NMR ($CDCl_3$, major isomer) δ 0.99 (d, 3H, *J* = 6.5), 1.02 (d, 3H, *J* = 6.8), 1.95-2.20 (m, 3H), 2.78-2.88 (m, 1H), 2.94 (dd, 1H, *J* = 7.0, 4.2), 3.03-3.17 (m, 2H), 4.37-4.43 (m, 1H), 6.97-7.09 (m, 2H), 7.14-7.21 (m, 2H).

Preparation of Intermediate {2-Methyl-1*S*-(4*R*-(4-fluorobenzyl)-5-oxotetrahydrofuran-2*S*-yl)propyl}-carbamic Acid *tert*-Butyl Ester.

A suspension of 5*S*-(1*S*-azido-2-methylpropyl)-3*R*-(4-fluorobenzyl)dihydrofuran-2-one (2.02 g, 6.93 mmol, 1 equiv.), di-*tert*-butyl dicarbonate (2.12 g, 9.71 mmol, 1.4 equiv.) and Pd/C (10%, 0.20 g) in CH_3OH (100 mL) was stirred under a hydrogen atmosphere (balloon) for 16 hours. The reaction mixture was vacuum filtered through Whatman #3 paper and concentrated. Purification of the residue by flash column chromatography (15% EtOAc in

hexanes) provided {2-methyl-1*S*-(4*R*-(4-fluorobenzyl)-5-oxotetrahydrofuran-2*S*-yl)propyl}-carbamic acid *tert*-butyl ester (1.58 g, 62%) as a white foam: R_f = 0.80 (5% MeOH in CH_2Cl_2); IR (cm^{-1}) 3331, 1766, 1702; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3H, *J* = 6.8), 0.95 (d, 3H, *J* = 6.5), 1.41 (s, 9H), 1.71-1.83 (m, 1H), 1.95-2.06 (m, 1H), 2.16-2.27 (m, 1H), 2.80 (dd, 1H, *J* = 13.5, 8.6), 2.88-2.99 (m, 1H), 3.09 (dd, 1H, *J* = 13.5, 4.4), 3.32-3.40 (m, 1H), 4.42-4.48 (m, 2H), 6.95-7.03 (m, 2H), 7.11-7.18 (m, 2H); Anal. ($C_{20}H_{28}FNO_4$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-Propenoate.

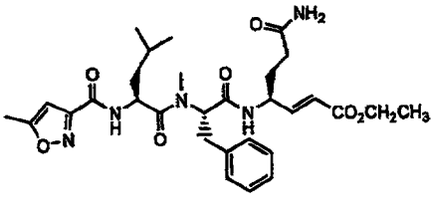
Lithium hydroxide (9.62 mL of a 1 M aqueous solution, 9.62 mmol, 5 equiv.) was added to a solution of {2-methyl-1*S*-(4*R*-(4-fluorobenzyl)-5-oxotetrahydrofuran-2*S*-yl)propyl}-carbamic acid *tert*-butyl ester (0.703 g, 1.92 mmol, 1 equiv.) in DME (25 mL) at 23°C. The resulting suspension was stirred at 23°C for 30 min., and then was partitioned between 10% $KHSO_4$ (50 mL) and CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue dissolved in CH_2Cl_2 (30 mL). Powdered 4Å molecular sieves (0.70 g), 4-methylmorpholine *N*-oxide (0.451 g, 3.85 mmol, 2 equiv.), and tetrapropylammonium perruthenate (0.068 g, 0.19 mmol, 0.10 equiv.) were added sequentially. The resulting dark reaction mixture was stirred for 1.33 hours at 23°C, then was vacuum filtered through Whatman #3 paper and then through Whatman #5 paper. The filtrate was concentrated under reduced pressure to provide a dark residue, which was dissolved in CH_2Cl_2 (30 mL). Crude ethyl-3-(H_2N-L-(Tr-*Gln*))-E-propenoate•HCl (2.30 mmol, 1.2 equiv., prepared as described in Example 2 for the preparation of ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate), 4-methylmorpholine (0.846 mL, 7.69 mmol, 4 equiv.), HOBt (0.390 g, 2.89 mmol, 1.5 equiv.), and EDC (0.553 g, 2.88 mmol, 1.5 equiv.) were added sequentially, and the reaction mixture was stirred for 19 hours at 23°C and then was partitioned between brine (100 mL) and CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution 35→40% EtOAc in hexanes) provided ethyl-3-{Boc-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (0.820 g, 53%) as a tan foam: R_f = 0.50 (50% EtOAc in hexanes); IR (cm^{-1}) 3307, 1708, 1666; ^1H NMR ($CDCl_3$) δ 0.67 (d, 3H, *J* = 6.8), 0.92 (d, 3H, *J* = 6.8), 1.28 (t, 3H, *J* = 7.2), 1.40 (s, 9H), 1.53-1.67 (m, 1H), 1.91-2.04 (m, 2H), 2.32-2.41 (m, 2H), 2.46-2.55 (m, 1H), 2.63 (dd, 1H, *J* = 12.1, 5.9), 2.69-2.80 (m, 1H), 2.83 (dd, 1H, *J* = 12.1, 8.2), 3.03 (dd, 1H, *J* = 17.7, 10.0), 4.05-4.11 (m, 1H), 4.17 (q, 2H, *J* =

7.2), 4.40-4.50 (m, 1H), 4.84 (d, 1H, J = 8.4), 5.38 (d, 1H, J = 15.7), 6.01 (d, 1H, J = 8.4), 6.60 (dd, 1H, J = 15.7, 5.0), 6.92-6.99 (m, 2H), 7.03-7.12 (m, 3H), 7.17-7.30 (m, 15H); Anal. ($C_{48}H_{56}FN_3O_7$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-*Gln*}-E-Propenoate

Ethyl-3-{Boc-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-ValΨ(COCH$_2$)-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to that described in Example 2 above for the conversion of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate: mp = 220°C (dec); R_f = 0.35 (10% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3277, 1715, 1643; ^1H NMR (DMSO-d_6) δ 0.81 (d, 3H, J = 6.2), 0.87 (d, 3H, J = 6.9), 1.21 (t, 3H, J = 6.5), 1.59-1.67 (m, 2H), 2.03 (s, br, 2H), 2.21-2.24 (m, 1H), 2.46 (s, 3H), 2.57-2.68 (m, 3H), 2.80-2.95 (m, 2H), 4.09 (q, 2H, J = 6.5), 4.30-4.34 (m, 2H), 5.41 (d, 1H, J = 15.5), 6.55 (s, 1H), 6.61 (dd, 1H, J = 15.5, 5.5), 6.73 (s, 1H), 6.99-7.16 (m, 5H), 8.01 (d, 1H, J = 7.8), 8.69 (d, 1H, J = 8.7); Anal. ($C_{29}H_{37}FN_4O_7$) C, H, N.

Example 11 - Preparation of Compound A-10: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Leu-NCH$_3$-L-Phe-L-*Gln*}-E-Propenoate



(A-10)

Preparation of Intermediate Boc-L-Leu-NCH$_3$-L-Phe-OCH$_3$

NCH$_3$-L-Phe-OCH$_3$•HCl (1.4 g) was dissolved in CH_2Cl_2 (50 mL) and poured into a combination of aqueous (aq) 1 N NaOH (7 mL) and saturated aqueous $NaHCO_3$ (25 mL). After mixing, the organic phase was separated and the aqueous phase was washed with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give the free amine as a clear colorless oil (1.14 g, 5.90 mmol). A solution of this amine and $(iPr)_2NEt$ (1.13 mL, 6.49 mmol) in DMF (10 mL) was added dropwise to a 0°C solution of Boc-L-Leu-OH (1.50 g, 6.49 mmol) and HOBt (0.877 g, 6.49 mmol) in DMF (10 mL). DCC (1.47 g, 7.12 mmol) was added. The reaction mixture was stirred at 0°C for 1 h, and was then

stirred at 23°C for 48 h. The mixture was filtered to remove the precipitate (ppt) and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ (40 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to give Boc-L-Leu-NCH_3-L-Phe-OCH_3 as a white solid (2.04 g, 85%): mp = 126-127°C; IR (cm^{-1}) 3401, 3319, 1743, 1708, 1649; ^1H NMR ($CDCl_3$) (major isomer) δ 0.92 (d, 3H, *J* = 6.8), 0.95 (d, 3H, *J* = 6.5), 1.32-1.48 (m, 2H), 1.41 (s, 9H), 1.61-1.77 (m, 1H), 2.90 (s, 3H), 3.04 (dd, 1H, *J* = 14.5, 10.5), 3.37 (dd, 1H, *J* = 14.5, 5.5), 3.72 (s, 3H), 4.48-4.57 (m, 1H), 4.98-5.04 (m, 1H), 5.20 (dd, 1H, *J* = 10.5, 5.5), 7.16-7.32 (m 5H); Anal. ($C_{22}H_{34}N_2O_5$) C, H, N.

Preparation of Intermediate Boc-L-Leu-NCH_3-L-Phe-OH

Boc-L-Leu-NCH_3-L-Phe-OCH_3 (0.625 g, 1.54 mmol) was dissolved in CH_3OH (20 mL) and cooled to 0°C. Aqueous NaOH (6.15 mL of a 2N solution, 12.3 mmol) was added dropwise. The reaction mixture was stirred for 3 h at 23°C, and then poured into 10% aqueous $KHSO_4$ (150 mL). This mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated to give Boc-L-Leu-NCH_3-L-Phe-OH as a white foam (0.617 g, quant.), which was used without purification.

Preparation of Intermediate Ethyl-3-{Boc-L-Leu-NCH_3-L-Phe-L-(Tr-*Gln*)}-E-Propenoate

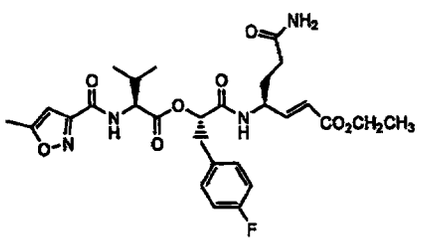
This intermediate was prepared from Boc-L-Leu-NCH_3-L-Phe-OH and ethyl-3-{H_2N-L-(Tr-*Gln*)}-E-propenoate•HCl (prepared as described in Example 2) in a manner analogous to that described for the preparation of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate in Example 2 above: IR (cm^{-1}) 3295, 1713, 1672, 1649; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, *J* = 6.2), 0.66 (d, *J* = 6.5), 0.84 (d, *J* = 6.5), 0.88 (d, *J* = 6.5), 1.02-1.22 (m), 1.23-1.38 (m), 1.33 (s), 1.41 (s), 1.55-1.82 (m), 1.89-2.07 (m), 2.23-2.30 (m), 2.90 (s), 2.94 (s), 3.01 (dd, *J* = 14.6, 10.9), 3.03-3.13 (m), 3.26-3.37 (m), 3.27 (dd, *J* = 14.6, 3.4), 3.42-3.54 (m), 4.00-4.22 (m), 4.37-4.73 (m), 4.82-4.89 (m), 5.63-5.70 (m), 5.95 (dd, *J* = 15.9, 1.2), 6.23-6.28 (m), 6.66-6.75 (m), 6.79-6.89 (m), 7.09-7.34 (m), 8.14 (d, *J* = 8.7); Anal. ($C_{49}H_{60}N_4O_7$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Leu-NCH_3-L-Phe-L-*Gln*}-E-Propenoate

Ethyl-3-{Boc-L-Leu-NCH_3-L-Phe-L-(Tr-*Gln*)}-E-propenoate was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-NCH_3-L-Phe-L-*Gln*}-E-propenoate in a

manner analogous to that described in Example 2 above for the conversion of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate: R_f= 0.23 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3295, 1713, 1666, 1637; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, J= 6.5), 0.71 (d, J= 6.5), 0.93 (d, J= 6.5), 0.94 (d, J= 6.5), 1.30 (t, J= 7.2), 1.24-1.73 (m), 1.81-2.22 (m), 2.45 (s), 2.48 (s), 2.86-2.93 (m), 2.96 (s), 2.97 (s), 3.03-3.14 (m), 3.21-3.31 (m), 3.48 (dd, J= 14.0, 5.9), 4.19 (q, J= 7.2), 4.20 (q, J= 7.2), 4.38-4.45 (m), 4.52-4.70 (m), 4.74-4.81 (m), 5.62-5.67 (m), 5.73-5.79 (m), 5.81 (dd, J= 15.6, 1.6), 5.99 (dd, J= 15.6, 1.6), 6.03-6.09 (m), 6.35 (s), 6.39 (s), 6.40-6.45 (m), 6.77-6.94 (m), 7.42 (d, J= 7.2), 8.13 (d, J= 7.8).

Example 12 - Preparation of Compound C-1: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(C-1)

Preparation of Intermediate Allyl (*S*)-1-Hydroxy-3-(4-fluorophenyl)propionate

In a flask fitted with a thermometer and a reflux condenser was dissolved methyl (*S*)-1-hydroxy-3-(4-fluorophenyl)propionate (prepared from L-H_2N-(4-F-Phe)-OCH_3 by the method described in Hoffman et al., *Tetrahedron* **1992**, vol. 48, 3007) (0.99 g, 5.0 mmol) in allyl alcohol (50 mL). Titanium tetraisopropoxide (1.53 mL, 5.0 mmol) was added, and the reaction brought to 90°C for 3.5 h. The reaction was cooled to room temperature and poured into 250 mL of 1:1 EtOAc/saturated NH_4Cl solution. The organic phase was separated and washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), and the solvent removed. The residue was subjected to flash column chromatography eluting with a gradient of 5-10% EtOAc/hexanes to afford 0.77 g (68%) of allyl (*S*)-1-hydroxy-3-(4-fluorophenyl)propionate as a clear liquid: R_f= 0.21 (15% EtOAc/hexanes); IR (neat) 3470 (broad), 1734, 1510, 1221 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.24-1.27 (m, 1H), 2.92-2.99 (m, 1H), 3.09-3.15 (m, 1H), 4.43-4.47 (m, 1H), 4.65 (d, 2H, J= 5.9), 5.28-5.37 (m, 2H), 5.86-5.95 (m, 1H), 6.95-7.01 (m, 2H), 7.16-7.21 (m, 2H).

Preparation of Intermediate Boc-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$

Allyl (*S*)-1-hydroxy-3-(4-fluorophenyl)propionate (0.070 g, 0.31 mmol) was dissolved in CH_2Cl_2 (20 mL). Boc-L-Val-OH (0.068 g, 0.31 mmol) was added, followed by DMAP (0.004 g, 0.03 mmol) and DCC (0.067 g, 0.33 mmol). The reaction was stirred at room temperature overnight, and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography eluting with a gradient of 3-5% EtOAc/hexanes. The Boc-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$ product was obtained as 0.12 g (90%) of a clear oil: R_f= 0.18 (10% EtOAc/hexanes); IR (neat) 1752, 1717 1510 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.80-0.85 (m, 6H), 1.36 (s, 9H), 1.97-2.04 (m, 1H), 3.07-3.15 (m, 2H), 3.89-3.94 (m, 1H), 4.51-4.55 (m, 2H), 5.17-5.30 (m, 3H), 5.75-5.84 (m, 1H), 7.06-7.17 (m, 3H), 7.27-7.32 (m, 2H); Anal. ($C_{22}H_{30}NO_6F$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-Val-O-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-Propenoate

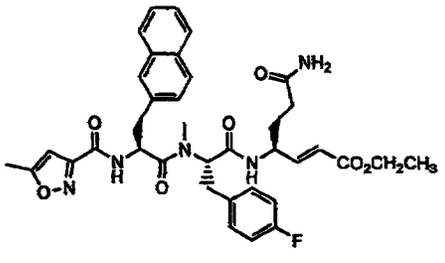
Boc-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$ (0.65 g, 1.52 mmol) was dissolved in THF (15 mL). Tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.03 mmol) was added, and the reaction stirred 5 min. at 23°C. Morpholine (0.16 mL, 1.83 mmol) was added dropwise, and the reaction stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue taken up in 50 mL of 4:1 hexanes/Et_2O. The product was extracted into sat. $NaHCO_3$ solution (50 mL), and the organic phase discarded. The aqueous phase was acidified to pH = 1-2 with solid $KHSO_4$, and the product re-extracted into EtOAc (50 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give 0.50 g (86%) of the free acid as a clear oil. This material was dissolved in DMF (6 mL). Diisopropylethylamine (0.43 mL, 2.50 mmol) was added, followed by ethyl-3-{H_2N-L-(Tr-*Gln*)}-E-propenoate•HCl (prepared as described in Example 2 above, 0.55 g, 1.25 mmol). The reaction was cooled to 0°C. HATU (0.48 g, 1.25 mmol) was added, and the reaction allowed to warm to room temperature. The DMF was removed *in vacuo*. The residue was dissolved with EtOAc (30 mL), and the organic phase washed consecutively with 10% HCl solution (25 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash column chromatography (0→1.0% MeOH/CH_2Cl_2) to give 0.40 g (39%) of ethyl-3-{Boc-L-Val-O-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate as a white amorphous solid: R_f= 0.25 (3%

MeOH/$CHCl_3$); IR(KBr) 1691, 1512, 1159 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.78-0.83 (m, 6H), 1.20 (t, 3H, J = 7.0), 1.35 (s, 9H), 1.58-1.66 (m, 2H), 1.96-2.02 (m, 1H), 2.19-2.33 (m, 2H), 2.99-3.02 (m, 2H), 3.82-3.87 (m, 1H), 4.09 (q, 2H, J = 7.0), 4.33-4.37 (m, 1H), 5.03-5.08 (m, 1H), 5.60 (d, 1H, J = 15.8), 6.67 (dd, 1H, J = 15.8, 5.5), 7.02-7.08 (m, 2H), 7.14-7.28 (m, 18H), 8.12 (d, 1H, J = 8.1), 8.59 (s, 1H); Anal. ($C_{47}H_{54}N_3O_8F$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-*Gln*}-E-Propenoate

Ethyl-3-{Boc-L-Val-O-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to that described in Example 2 above for the conversion of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate: R_f = 0.05 (3% MeOH/$CHCl_3$); IR (KBr) 1746, 1719, 1661, 1549 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.87 (d, 3H, J = 6.6), 0.92 (d, 3H, J = 6.6), 1.20 (t, 3H, J = 7.0), 1.61-1.74 (m, 2H), 1.96-2.01 (m, 2H), 2.15-2.22 (m, 1H), 2.46 (s, 3H), 3.00-3.03 (m, 2H), 4.10 (q, 2H, J = 7.0), 4.27-4.32 (m, 1H), 4.33-4.38 (m, 1H), 5.06-5.11 (m, 1H), 5.63 (d, 1H, J = 15.6), 6.54 (s, 1H), 6.68 (dd, 1H, J = 15.6, 5.5), 6.78 (s, br, 1H), 6.95-7.00 (m, 2H), 7.20-7.24 (m, 3H), 8.06 (d, 1H, J = 8.1), 8.87 (d, 1H, J = 7.7); Anal. ($C_{28}H_{35}N_4O_8F$) C, H, N.

Example 13 - Preparation of Compound A-11: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(A-11)

Preparation of Intermediate Ethyl-3-{Boc-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-Propenoate

Boc-(4-F-Phe)-OH (4.46 g, 15.75 mmol, 1 equiv.) and CH_3I (7.84 mL, 126 mmol, 8 equiv.) were dissolved in dry THF (100 mL) and cooled to 0°C. NaH (1.89 g, 47.25 mmol, 3 equiv.) was added to this solution with vigorous stirring. After stirring at 23°C for 24 h, EtOAc (3 mL) and H_2O (3 mL) were added carefully to the mixture, and the resulting suspension was evaporated to dryness. After dissolving in H_2O (100 mL), the reaction mixture

was washed with Et_2O (2 x 100 mL). .The aqueous layer was acidified to pH = 3 with 10% citric acid solution, and then extracted with EtOAc (2 x 100 mL). The combined EtOAc extracts were washed successively with half-saturated $NaHCO_3$ (150 mL), 5% $Na_2S_2O_3$ (150 mL), and H_2O (150 mL), dried over Na_2SO_4, and concentrated to give Boc-NCH_3-(4-F-Phe)-OH as a pale yellow foam (4.37 g, 80%), which was used without further purification: ^1H NMR ($CDCl_3$, mixture of isomers) δ 1.35 (s), 1.40 (s), 2.69 (s), 2.75 (s), 2.96-3.13 (m), 3.23-3.33 (m), 4.54-4.58 (m), 4.76-4.81 (m), 6.96-7.01 (m), 7.15-7.17 (m).

A solution of HCl in 1,4-dioxane (4.0 M, 15 mL) was added to a solution of ethyl-3-(Boc-L-(Tr-*Gln*))-E-propenoate (prepared as described in Example 2 above, 3.57 g, 6.73 mmol, 1 equiv.) in the same solvent (15 mL) at 23°C. After 2 h, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and Boc-NCH_3-(4-F-Phe)-OH (prepared as in the preceding paragraph, 2.0 g, 6.73 mmol, 1.0 equiv.), HOBt (1.23 g, 9.09 mmol, 1.5 equiv), 4-methylmorpholine (2.0 mL, 18.19 mmol, 3 equiv.), and EDC (1.74 g, 9.09 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was stirred at 23°C overnight, and then was partitioned between water (100 mL) and CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the residue was purified by flash column chromatography (30% EtOAc in hexane) to afford ethyl-3-{Boc-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (4.07 g, 84%) as white foam: IR (cm^{-1}) 1666, 1510, 1167; ^1H NMR ($CDCl_3$, mixture of isomers) δ 1.29 (t, J = 7.2), 1.37 (s), 1.65-1.75 (m), 1.95-2.06 (m), 2.29-2.33 (m), 2.66 (s), 2.91-2.99 (m), 3.22-3.29 (m), 4.18 (q, J = 7.2), 4.52-4.58 (m), 5.68 (d, J = 15.9), 6.45 (d, J = 8.4), 6.74 (dd, J = 15.6, 5.4), 6.91-6.99 (m), 7.11-7.33 (m); Anal. ($C_{43}H_{48}FN_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-Propenoate

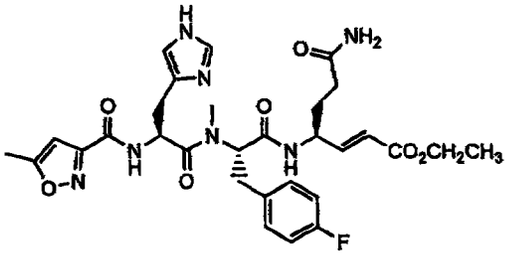
A solution of HCl in 1,4-dioxane (4.0 M, 3 mL), was added to a solution of ethyl-3-{Boc-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (0.388 g, 0.54 mmol, 1 equiv.) in the same solvent (3 mL) at 23°C. After 2 h, the volatiles were removed under reduced pressure. The residue was dissolved in DMF (10 mL), cooled at 0°C, and DIEA (0.188 mL, 1.08 mmol, 2 equiv.), Boc-L-(2-Naphth)-OH (0.170 g, 0.54 mmol, 1.0 equiv.) and HATU (0.205 g, 0.54 mmol, 1 equiv.) were added sequentially. The reaction mixture was stirred at 23°C for 1 h. The volatiles were removed under reduced pressure, and the resulting residue was taken into

EtOAc (50 mL), and washed with 0.5 N HCl (50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, concentrated, and the residue was purified by flash column chromatography (40% EtOAc in hexane) to afford ethyl-3-{Boc-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (0.437 g, 88%) as white foam: IR (cm^{-1}) 1656, 1509, 1162; ^1H NMR ($CDCl_3$, mixture of isomers) δ 0.88 (t, J = 7.2), 1.27 (s), 1.30 (s), 1.48-1.58 (m), 1.64-1.67 (m), 1.97-2.11 (m), 2.23-2.28 (m), 2.42-2.50 (m), 2.62-2.69 (m), 2.80 (s), 2.90 (s), 3.00-3.07 (m), 3.15-3.20 (m), 3.25-3.32 (m), 4.18 (q, J = 7.2), 4.42-4.46 (m), 4.53-4.56 (m), 4.61-4.66 (m), 4.72-4.82 (m), 5.94-5.00 (m), 5.63 (d, J = 15.6), 6.12 (d, J = 15.6), 6.60 (dd, J = 15.6, 5.4), 6.75-6.89 (m), 6.70-7.08 (m), 7.19-7.30 (m), 7.41-7.50 (m), 7.70-7.82 (m), 8.80 (d, J = 8.4); Anal. ($C_{56}H_{59}FN_4O_7$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-*Gln*}-E-Propenoate

Ethyl-3-{Boc-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH_3-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to that described in Example 2 above for the conversion of ethyl-3-{Boc-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-L-Phe-L-*Gln*}-E-propenoate IR (cm^{-1}) 3296, 1654, 1510; ^1H NMR (DMSO-d_6, mixture of isomers) δ 1.17-1.24 (m), 1.62-1.78 (m), 2.04-2.15 (m), 2.38 (s), 2.42 (s), 2.71-2.79 (m), 2.84 (s), 2.87-2.92 (m), 3.03 (s), 3.15 (d, J = 7.5), 3.98-4.06 (m), 4.08-4.12 (m), 4.38-4.42 (m), 4.94 (m), 5.03-5.07 (m), 5.09-5.18 (m), 5.66-5.82 (m), 6.42 (s), 6.43 (s), 6.66-6.81 (m), 6.88-6.94 (m), 7.01-7.06 (m), 7.13-7.17 (m), 7.24-7.34 (m), 7.43-7.46 (m), 7.56 (s), 7.76-7.84 (m), 8.08 (d, J = 7.8), 8.60 (d, J = 8.4), 9.01 (d, J = 7.2); Anal. ($C_{37}H_{40}FN_5O_7 \cdot 0.75H_2O$) C, H, N.

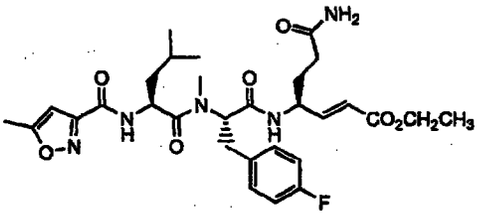
Example 14 - Preparation of Compound A-9: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-His-NCH_3-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(A-9)

Ethyl-3-{Boc-NCH3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (described in Example 13 above) was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-His-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to the preparation of product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate described in Example 13 above (utilizing Boc-L-(Tr-His)-OH in lieu of Boc-L-(2-Naphth)-OH): IR (cm^{-1}) 3302, 1665, 1202; ^1H NMR (DMSO-d_6, mixture of isomers) δ 1.21 (t, J = 7.2), 1.70-1.78 (m), 2.05-2.09 (m), 2.41 (s), 2.44 (s), 2.69-3.26 (m), 4.11 (q, J = 7.2), 4.38-4.53 (m), 5.07-5.19 (m), 6.51-5.84 (m), 6.44 (s), 6.48 (s), 6.63-6.86 (m), 6.89-7.01 (m), 7.09-7.19 (m), 7.23-7.42 (m), 8.02 (d, J = 8.7), 8.15 (d, J = 8.1), 8.59 (d, J = 8.7), 8.94 (s), 9.04 (s), 9.14 (d, J = 6.9); Anal. ($C_{30}H_{36}FN_7O_7$•TFA•H_2O) C, H, N.

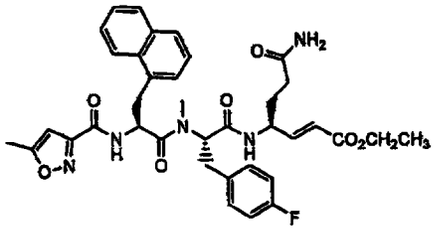
Example 15 - Preparation of Compound A-12: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Leu-NCH3-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(A-12)

Ethyl-3-{Boc-NCH3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (described in Example 13 above) was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Leu-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to the preparation of product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate described in Example 13 above (utilizing Boc-L-Leu-OH in lieu of Boc-L-(2-Naphth)-OH): IR (cm^{-1}) 3325, 1663, 1171; ^1H NMR (DMSO-d_6, mixture of isomers) δ 0.64-0.67 (m), 0.86-0.88 (m), 1.17-1.23 (m), 1.32-1.40 (m), 1.59-1.75 (m), 1.98-2.07 (m), 2.42 (s), 2.45 (s), 2.08 (s), 2.86-2.93 (m), 2.99 (s), 3.12-3.20 (m), 4.05-4.15 (m), 4.41-4.50 (m), 4.82-5.07 (m), 5.62 (d, J = 15.9), 5.86 (d, J = 15.9), 6.51 (s), 6.53 (s), 6.68-6.73 (m), 6.93-6.99 (m), 7.09-7.21 (m), 7.26-7.31 (m), 8.03 (d, J = 7.8), 8.08 (d, J = 7.8), 8.41 (d, J = 8.1), 8.94 (d, J = 7.2); Anal. ($C_{30}H_{40}FN_5O_7$•1.25CH_2Cl_2) C, H, N.

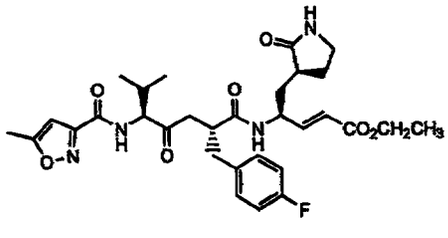
Example 16 - Preparation of Compound A-13: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-(1-Naphth)-NCH3-L-(4-F-Phe)-L-*Gln*}-E-Propenoate



(A-13)

Ethyl-3-{Boc-NCH3-L-(4-F-Phe)-L-(Tr-*Gln*)}-E-propenoate (described in Example 13 above) was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-(1-Naphth)-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate in a manner analogous to the preparation of product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-(2-Naphth)-NCH3-L-(4-F-Phe)-L-*Gln*}-E-propenoate described in Example 13 above, but utilizing Boc-L-(1-Naphth)-OH in lieu of Boc-L-(2-Naphth)-OH: IR (cm^{-1}) 3308, 1659, 1169; ^1H NMR (DMSO-d_6, mixture of isomers) δ 1.16-1.23 (m), 1.61-1.78 (m), 1.98-2.02 (m), 2.07-2.12 (m), 2.41 (s), 2.43 (s), 2.77 (s), 2.78 (s), 2.84-2.87 (m), 2.93-3.03 (m), 3.08-3.14 (m), 3.31-3.38 (m), 4.00-4.15 (m), 4.27-4.32 (m), 4.40-4.46 (m), 4.58-4.64 (m), 5.07-5.17 (m), 5.57-5.73 (m), 6.45 (s), 6.57-6.61 (m), 6.71-6.88 (m), 6.89-6.91 (m), 7.11-7.19 (m), 7.31-7.38 (m), 7.50-7.58 (m), 7.73-7.78 (m), 7.83-7.94 (m), 8.08 (d, J = 8.1), 8.13 (d, J = 8.7), 8.62 (d, J = 8.1), 9.14 (d, J = 8.1); Anal. ($C_{37}H_{40}FN_5O_7$) C, H, N.

Example 17 - Preparation of Compound B-2: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ(COCH2)-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-Propenoate



(B-2)

Preparation of Intermediate Ethyl-3-{Boc-L-ValΨ(COCH2)-L-(4-F-Phe)-L-{(*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*}-E-Propenoate

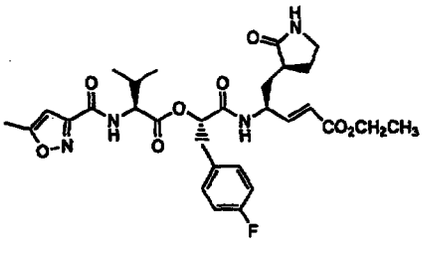
This intermediate was prepared from {2-methyl-1*S*-(4*R*-(4-fluorobenzyl)-5-oxotetrahydrofuran-2*S*-yl)propyl}-carbamic acid *tert*-butyl ester (described in Example 10) and ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (described in Example 6) in a manner analogous to the preparation of ethyl-3-{Boc-L-(4-Me-Phe)-L-(Tr-

Gln)}-E-propenoate (Example 4) above: R_f = 0.24 (60% EtOAc in hexanes); IR (cm^{-1}) 3293, 1717, 1668; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* = 6.8), 1.01 (d, 3H, *J* = 6.8), 1.30 (t, 3H, *J* = 7.2), 1.51-1.65 (m, 2H), 1.84-1.96 (m, 1H), 2.16-2.37 (m, 2H), 2.47 (s, 3H), 2.49-2.55 (m, 3H), 2.85-3.01 (m, 2H), 3.12-3.25 (m, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 4.18 (q, 2H, *J* = 7.2), 4.31-4.49 (m, 3H), 4.65-4.70 (m, 1H), 5.53 (dd, 1H, *J* = 15.7, 1.4), 6.39-6.44 (m, 3H), 6.63 (dd, 1H, *J* = 15.7, 5.4), 6.93-7.01 (m, 2H), 7.05-7.10 (m, 1H), 7.12-7.18 (m, 2H), 7.24 (d, 1H, *J* = 8.7), 7.47 (d, 1H, *J* = 6.5); Anal. ($C_{40}H_{49}FN_4O_9 \cdot 0.5H_2O$) C, H, N.

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ($COCH_2$)-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-Propenoate

Ethyl-3-{Boc-L-ValΨ($COCH_2$)-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate was converted to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-ValΨ($COCH_2$)-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-propenoate in a manner analogous to the conversion of ethyl-3-{Boc-L-Val-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-propenoate described in Example 6 above: mp = 178-181°C; R_f = 0.49 (10% CH_3OH in $CHCl_3$); IR (cm^{-1}) 3295, 1678 br; ^1H NMR ($CDCl_3$) δ 0.85 (d, 3H, *J* = 6.8), 1.03 (d, 3H, *J* = 6.5), 1.30 (t, 3H, *J* = 7.2), 1.51-1.62 (m, 1H), 1.71-1.93 (m, 2H), 2.27-2.40 (m, 2H), 2.47 (s, 3H), 2.51-2.75 (m, 3H), 2.82-2.98 (m, 2H), 3.11-3.24 (m, 1H), 3.26-3.42 (m, 2H), 4.18 (q, 2H, *J* = 7.2), 4.41-4.53 (m, 1H), 4.63-4.72 (m, 1H), 5.50 (d, 1H, *J* = 15.4), 5.88 (s, 1H), 6.39 (s, 1H), 6.63 (dd, 1H, *J* = 15.4, 5.3), 6.92-7.03 (m, 2H), 7.08-7.31 (m, 4H); Anal. ($C_{31}H_{39}FN_4O_7$) C, H, N.

Example 18 - Preparation of Compound C-2: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-*(S)-Pyrrol-Ala*)}-E-Propenoate



(C-2)

Preparation of Intermediate (5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$

Boc-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$ (prepared as described in Example 12 above, 0.91 g, 2.15 mmol) was dissolved in 1,4-dioxane (28 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 14 mL) was added. The reaction was stirred at room temperature for 14 h. The solvent was removed by evaporation, and the residue taken up in EtOAc (50 mL). The organic phase was washed with saturated $NaHCO_3$ solution (50 mL) and then brine (50 mL), dried ($MgSO_4$), and the solvent removed to give 0.66 g (quant.) of a clear oil.

This material was dissolved in CH_2Cl_2 (20 mL). Pyridine (0.17 mL, 2.08 mmol) was added, and the reaction was cooled to 0°C. 5-Methylisoxazole-3-carbonyl chloride (0.33 g, 2.27 mmol) dissolved in 2 mL of CH_2Cl_2 was added, and the reaction warmed to room temperature over 1 h. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography eluting with a gradient of 5→10% EtOAc/hexanes. The (5'-methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$ product was obtained as 0.70 g (82%) of a white crystalline solid: R_f = 0.20 (30% EtOAc/hexanes); IR (KBr) 1745, 1661, 1553, 1186 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85-0.92 (m, 6H), 2.14-2.21 (m, 1H), 2.46 (s, 3H), 3.05-3.19 (m, 2H), 4.32-4.37 (m, 1H), 4.53-4.60 (m, 2H), 5.16-5.28 (m, 3H), 5.74-5.85 (m, 1H), 6.56 (s, 1H), 7.01-7.07 (m, 2H), 7.26-7.29 (m, 2H), 8.76 (d, 1H, J = 8.1); Anal. ($C_{22}H_{25}N_2O_6F$) C, H, N.

Preparation of Intermediate Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-$OCH_2CH=CH_2$ (0.67 g, 1.55 mmol) was dissolved in THF (15 mL). Tetrakis(triphenylphosphine)palladium(0) (0.036 g, 0.03 mmol) was added, and the reaction mixture was stirred for 5 minutes. Morpholine (0.16 mL, 1.86 mmol) was added dropwise, and the reaction stirred at room temperature for 6 h. The solvent was removed *in vacuo*, and the residue taken up in 50 mL of Et_2O. The product was extracted twice into saturated $NaHCO_3$ solution (50 mL), and the organic phase discarded. The aqueous phase was acidified to pH = 1-2 with 10% HCl, and the product extracted twice with EtOAc (40 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give 0.57 g (95%) of an oil which crystallized upon standing.

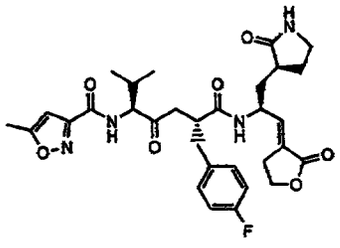
A portion of this material (0.19 g, 0.50 mmol) was dissolved in DMF (3 mL). Diisopropylethylamine (0.34 mL, 1.0 mmol) was added, followed by ethyl-3-{H_2N-L-((*N*-2,4-

dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate•HCl (prepared as described in Examples 4 and 6 above, 0.19 g, 0.50 mmol). The reaction was cooled to 0 °C. HATU (0.19 g, 0.50 mmol) was added, and the reaction was allowed to warm to room temperature. The DMF was removed *in vacuo*. The residue was dissolved with EtOAc (30 mL), and the organic phase washed consecutively with 10% HCl solution (25 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL). The solvent was dried ($MgSO_4$) and filtered, and the residue purified by flash column chromatography (0→1.0% MeOH/CH_2Cl_2) to give ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (0.27 g, 72%) as a white amorphous solid: R_f = 0.18 (3% MeOH/$CHCl_3$); IR(KBr) 1671, 1547, 1510, 1209 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.88 (d, 3H, *J* = 7.0), 0.93 (d, 3H, *J* = 7.0), 1.20 (t, 3H, *J* = 7.0), 1.41-1.58 (m, 2H), 1.79-1.98 (m, 2H), 2.07-2.24 (m, 2H), 2.44 (s, 3H), 3.01-3.13 (m, 4H), 3.73 (s, 3H), 3.76 (s, 3H), 4.09 (q, 2H, *J* = 7.0), 4.24 (s, 2H), 4.30 (t, 1H, *J* = 7.4), 4.45-4.48 (m, 1H), 5.12 (t, 1H, *J* = 6.3), 5.59 (d, 1H, *J* = 15.8), 6.45 (dd, 1H, *J* = 8.5, 2.2), 6.54-6.56 (m, 2H), 6.73 (dd, 1H, *J* = 15.5, 4.8), 6.89-6.95 (m, 3H), 7.20 (d, 1H, *J* = 8.5), 7.22 (d, 1H, *J* = 8.5), 8.08 (d, 1H, *J* = 8.8), 8.89 (d, 1H, *J* = 7.4).

Preparation of Product Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-((*S*)-*Pyrrol-Ala*)}-E-Propenoate

Ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (0.25 g, 0.33 mmol) was dissolved in $CHCl_3$ (6 mL). Two drops of water were added, followed by DDQ (0.10 g, 0.43 mmol). The reaction was heated to 50-55°C for 8 h. Upon cooling, the reaction mixture was poured into EtOAc (30 mL). The organic phase was washed with 30 mL of 2:1 $NaHCO_3$/1N NaOH solution and then brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to flash column chromatography eluting with 0→2% MeOH/CH_2Cl_2. The ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-O-L-(4-F-Phe)-L-((*S*)-*Pyrrol-Ala*)}-E-propenoate product was obtained as 0.18 g (90%) of a white amorphous solid: R_f = 0.09 (3% MeOH/$CHCl_3$); IR(KBr) 1680, 1549 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.91 (d, 3H, *J* = 6.6), 0.95 (d, 3H, *J* = 6.6), 1.20 (t, 3H, *J* = 7.0), 1.36-1.44 (m, 1H), 1.56-1.61 (m, 1H), 1.74-1.82 (m, 1H), 1.94-1.99 (m, 2H), 2.18-2.25 (m, 1H), 2.45 (s, 3H), 2.98-3.18 (m, 4H), 4.09 (q, 2H, *J* = 7.0), 4.28-4.32 (m, 1H), 4.43-4.46 (m, 1H), 5.12 (m, 1H), 5.58 (d, 1H, *J* = 15.8), 6.56 (s, 1H), 6.72 (dd, 1H, *J* = 15.8, 4.8), 6.91-6.97 (m, 2H), 7.21 (d, 1H, *J* = 5.9), 7.23 (d, 1H, *J* = 5.9), 7.59 (s, 1H), 8.06 (d, 1H, *J* = 8.8), 8.92 (d, 1H, *J* = 7.4); Anal. ($C_{30}H_{37}N_4O_8F$) C, H, N.

Example 19 - Preparation of Compound B-3: 2-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ(COCH2)-L-(4-F-Phe)-L-((S)-Pyrrol-Ala)}-E-(α-Vinyl-γ-Butyrolactone)



(B-3)

Preparation of Intermediate Boc-L-{(*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*}-E-(α-Vinyl-γ-Butyrolactone)

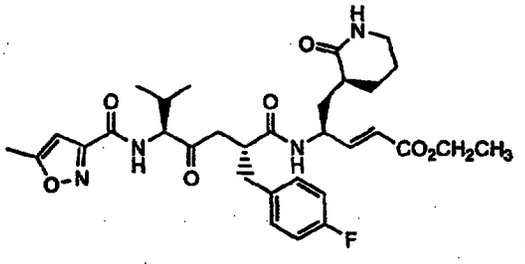
(1*S*,3'*S*)-{2-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester (0.360 g, 0.881 mmol, 1 equiv.) was oxidized to the corresponding aldehyde in the manner described in the preparation of ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (Example 6). This aldehyde was combined with 3-(triphenyl-λ^5-phosphanylidene)-dihydrofuran-2-one (prepared in a manner analogous to that described in Baldwin et al., *J. Org. Chem.* **1971**, vol. 36, 1441) (0.320 g, 0.924 mmol, 1.05 equiv.) in a mixture of ethylene glycol dimethyl ether (10 mL) and DMF (2 mL). The reaction mixture was warmed in a 100°C oil bath for 1.5 h, allowed to cool to 23°C overnight, and then diluted with MTBE (200 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (2.5% CH_3OH in CH_2Cl_2, then 67% EtOAc in CH_2Cl_2) to give Boc-L-{(*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*}-E-(α-vinyl-γ-butyrolactone) as an oil (0.250 g, 60%): R_f= 0.50 (67% EtOAc in CH_2Cl_2); IR (cm^{-1}) 3307, 1754, 1678; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.46-1.68 (m, 2H), 2.02-2.13 (m, 1H), 2.18-2.30 (m, 1H), 2.44-2.56 (m, 1H), 2.91-3.04 (m, 1H), 3.15-3.27 (m, 3H), 3.80 (s, 6H), 4.34-4.43 (m, 5H), 5.63-5.69 (m, 1H), 6.42-6.47 (m, 2H), 6.48-6.53 (m, 1H), 7.09-7.13 (m, 1H).

Preparation of Product 2-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ(COCH2)-L-(4-F-Phe)-L-((S)-Pyrrol-Ala)}-E-(α-Vinyl-γ-Butyrolactone)

Boc-L-{(*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*}-E-(α-vinyl-γ-butyrolactone) was converted to product 2-{(5'-methylisoxazole-3'-carbonyl)-L-ValΨ(COCH2)-L-(4-F-Phe)-L-((*S*)-*Pyrrol-Ala*)}-E-(α-vinyl-γ-butyrolactone) in a manner analogous to that described above for the preparation of product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-ValΨ(COCH2)-L-

(4-F-Phe)-L-(*(S)-Pyrrol-Ala*)}-E-propenoate (Example 17): R_f = 0.28 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3378 br, 1749, 1678 br; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 6.8), 1.03 (d, 3H, *J* = 6.8), 1.45-1.55 (m, 1H), 1.75-2.00 (m, 2H), 2.25-2.43 (m, 2H), 2.46-2.59 (m, 2H), 2.48 (s, 3H), 2.63-2.72 (m, 1H), 2.77-2.90 (m, 3H), 3.06-3.26 (m, 2H), 3.29-3.44 (m, 2H), 4.32-4.46 (m, 3H), 4.65-4.71 (m, 1H), 5.72 (s, 1H), 6.14-6.20 (m, 1H), 6.40 (s, 1H), 6.94-7.02 (m, 2H), 7.03-7.11 (m, 2H), 7.24 (d, 1H, *J* = 9.0), 7.60 (d, 1H, *J* = 6.2); Anal. ($C_{31}H_{37}FN_4O_7$) C, H, N.

Example 20 - Preparation of Compound B-4: Ethyl-3-{(5'-Methylisoxazole-3'-carbonyl)-L-ValΨ($COCH_2$)-L-(4-F-Phe)-L-*((S)-Piper-Ala)*}-E-Propenoate

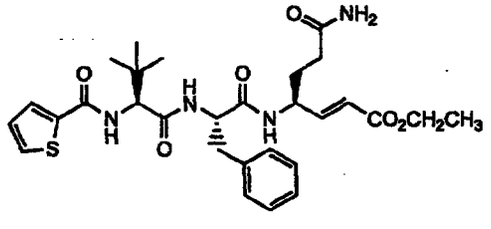


(B-4)

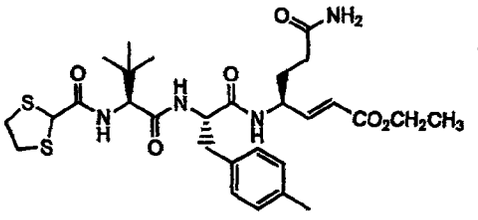
This product was prepared in analogy to product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-Val-L-(4-F-Phe)-L-*((S)-Piper-Ala)*}-E-propenoate (Example 9) and product ethyl-3-{(5'-methylisoxazole-3'-carbonyl)-L-ValΨ($COCH_2$)-L-(4-F-Phe)-L-*Gln*}-E-propenoate (Example 10) described above: mp = 161-162°C; R_f = 0.30 (5% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3295, 1713, 1649; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 6.8), 1.03 (d, 3H, *J* = 6.8), 1.30 (t, 3H, *J* = 7.2), 1.43-1.55 (m, 2H), 1.77-1.90 (m, 2H), 1.95-2.12 (m, 2H), 2.27-2.38 (m, 1H), 2.44-2.58 (m, 2H), 2.48 (s, 3H), 2.66-2.76 (m, 1H), 2.80-2.93 (m, 2H), 3.12-3.42 (m, 3H), 4.18 (q, 2H, *J* = 7.2), 4.39-4.49 (m, 1H), 4.65-4.72 (m, 1H), 5.50 (dd, 1H, *J* = 15.9, 1.6), 5.80 (s, 1H), 6.38-6.41 (m, 1H), 6.62 (dd, 1H, *J* = 15.9, 5.3), 6.94-7.02 (m, 2H), 7.08-7.28 (m, 4H).

Examples 21 through 30

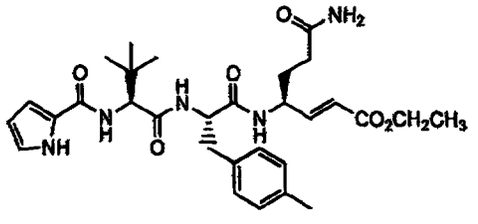
For Examples 21-30, the following Compounds **(A-14)** through **(A-23)**, respectively, were prepared using synthetic methods analogous to those described above for compounds of the formula I-A:



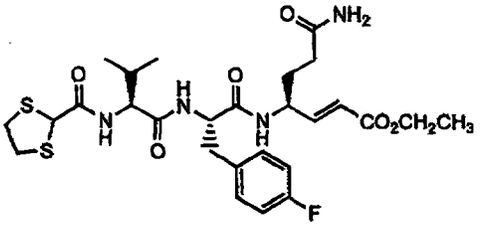
(A-14)



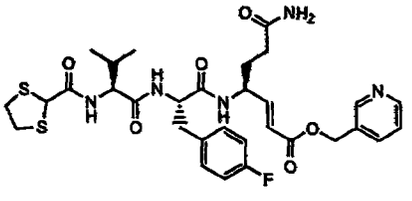
(A-15)



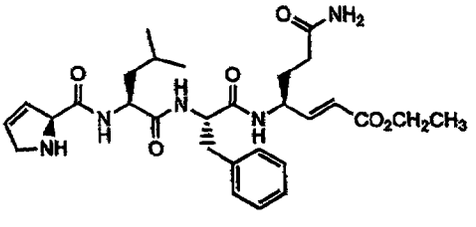
(A-16)



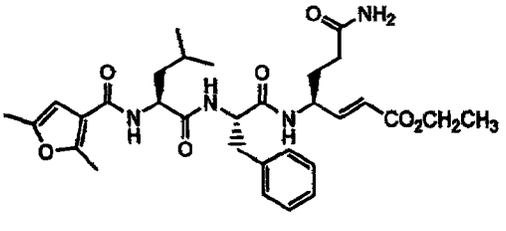
(A-17)



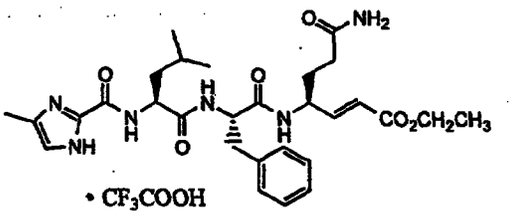
(A-18)



(A-19)

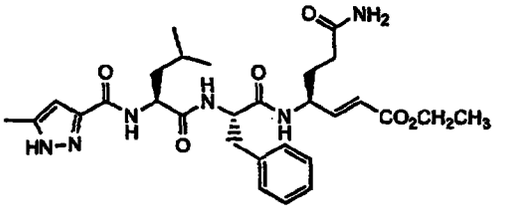


(A-20)

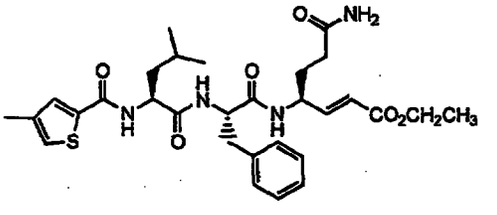


• CF_3COOH

(A-21)

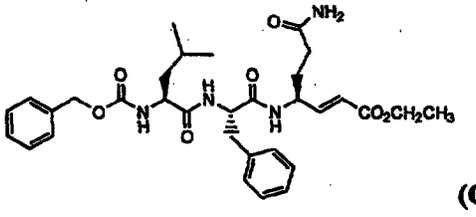


(A-22)



(A-23)

Example 31 - Preparation of Comparison Compound #2: Ethyl-3-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-Propenoate



(Comparison Compound #2)

Preparation of Intermediate [Boc-L-(Tr-Gln)]-N(OMe)Me

Isobutyl chloroformate (4.77 mL, 36.8 mmol, 1.0 equiv.) was added to a solution of *N*-α-Boc-γ-trityl-L-glutamine (18.7 g, 36.7 mmol, 1 equiv.) and 4-methylmorpholine (8.08 mL, 73.5 mmol, 2.0 equiv.) in CH_2Cl_2 (250 mL) at 0°C. The reaction mixture was stirred at 0°C for 20 minutes, and then *N,O*-dimethylhydroxylamine hydrochloride (3.60 g, 36.7 mmol, 1.0 equiv.) was added. The resulting solution was stirred at 0°C for 20 minutes and at 23°C for 2 hours, and then was partitioned between water (150 mL) and CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution 40→20% hexanes in EtOAc) provided {Boc-L-(Tr-Gln)}-N(OMe)Me (16.1 g, 82%) as a white foam: IR (cm^{-1}) 3411, 3329, 3062, 1701, 1659; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.63-1.77 (m, 1H), 2.06-2.17 (m, 1H),

2.29-2.43 (m, 2H), 3.17 (s, 3H), 3.64 (s, 3H), 4.73 (s, br, 1H), 5.38-5.41 (m, 1H), 7.20-7.31 (m, 15H); Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

Preparation of Intermediate {Boc-L-(Tr-Gln)}-H

Diisobutylaluminum hydride (50.5 mL of a 1.5 M solution in toluene, 75.8 mmol, 2.5 equiv.) was added to a solution of {Boc-L-(Tr-Gln)}-N(OMe)Me (16.1 g, 30.3 mmol, 1 equiv.) in THF at -78°C, and the reaction mixture was stirred at -78°C for 4 h. Methanol (4 mL) and 1.0 M HCl (10 mL) were added sequentially, and the mixture was warmed to 23°C. The resulting suspension was diluted with Et_2O (150 mL) and was washed with 1.0 M HCl (3 x 100 mL), half-saturated $NaHCO_3$ (100 mL), and water (100 mL). The organic layer was dried over $MgSO_4$, filtered, and was concentrated to give crude {Boc-L-(Tr-Gln)}-H (13.8 g, 97%) as a white solid: mp = 114-116°C; IR (cm^{-1}) 3313, 1697, 1494; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.65-1.75 (m, 1H), 2.17-2.23 (m, 1H), 2.31-2.54 (m, 2H), 4.11 (s, br, 1H), 5.38-5.40 (m, 1H), 7.11 (s, 1H), 7.16-7.36 (m, 15H), 9.45 (s, 1H).

Preparation of Intermediate Ethyl-3-{Boc-L-(Tr-*Gln*)}-E-Propenoate

Sodium bis(trimethylsilyl)amide (22.9 mL of a 1.0 M solution in THF, 22.9 mmol, 1.0 equiv.) was added to a solution of triethyl phosphonoacetate (5.59 g, 22.9 mmol, 1.0 equiv.) in THF (200 mL) at -78°C, and the resulting solution was stirred for 20 minutes at that temperature. Crude {Boc-L-(Tr-Gln)}-H (10.8 g, 22.9 mmol, 1 equiv.) in THF (50 mL) was added via cannula, and the reaction mixture was stirred for 2 hours at -78°C, warmed to 0°C for 10 minutes, and partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) provided ethyl-3-{Boc-L-(Tr-*Gln*)}-E-propenoate (10.9 g, 88%) as a white foam: IR (cm^{-1}) 3321, 1710; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2), 1.42 (s, 9H), 1.70-1.78 (m, 1H), 1.80-1.96 (m, 1H), 2.35 (t, 2H, J = 7.0), 4.18 (q, 2H, J = 7.2), 4.29 (s, br, 1H), 4.82-4.84 (m, 1H), 5.88 (dd, 1H, J = 15.7, 1.6), 6.79 (dd, 1H, J = 15.7, 5.3), 6.92 (s, 1H), 7.19-7.34 (m, 15H); Anal. ($C_{33}H_{38}N_2O_5$) C, H, N.

Preparation of Intermediate Ethyl-3-{Cbz-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-Propenoate

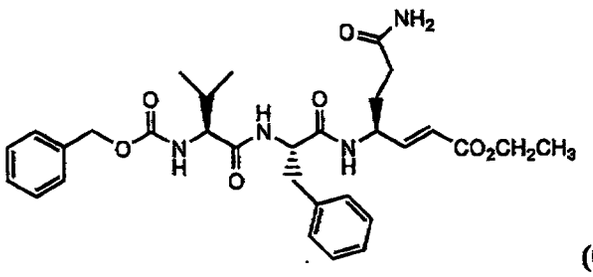
A solution of HCl in 1,4-dioxane (4.0 M, 20 mL), was added to a solution of ethyl-3-{Boc-L-(Tr-*Gln*)}-E-propenoate (1.00 g, 1.84 mmol, 1 equiv.) in the same solvent (20 mL) at 23°C. After 3 hours, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and Cbz-L-Leu-L-Phe-OH (0.759 g, 1.84 mmol, 1.0 equiv.),

HOBt (0.373 g, 2.76 mmol, 1.5 equiv.), 4-methylmorpholine (0.809 mL, 7.36 mmol, 4.0 equiv.), and EDC (0.529 g, 2.76 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was stirred at 23°C for 18 hours, and then was partitioned between water (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Flash chromatographic purification of the residue (5% CH_3OH in CH_2Cl_2) afforded ethyl-3-{Cbz-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate (1.25 g, 83%) as a white solid: mp = 192-194°C; IR (cm^{-1}) 3295, 1696, 1678, 1655, 1519; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 6.5), 0.86 (d, 3H, *J* = 6.5), 1.24-1.32 (m, 1H), 1.28 (t, 3H, *J* = 7.2), 1.43-1.75 (m, 3H), 1.91-2.06 (m, 1H), 2.20-2.38 (m, 2H), 2.93-3.02 (m, 1H), 3.07-3.18 (m, 1H), 3.95-4.02 (m, 1H), 4.17 (q, 2H, *J* = 7.2), 4.43-4.55 (m, 2H), 4.82-4.95 (m, 2H), 5.69 (d, 1H, *J* = 15.7), 6.46 (d, 1H, *J* = 7.5), 6.60 (d, 1H, *J* = 8.1), 6.69 (dd, 1H, *J* = 15.7, 5.1), 7.09-7.38 (m, 27H); Anal. ($C_{51}H_{56}N_4O_7$) C, H, N.

Preparation of Product Ethyl-3-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-Propenoate

Trifluoroacetic acid (20 mL) was added to a solution of ethyl-3-{Cbz-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate (1.25 g, 1.49 mmol, 1 equiv.) and triisopropylsilane (1.53 mL, 7.47 mmol, 5.0 equiv.) in CH_2Cl_2 (20 mL) at 23°C, producing a bright yellow solution. The reaction mixture was stirred for 20 minutes at 23°C, during which time it became colorless. Carbon tetrachloride (20 mL) was added, and the volatiles were removed under reduced pressure. The residue was triturated with Et_2O (20 mL), and the resulting white solid was collected by vacuum filtration, washed with Et_2O (3 x 50 mL), and air-dried to afford ethyl-3-(Cbz-L-Leu-L-Phe-L-*Gln*)-E-propenoate (0.717 g, 81%): mp = 219-221°C; IR (cm^{-1}) 3300, 1672, 1535; ^1H NMR (DMSO-d_6) δ 0.78 (d, 3H, *J* = 6.8), 0.82 (d, 3H, *J* = 6.5), 1.21 (t, 3H, *J* = 7.0), 1.25-1.37 (m, 2H), 1.42-1.54 (m, 1H), 1.58-1.80 (m, 2H), 2.02-2.09 (m, 2H), 2.84 (dd, 1H, *J* = 13.2, 8.9), 2.97 (dd, 1H, *J* = 13.2, 5.8), 3.93-4.01 (m, 1H), 4.11 (q, 2H, *J* = 7.0), 4.33-4.52 (m, 2H), 4.97 (d, 1H, *J* = 12.3), 5.04 (d, 1H, *J* = 12.3), 5.64 (d, 1H, *J* = 15.9), 6.69 (dd, 1H, *J* = 15.9, 5.4), 6.76 (s, 1H), 7.13-7.37 (m, 11H), 7.43 (d, 1H, *J* = 7.8), 7.99 (d, 1H, *J* = 8.1), 8.04 (d, 1H, *J* = 8.1); Anal. ($C_{32}H_{42}N_4O_7$) C, H, N.

Example 32 - Preparation of Comparison Compound #3: Ethyl-3-(Cbz-L-Val-L-Phe-L-*Gln*)-E-Propenoate



(Comparison Compound #3)

Preparation of Intermediate Ethyl-3-{Boc-L-Phe-L-(Tr-*Gln*)}-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added to a solution of ethyl-3-{Boc-L-(Tr-*Gln*)}-E-propenoate (prepared as described in Example 31, 3.05 g, 5.62 mmol, 1 equiv.) in the same solvent (20 mL) at 23°C. After 3 hours, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and Boc-L-Phe-OH (1.49 g, 5.62 mmol, 1.0 equiv.), HOBt (0.911 g, 6.74 mmol, 1.2 equiv.), 4-methylmorpholine (1.85 mL, 16.8 mmol, 3.0 equiv.) and EDC (1.29 g, 6.73 mmol, 1.2 equiv.) were added sequentially. The reaction mixture was stirred at 23°C for 18 hours, and was then partitioned between water (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Flash chromatographic purification of the residue (gradient elution, 40→50% EtOAc in hexanes) afforded ethyl-3-{Boc-L-Phe-L-(Tr-*Gln*)}-E-propenoate (2.77 g, 71%) as a white foam: IR (cm^{-1}) 3306, 1706, 1661; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2), 1.38 (s, 9H), 1.65-1.76 (m, 1H), 1.87-1.99 (m, 1H), 2.25-2.27 (m, 2H), 2.94-3.01 (m, 2H), 4.14-4.26 (m, 3H), 4.48-4.53 (m, 1H), 4.95 (s, br, 1H), 5.64 (d, 1H, J = 15.8), 6.29 (d, 1H, J = 8.1), 6.64 (dd, 1H, J = 15.8, 5.4), 6.80 (s, br, 1H), 7.14-7.32 (m, 20H); Anal. ($C_{42}H_{47}N_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-{Cbz-L-Val-L-Phe-L-(Tr-*Gln*)}-E-Propenoate

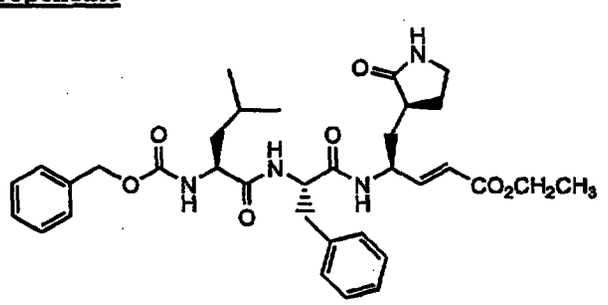
A solution of HCl in 1,4-dioxane (4.0 M, 8 mL) was added to a solution of ethyl-3-{Boc-L-Phe-L-(Tr-*Gln*)}-E-propenoate (0.296 g, 0.429 mmol, 1 equiv.) in the same solvent (10 mL) at 23°C. After 3 hours, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and then Cbz-L-Val-OH (0.108 g, 0.430 mmol, 1.0 equiv.), HOBt (0.070 g, 0.518 mmol, 1.2 equiv.), 4-methylmorpholine (0.142 mL, 1.29 mmol, 3.0 equiv.) and EDC (0.099 g, 0.516 mmol, 1.2 equiv.) were added sequentially. The reaction mixture was stirred at 23°C for 4 hours, and then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and were

concentrated. Flash chromatographic purification of the residue (3% CH_3OH in CH_2Cl_2) afforded ethyl-3-{Cbz-L-Val-L-Phe-L-(Tr-*Gln*)}-E-propenoate (0.220 g, 62%) as a white solid: mp = 195-198°C; IR (cm^{-1}) 3284, 1689, 1646; ^1H NMR ($CDCl_3$) δ 0.69 (d, 3H, *J* = 6.9), 0.82 (d, 3H, *J* = 6.5), 1.28 (t, 3H, *J* = 7.2), 1.63-1.74 (m, 1H), 1.96-2.02 (m, 2H), 2.22-2.35 (m, 2H), 2.93 (dd, 1H, *J* = 14.0, 7.6), 3.10 (dd, 1H, *J* = 14.0, 6.7), 3.81-3.85 (m, 1H), 4.17 (q, 2H, *J* = 7.2), 4.48-4.58 (m, 2H), 4.87 (d, 1H, *J* = 12.0), 4.94 (d, 1H, *J* = 12.0), 5.06 (d, 1H, *J* = 6.9), 5.67 (d, 1H, *J* = 15.6), 6.43 (d, 1H, *J* = 7.5), 6.63-6.72 (m, 2H), 7.10-7.40 (m, 26H); Anal. ($C_{50}H_{54}N_4O_7$) C, H, N.

Preparation of Product Ethyl-3-(Cbz-L-Val-L-Phe-L-*Gln*)-E-Propenoate

Trifluoroacetic acid (5 mL) was added to a solution of ethyl-3-{Cbz-L-Val-L-Phe-L-(Tr-*Gln*)}-E-propenoate (0.188 g, 0.229 mmol, 1 equiv.) and triisopropylsilane (0.300 mL, 1.46 mmol, 6.4 equiv.) in CH_2Cl_2 (10 mL) at 23°C, producing a bright yellow solution. The reaction mixture was stirred for 20 min. at 23°C, during which time it became colorless. Carbon tetrachloride (10 mL) was added, and the volatiles were removed under reduced pressure. The residue was triturated with Et_2O (20 mL), and the resulting white solid was collected by vacuum filtration, washed with Et_2O (3 x 50 mL), and air-dried to afford ethyl-3-(Cbz-L-Val-L-Phe-L-*Gln*)-E-propenoate (0.094 g, 71%): mp = 240°C (dec); IR (cm^{-1}) 3263, 1686, 1640; ^1H NMR (DMSO-d_6) δ 0.73 (d, 6H, *J* = 6.9), 1.21 (t, 3H, *J* = 7.2), 1.60-1.75 (m, 2H), 1.83-1.90 (m, 1H), 2.03-2.08 (m, 2H), 2.83 (dd, 1H, *J* = 13.6, 8.6), 2.96 (dd, 1H, *J* = 13.6, 6.2), 3.79-3.84 (m, 1H), 4.10 (q, 2H, *J* = 7.2), 4.37-4.49 (m, 1H), 4.51-4.56 (m, 1H), 4.99 (d, 1H, *J* = 12.5), 5.06 (d, 1H, *J* = 12.5), 5.61 (d, 1H, *J* = 15.5), 6.67 (dd, 1H, *J* = 15.5, 5.5), 6.76 (s, 1H), 7.13-7.36 (m, 12H), 8.06 (d, 2H, *J* = 8.1); Anal. ($C_{31}H_{40}N_4O_7$) C, H, N.

Example 33 - Preparation of Compound (A-24): Ethyl-3-{Cbz-L-Leu-L-Phe-L-*((S)-Pyrrol-Ala)*}-E-Propenoate



(A-24)

Preparation of Intermediate Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 *M*, 4 mL) was added to a solution of ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-pyrrol-Ala*)}-E-propenoate (prepared as described in Example 6) (0.139 g, 0.292 mmol, 1 equiv.) in 1,4-dioxane (4 mL). After stirring 1.5 h, the volatiles were evaporated to give the crude amine salt, which was used without purification.

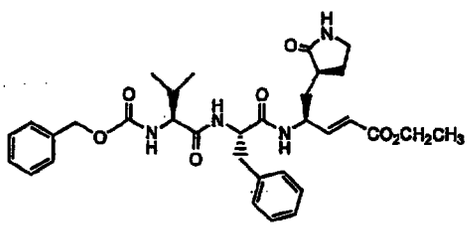
This amine salt was dissolved in CH_2Cl_2 (7 mL), and then Cbz-L-Leu-L-Phe-OH (0.156 g, 0.378 mmol, 1.3 equiv.), 4-methylmorpholine (0.128 mL, 1.16 mmol, 4 equiv.), HOBt (0.067 g, 0.50 mmol, 1.7 equiv.) and EDC (0.095 g, 0.50 mmol, 1.7 equiv) were added sequentially. After stirring 20 hours, the reaction mixture was poured into brine (15 mL) and extracted with 10% CH_3OH in CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. Purification of the residue by flash column chromatography (60% EtOAc in hexanes) provided ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (0.158 g, 70%) as a foam: ^{1}H NMR ($CDCl_3$) δ 0.87-0.92 (m, 6H), 1.28 (t, 3H, J = 7.2), 1.46-1.68 (m, 5H), 1.74-1.86 (m, 1H), 1.97-2.19 (m, 2H), 3.02 (dd, 1H, J = 13.7, 5.6), 3.11-3.24 (m, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.17 (q, 2H, J = 7.2), 4.20-4.30 (m, 2H), 4.35-4.45 (m, 2H), 4.82-4.90 (m, 1H), 5.07 (d, 1H, J = 12.3), 5.13 (d, 1H, J = 12.3), 5.36 (d, 1H, J = 7.8), 5.82 (dd, 1H, J = 15.6, 1.2), 6.42-6.46 (m, 2H), 6.72 (dd, 1H, J = 15.6, 5.3), 6.88 (d, 1H, J = 8.7), 7.09 (d, 1H, J = 9.0), 7.13-7.20 (m, 5H), 7.29-7.37 (m, 5H), 8.09 (d, 1H, J = 6.5).

Preparation of Product Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*S)-Pyrrol-Ala*)}-E-Propenoate

Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (0.156 g, 0.202 mmol, 1 equiv.) and ammonium cerium(IV) nitrate (0.277 g, 0.505 mmol, 2,5 equiv.) were combined in a mixture of THF/water 2:1 (3 mL) and stirred 2 hours. The reaction mixture was poured into brine (15 mL) and extracted with 10% CH_3OH in CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. Purification of the residue by flash column chromatography (gradient elution, 2→5% CH_3OH in CH_2Cl_2) provided ethyl-3-{Cbz-L-Leu-L-Phe-L-((*S)-Pyrrol-Ala*)}-E-propenoate (0.059 g, 47%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.85-0.92 (m, 6H), 1.28 (t, 3H, J = 7.2), 1.39-1.65 (m, 4H), 1.68-1.93 (m, 2H), 2.08-2.20 (m, 1H), 2.27-2.38 (m, 1H), 3.02-3.13 (m, 2H), 3.24-3.32 (m, 2H), 4.11-4.20 (m, 1H), 4.18 (q, 2H, J = 7.2), 4.47-4.58 (m, 1H), 4.81-4.89 (m, 1H), 5.05 (d, 1H, J = 12.1), 5.12 (d, 1H, J = 12.1), 5.26 (d, 1H, J = 8.1), 5.78 (dd, 1H, J = 15.7,

1.2), 6.23 (s, 1H), 6.72 (dd, 1H, J = 15.7, 5.3), 7.13-7.25 (m, 6H), 7.30-7.37 (m, 5H), 7.54 (d, 1H, J = 7.2).

Example 34 - Preparation of Compound (A-25): Ethyl-3-{Cbz-L-Val-L-Phe-L-*((S)-Pyrrol-Ala)*}-E-Propenoate



(A-25)

Preparation of Intermediate Ethyl-3-{Cbz-L-Val-L-Phe-L-((*N*-2,4-Dimethoxybenzyl)-*(S)-Pyrrol-Ala)*}-E-Propenoate

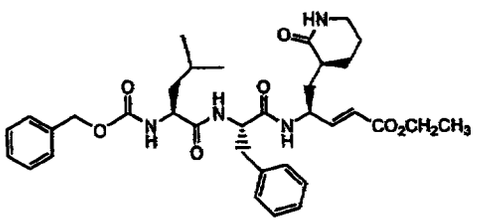
In a manner analogous to that used for the conversion of ethyl-3-{Boc-L-(Tr-*Gln*)}-E-propenoate to ethyl-3-{Cbz-L-Leu-L-Phe-L-(Tr-*Gln*)}-E-propenoate described in Example 31, ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (prepared as in Example 33) was coupled with Cbz-L-Val-L-Phe-OH to afford ethyl-3-{Cbz-L-Val-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate: IR (cm^{-1}) 3288, 1699, 1652; ^1H NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 6.8), 0.95 (d, 3H, J = 6.5), 1.28 (t, 3H, J = 7.2), 1.48-1.60 (m, 2H), 1.70-1.84 (m, 1H), 1.95-2.20 (m, 3H), 3.01 (dd, 1H, J =13.4, 5.6), 3.09-3.25 (m, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.03-4.10 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.24 (d, 1H, J = 14.2), 4.33-4.44 (m, 1H), 4.38 (d, 1H, J = 14.2), 4.85-4.94 (m, 1H), 5.08 (d, 1H, J = 12.1), 5.14 (d, 1H, J = 12.1), 5.39 (d, 1H, J = 8.1), 5.80 (dd, 1H, J = 15.6, 1.2), 6.42-6.47 (m, 2H), 6.70 (dd, 1H, J = 15.6, 5.3), 6.81 (d, 1H, J = 9.0), 7.11-7.20 (m, 6H), 7.31-7.39 (m, 5H), 8.11 (d, 1H, J = 6.2); Anal. ($C_{42}H_{52}N_4O_9$) C, H, N.

Preparation of Product Ethyl-3-{Cbz-L-Val-L-Phe-L-((*S*)-Pyrrol-Ala)}-E-Propenoate

A suspension of ethyl-3-{Cbz-L-Val-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate (0.215 g, 0.284 mmol, 1 equiv.), DDQ (0.071 g. 0.31 mmol, 1.1 equiv.) and water (3 drops) in $CHCl_3$ (4 mL) was stirred 1 h at 23°C, and was then warmed to reflux for 6 h. After cooling overnight, more DDQ (0.019 g, 0.084 mmol, 0.3 equiv.) was added, and the mixture was warmed to 67°C for 1 h and then evaporated. Purification of the residue by flash column chromatography (gradient elution, 2→5% CH_3OH in CH_2Cl_2) provided slightly impure material, which was dissolved in CH_2Cl_2 (70 mL) and washed with saturated $NaHCO_3$ (2 x 30 mL) and brine (30 mL), and then dried over Na_2SO_4 and evaporated. The residue was stirred in Et_2O (10 mL) for 20 minutes, and the solid was collected by filtration and dried

under vacuum to provide ethyl-3-{Cbz-L-Val-L-Phe-L-*((S)-Pyrrol-Ala)*}-E-propenoate (0.060 g, 35%) as a an off-white solid: mp = 215-217°C; IR (cm^{-1}) 3413, 3295, 1696, 1649; ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, *J* = 6.5), 0.91 (d, 3H, *J* = 6.8), 1.28 (t, 3H, *J* = 7.2), 1.50-1.59 (m, 1H), 1.70-1.91 (m, 2H), 2.03-2.17 (m, 2H), 2.26-2.38 (m, 1H), 3.03 (dd, 1H, *J* = 13.5, 6.4), 3.12 (dd, 1H, *J* = 13.5, 6.4), 3.21-3.34 (m, 2H), 3.96 (dd, 1H, *J* = 8.3, 6.4), 4.17 (q, 2H, *J* = 7.2), 4.45-4.56 (m, 1H), 4.83-4.92 (m, 1H), 5.07 (d, 1H, *J* = 12.1), 5.13 (d, 1H, *J* = 12.1), 5.29 (d, 1H, *J* = 8.3), 5.77 (dd, 1H, *J* = 15.8, 1.2), 5.94 (s, 1H), 6.71 (dd, 1H, *J* = 15.8, 5.3), 6.95 (d, 1H, *J* = 9.0), 7.14-7.27 (m, 5H), 7.31-7.38 (m, 5H), 7.57 (d, 1H, *J* = 7.2); Anal. ($C_{33}H_{42}N_4O_7$) C, H, N.

Example 35 - Preparation of Compound (A-26): Ethyl-3-{Cbz-L-Leu-L-Phe-L-*((S)-Piper-Ala)*}-E-Propenoate

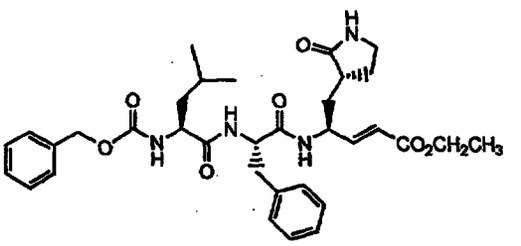


(A-26)

Preparation of Product Ethyl-3-{Cbz-L-Leu-L-Phe-L-*((S)-Piper-Ala)*}-E-Propenoate

(1*S*,3'*S*)-{2-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-piperidin-3'-yl)-1-hydroxy-methylethyl}-carbamic acid *tert*-butyl ester (prepared as described in Example 8) was converted to the product ethyl-3-{Cbz-L-Leu-L-Phe-L-*((S)-Piper-Ala)*}-E-propenoate in a manner analogous to the conversion of (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethyl-ethyl}-carbamic acid *tert*-butyl ester to product ethyl-3-{Cbz-L-Leu-L-Phe-L-*((S)-Pyrrol-Ala)*}-E-propenoate as described in Example 34: IR (cm^{-1}) 3422, 3307, 1713, 1649; ^1H NMR ($CDCl_3$) δ 0.86-0.92 (m, 6H), 1.28 (t, 3H, *J* = 7.2), 1.38-1.75 (m, 6H), 1.77-1.89 (m, 1H), 1.96-2.11 (m, 2H), 3.07 (d, 2H, *J* = 6.2), 3.20-3.27 (m, 2H), 4.13-4.24 (m, 1H), 4.18 (q, 2H, *J* = 7.2), 4.41-4.53 (m, 1H), 4.76-4.85 (m, 1H), 5.06 (d, 1H, *J* = 12.1), 5.12 (d, 1H, *J* = 12.1), 5.34 (d, 1H, *J* = 7.8), 5.78 (dd, 1H, *J* = 15.6, 5.4), 6.17 (s, 1H), 6.70 (dd, 1H, *J* = 15.6, 5.4), 7.00 (d, 1H, *J* = 8.4), 7.13-7.27 (m, 6H), 7.30-7.37 (m, 5H), 7.83 (d, 1H, *J* = 6.8); Anal. ($C_{35}H_{46}N_4O_7 \cdot 0.5H_2O$) C, H, N.

Example 36 - Preparation of Compound (A-27): Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*R*)-*Pyrrol-Ala*)}-E-Propenoate



(A-27)

Preparation of Intermediate (4*S*,4''*R*)-4-{3'-(4''-Benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

Triethylamine (6.43 mL, 46.1 mmol, 3.0 equiv.) and pivaloyl chloride (1.89 mL, 15.3 mmol, 1.0 equiv.) were added sequentially to a solution of (4*S*)-4-(2'-carboxyethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4.20 g, 15.3 mmol, 1 equiv.) in THF (300 mL) at 0°C. The cloudy reaction mixture was stirred at 0°C for 3.5 h, and then lithium chloride (0.716 g, 16.9 mmol, 1.1 equiv.) and (*R*)-(+)-4-benzyl-2-oxazolidinone (2.59 g, 14.6 mmol, 0.95 equiv.) were added sequentially. After warming to 23°C and stirring for 19h, the reaction mixture was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were washed with half-saturated Na_2CO_3 (150 mL), dried over $MgSO_4$, and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% EtOAc in hexanes) to give (4*S*,4''*R*)-4-{3'-(4''-benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6.15 g, 97%) as a colorless oil: IR (cm^{-1}) 2978, 1783, 1694; ^1H NMR ($CDCl_3$, mixture of isomers) δ 1.46 (s), 1.58 (s), 1.63 (s), 2.01-2.05 (m), 2.72-3.13 (m), 3.29-3.33 (m), 3.74-3.79 (m), 3.82-4.09 (m), 4.11-4.25 (m), 4.67-4.70 (m), 7.20-7.37 (m); Anal. ($C_{23}H_{32}N_2O_6$) C, H, N.

Preparation of Intermediate (2'*R*,4*S*,4''*R*)-4-{2'-(4''-Benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester

A solution of (4*S*,4''*R*)-4-{3'-(4''-benzyl-2''-oxo-oxazolidin-3''-yl)-3'-oxopropyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6.15 g, 14.2 mmol, 1 equiv.) in THF (25 mL) was added to a solution of sodium bis(trimethylsilyl)amide (14.2 mL of a 1.0 M solution in THF, 14.2 mmol, 1.0 equiv.) in the same solvent (50 mL) at -78°C. The reaction mixture was stirred for 15 minutes at -78°C, and then allyl iodide (3.90 mL, 42.6 mmol, 3.0 equiv.) was added. After stirring an additional 2 h at -78°C, the reaction mixture was

maintained at -45°C for 2 h, and then was partitioned between a 2:1 mixture of half-saturated NH_4Cl and 5% $Na_2S_2O_3$ (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$, and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (15% EtOAc in hexanes) to provide (2'*R*,4*S*,4''*R*)-4-{2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3.12 g, 46%) as a viscous foam: IR (cm^{-1}) 2978, 1782, 1685; ^1H NMR ($CDCl_3$, mixture of isomers) δ 1.42 (s), 1.45 (s), 1.49 (s), 1.52 (s), 1.62-1.78 (m), 1.80-2.01 (m), 2.23-2.49 (m), 2.51-2.56 (m), 2.76 (dd, *J* = 13.3, 9.7), 3.26 (dd, *J* = 13.3, 3.6), 3.58-3.64 (m), 3.67 (d, *J* = 8.7), 3.90-3.98 (m), 4.02-4.15 (m), 4.16-4.30 (m), 4.75-4.82 (m), 5.06-5.11 (m), 5.74-5.88 (m), 7.22-7.36 (m); Anal. ($C_{26}H_{36}N_2O_6$) C, H, N.

Preparation of Intermediate (1*S*,3'*R*)-{2-(1'-(2'',4''-Dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic Acid *tert*-Butyl Ester

Ozone was bubbled through a solution of (2'*R*,4*S*,4''*R*)-4-{2'-(4''-benzyl-2''-oxo-oxazolidine-3''-carbonyl)-pent-4'-enyl}-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3.12 g, 6.60 mmol, 1 equiv.) in CH_2Cl_2 (200 mL) and CH_3OH (0.535 mL, 13.2 mmol, 2.0 equiv.) at -78°C until a blue color persisted. The reaction mixture was then purged with argon until it became colorless. Methyl sulfide (4.85 mL, 66.0 mmol, 10 equiv.) was added, and the mixture was stirred at -78°C for 3.5 h and then was maintained at 0°C for an additional 1 h. After partitioning the reaction mixture between H_2O (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL), the combined organic layers were dried over $MgSO_4$ and gravity filtered. The filtrate was concentrated under reduced pressure, and the residue was immediately utilized without further purification.

The above residue was dissolved in a 2:1 mixture of THF, and then EtOH (180 mL) at 23°C and 2,4-dimethoxybenzylamine hydrochloride (5.38 g, 26.4 mmol, 4.0 equiv.), sodium acetate (2.17 g, 26.4 mmol, 4.0 equiv.), and sodium cyanoborohydride (0.829 g, 13.2 mmol, 2.0 equiv.) were added sequentially. The resulting suspension was stirred for 19 h at 23°C, and then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 100 mL). The combined organic layers were washed with half-saturated $NaHCO_3$ (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a short silica gel column (eluting with 50% EtOAc in hexanes) to give (3'*R*,4*S*)-4-{1'-(2'',4''-dimethoxybenzyl)-2'-

oxo-pyrrolidin-3'-ylmethyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester contaminated with (*R*)-(+)-4-benzyl-2-oxazolidinone.

This material was dissolved in CH_3OH (80 mL), and $TsOH \cdot H_2O$ (0.251 g, 1.32 mmol, 0.20 equiv.) was added. The reaction mixture was heated to 50°C and was maintained at that temperature for 4 h. After cooling to 23 °C, the reaction mixture was concentrated under reduced pressure to ~20 mL volume and was partitioned between half-saturated $NaHCO_3$ (150 mL) and a 9:1 mixture of CH_2Cl_2 and CH_3OH (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography (3% CH_3OH in CH_2Cl_2) afforded (1*S*,3'*R*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester (0.92 g, 34%) as a foam: IR (cm^{-1}) 3347 (br), 2937, 1669; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.62-1.77 (m, 2H), 1.94-2.04 (m, 1H), 2.15-2.26 (m, 1H), 2.40-2.50 (m, 1H), 3.13-3.24 (m, 2H), 3.56-3.77 (m, 3H), 3.80 (s, 6H), 3.82-4.16 (m, 1H), 4.37 (d, 1H, J = 14.3), 4.45 (d, 1H, J = 14.3), 5.49 (d, 1H, J = 7.8), 6.42-6.45 (m, 2H), 7.08-7.11 (m, 1H); Anal. ($C_{21}H_{32}N_2O_6 \cdot 0.25H_2O$) C, H, N.

Preparation of Intermediate Ethyl-3-{Boc-L-((*N*-2,4-Dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-Propenoate

In a manner analogous to the conversion of (1*S*,3'*S*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester to ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate described in Example 33, (1*S*,3'*R*)-{2-(1'-(2'',4''-dimethoxybenzyl)-2'-oxo-pyrrolidin-3'-yl)-1-hydroxymethylethyl}-carbamic acid *tert*-butyl ester was transformed into ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-propenoate: IR (cm^{-1}) 3307, 1713, 1674; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.2), 1.45 (s, 9H), 1.57-1.82 (m, 2H), 2.02-2.19 (m, 2H), 2.42-2.55 (m, 1H), 3.11-3.25 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 4.19 (q, 2H, J=7.2), 4.32-4.50 (m, 3H), 5.97 (dd, 1H, J= 15.7, 1.4), 6.38 (d, 1H, J= 7.8), 6.42-6.47 (m, 2H), 6.86 (dd, 1H, J= 15.7, 5.1), 7.08-7.13 (m, 1H); Anal. ($C_{25}H_{36}N_2O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-Dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-Propenoate

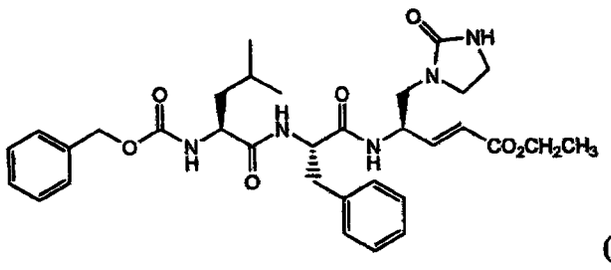
A solution of HCl in 1,4-dioxane (4.0 M, 6 mL) was added to a solution of ethyl-3-{Boc-L-((*N*-2,4-dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-propenoate (0.233 g, 0.489 mmol, 1 equiv.) in 1,4-dioxane (6 mL). After stirring 1.5 h, the volatiles were evaporated to give the crude amine salt, which was used without purification.

This amine salt was dissolved in DMF (4 mL) and cooled to 0°C. Cbz-L-Leu-L-Phe-OH (0.202 g, 0.490 mmol, 1 equiv.), DIEA (0.255 mL, 1.46 mmol, 3 equiv.) and HATU (0.186 g, 0.489 mmol, 1 equiv.) were added sequentially. After stirring 1.5 h, the reaction mixture was diluted with MTBE (100 mL), washed with 5% $KHSO_4$, saturated $NaHCO_3$ and brine (10 mL), dried over $MgSO_4$, and evaporated. Purification of the residue by flash column chromatography (gradient elution, 60→75% EtOAc in hexanes) provided ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-propenoate (0.208 g, 55%) as a white solid (after evaporation from Et_2O): mp = 174-176°C; IR (cm^{-1}) 3287, 1713, 1649; ^1H NMR ($CDCl_3$) δ 0.84-0.91 (m, 6H), 1.29 (t, 3H, *J* = 7.2), 1.42-1.66 (m, 4H), 1.67-1.77 (m, 1H), 1.84-1.95 (m, 1H), 2.20-2.12 (m, 1H), 2.33-2.45 (m, 1H), 3.04-3.23 (m, 4H), 3.78 (s, 3H), 3.79 (s, 3H), 4.15-4.29 (m, 1H), 4.17 (q, 2H, *J* = 7.2), 4.31 (d, 1H, *J* = 14.5), 4.40 (d, 1H, *J* = 14.5), 4.67-4.84 (m, 2H), 5.05 (d, 1H, *J* = 12.1), 5.11 (d, 1H, *J* = 12.1), 5.35 (d, 1H, *J* = 8.1), 5.76 (dd, 1H, *J* = 15.6, 1.6), 6.42-6.46 (m, 2H), 6.74-6.81 (m, 1H), 6.75 (dd, 1H, *J* = 15.6, 5.0), 7.06-7.10 (m, 1H), 7.15-7.24 (m, 5H), 7.29-7.36 (m, 5H), 8.79 (d, 1H, *J* = 5.9); Anal. ($C_{43}H_{54}N_4O_9$) C, H, N.

Preparation of Product Ethyl-3-{Cbz-L-Leu-L-Phe-L-*(R)-Pyrrol-Ala*)}-E-Propenoate

Ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(R)-Pyrrol-Ala*)}-E-propenoate was converted to the product ethyl-3-{Cbz-L-Leu-L-Phe-L-*(R)-Pyrrol-Ala*)}-E-propenoate in a manner analogous to the conversion of ethyl-3-{Cbz-L-Leu-L-Phe-L-((*N*-2,4-dimethoxybenzyl)-*(S)-Pyrrol-Ala*)}-E-propenoate to product ethyl-3-{Cbz-L-Leu-L-Phe-L-*(S)-Pyrrol-Ala*)}-E-propenoate described in Example 34: IR (cm^{-1}) 3290, 1702, 1642; ^1H NMR ($CDCl_3$) δ 0.85-0.92 (m, 6H), 1.30 (t, 3H, *J* = 7.2), 1.35-1.49 (m, 1H), 1.52-1.71 (m, 3H), 1.73-1.94 (m, 2H), 2.15-2.26 (m, 1H), 2.32-2.43 (m, 1H), 3.02-3.18 (m, 2H), 3.19-3.29 (m, 2H), 4.15-4.27 (m, 1H), 4.18 (q, 2H, *J* = 7.2), 4.65-4.74 (m, 1H), 4.76-4.85 (m, 1H), 5.07 (d, 1H, *J* = 12.3), 5.12 (d, 1H, *J* = 12.3), 5.18-5.25 (m, 1H), 5.76-5.84 (m, 2H), 6.64-6.78 (m, 2H), 7.15-7.40 (m, 10H), 7.91-7.98 (m, 1H); Anal. ($C_{34}H_{44}N_4O_7$) C, H, N.

Example 37 - Preparation of Compound (A-28): Ethyl-3-{Cbz-L-Leu-L-Phe-L-1-*(2-imidazolidone)Ala*}-E-Propenoate



(A-28)

Preparation of Intermediate Ethyl-3-{Cbz-L-Leu-L-Phe-L-*Boc-aminoAla*}-E-Propenoate

(Carbethoxymethlene)triphenylphosphorane (1.20 g, 3.28 mmol, 1.2 equiv.) was added to a solution of Cbz-L-Leu-L-Phe-L-*N*-Boc-aminoalaninal (prepared as described in Webber et al., *J. Med. Chem.* **1998**, vol. 41, 2786) (1.60 g, 2.73 mmol, 1 equiv.) in THF (55 mL), and the reaction was stirred at room temperature overnight. The volatiles were then removed *in vacuo*, and the residue was purified by flash column chromatography eluting (gradient elution, 0→1.5% CH_3OH in CH_2Cl_2) to give ethyl-3-{Cbz-L-Leu-L-Phe-L-*N-Boc-aminoAla*}-E-propenoate (0.968 g, contaminated with triphenylphosphine oxide). This material was used without further purification.

Preparation of Intermediate Ethyl-3-{Cbz-L-Leu-L-Phe-L-*(2-Boc-2-aminoethyl)aminoAla*}-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added to a solution of ethyl-3-{Cbz-L-Leu-L-Phe-L-*Boc-aminoAla*}-E-propenoate (0.95 g, 1.46 mmol, 1 equiv.) in the same solvent (20 mL) at 23°C. The reaction mixture was stirred at that temperature for 1.5 h, and then additional HCl in 1,4-dioxane (4.0 M, 10 mL) was added. After stirring overnight, the volatiles were removed *in vacuo* and the residue was triturated with Et_2O (20 mL). The resulting solids were filtered and were washed with Et_2O (3 x 10 mL) to give the crude amine salt (0.63 g 73%, 1.05 mmol) as a white solid.

This material was dissolved in CH_3OH (10 mL), and then N-Boc-2-aminoethanal (prepared as described in Bischofberger et al., *J. Org. Chem.* **1988**, vol. 53, 3457) (0.19 g, 1.16 mmol, 1.1 equiv.) and $NaBH_3CN$ (0.069 g, 1.05 mmol, 1.0 equiv.) were added sequentially. The reaction mixture was stirred at 23°C overnight, and then the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with water (25 mL) and brine (25 mL), and then dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (gradient elution, 0→3% CH_3OH in CH_2Cl_2) to provide ethyl-3-{Cbz-L-Leu-L-Phe-L-*(2-Boc-2-aminoethyl)aminoAla*}-E-propenoate (0.32 g, 44%) as a white amorphous solid: R_f = 0.20 (5% CH_3OH in $CHCl_3$); IR (cm^{-1}) 1712, 1649, 1537, 1252, 1175; ^1H NMR (DMSO-d_6) δ 0.79 (d, 3H, J = 6.6), 0.82 (d, 3H, J = 6.6), 1.21 (t, 3H, J = 7.0), 1.26-1.37 (m, 13H), 1.46-1.54 (m, 1H), 2.56-2.60 (m, 2H), 2.82-2.97 (m, 4H), 3.98-4.04 (m, 1H), 4.10 (q, 2H, J = 7.0), 4.42-4.49 (m, 2H), 4.98 (d, 1H, J = 12.5), 5.04 (d, 1H, J = 12.9), 5.59 (d, 1H, J = 15.8), 6.73-6.75 (m, 1H), 6.77 (dd, 1H, J = 15.8,

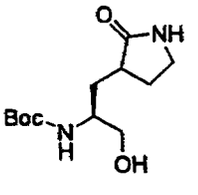
4.8), 7.20-7.34 (m, 10H), 7.41 (d, 1H, J = 8.1), 7.97 (d, 1H, J = 7.0), 8.07 (d, 1H, J = 7.0); Anal. ($C_{37}H_{53}N_5O_8 \cdot 0.50H_2O$) C, H, N.

Preparation of Product Ethyl-3-{Cbz-L-Leu-L-Phe-L-*1-(2-imidazolidone)Ala*}-E-Propenoate

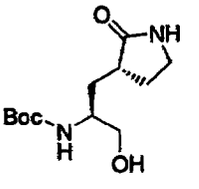
TFA (0.8 mL) was added to a solution of ethyl-3-{Cbz-L-Leu-L-Phe-L-*(2-Boc-2-aminoethyl)aminoAla*}-E-propenoate (0.29 g, 0.42 mmol, 1 equiv.) in CH_2Cl_2 (8 mL), and the reaction mixture was stirred at 23°C for 2 h. The volatiles were removed *in vacuo*, and the residue was dissolved in EtOAc (25 mL) and washed with saturated $NaHCO_3$ solution (25 mL), water (25 mL), and brine (25 mL). The organic layer was dried over $MgSO_4$ and was concentrated to give the crude diamine (0.23 g, 92%, 0.39 mmol) as a tan amorphous solid.

This material was dissolved in THF (4 mL), carbonyldiimidazole (0.06 g, 0.36 mmol, 0.92 equiv.) was added, and the reaction mixture was stirred at 23°C for 3.5 h. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (gradient elution, 0→2% CH_3OH in CH_2Cl_2) to give ethyl-3-{Cbz-L-Leu-L-Phe-L-*1-(2-imidazolidone)Ala*}-E-propenoate (0.12 g, 54%) as a white amorphous solid: mp = 161-164°C; R_f = 0.21 (5% CH_3OH in $CHCl_3$); IR (cm^{-1}) 1701, 1647, 1535, 1277; ^1H NMR (DMSO-d_6) δ 0.79 (d, 3H, J = 6.6), 0.82 (d, 3H, J = 6.6), 1.21 (t, 3H, J = 7.0), 1.27-1.35 (m, 2H), 1.48-1.52 (m, 1H), 2.79-2.86 (m, 1H), 2.92-3.05 (m, 3H), 3.14-3.19 (m, 2H), 3.25-3.30 (m, 2H), 3.98-4.03 (m, 1H), 4.10 (q, 2H, J = 7.0), 4.47-4.49 (m, 1H), 4.59-4.63 (m, 1H), 4.97-5.02 (m, 2H), 5.72 (d, 1H, J = 15.8), 6.37 (s, 1H), 6.71 (dd, 1H, J = 15.8, 5.5), 7.15-7.39 (m, 10H), 7.42 (d, 1H, J = 8.1), 8.00 (d, 1H, J = 8.1), 8.18 (d, 1H, J = 8.1); Anal. ($C_{33}H_{43}N_5O_7$) C, H, N.

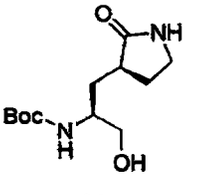
Example 38 - Synthesis of Intermediates Q1, Q2, and Q3



Q1



Q2



Q3

Preparation of Intermediate 1-Acetyl-3-(triphenylphosphanylidine)-pyrrolidin-2-one

2,4-Dibromobutyride (prepared according to Ikuta et al., *J. Med. Chem*, **1987**, vol. 30, 1995) (46.1 g, 188.2 mmol) in THF (1L) was cooled to 0°C and treated with a solution of lithium bis(trimethylsilylamide) (40.9 g, 244.6 mmol) in THF (200 mL). The solution was held at 0°C for 2.5 h, and then poured into brine (800 mL), extracted with ethyl acetate (2 L), and dried ($MgSO_4$). Evaporation yielded 25.5 g of 3-bromo-pyrrolidin-2-one as a brown oil.

This material was treated with Ac_2O (76 mL) and refluxed 5 hours. Evaporation followed by purification (silica gel filtration, EtOAc elutant) yielded 28 g of 1-acetyl-3-bromo-pyrrolidin-2-one as a dark oil. THF (272 mL) and triphenylphosphine (42.8 g, 163.3 mmol) were added and the resulting solution was refluxed for 8 hours. Upon cooling to 23°C, a precipitate of 1-acetyl-3-(triphenylphosphanyl)-pyrrolidin-2-one bromide formed and was collected by filtration (27.1 g). Concentration of the mother liquor, followed by cooling to 0°C, yielded an additional 6.6 g. The combined material in CH_2Cl_2 (1 L) was washed with 1N NaOH (100 mL) and then brine (2 x 100 mL). Evaporation of the organic layer yielded 26.9 g (37% overall) of 1-acetyl-3-(triphenylphosphanylidine)-pyrrolidin-2-one as a tan oil. ^1H NMR ($CDCl_3$) δ 7.76-7.32 (15H, m), 3.90-3.85 (2H, m), 2.50 (3H, s), 2.56-2.30 (2H, m).

Preparation of Intermediate 2-t-Butoxycarbonyl-3-(t-butyldimethylsilanoxy)-propionic acid methyl ester

Boc-D-serine methyl ester (20.0 g, 91.2 mmol) in DMF (300 mL) was treated with imidazole (18.6 g, 273.7 mmol) and then TBSCl (13.0 g, 86.7 mmol). The solution was held at room temperature (rt) for 8 h, and then washed with saturated aqueous ammonium chloride (300 mL), and extracted with ethyl acetate (800 mL). The organic layer was washed with brine (300 mL) and then dried ($MgSO_4$), to yield 30.2 g (100%) of 2-t-butoxycarbonyl-3-(t-butyldimethylsilanoxy)-propionic acid methyl ester as a colorless oil. ^1H NMR ($CDCl_3$) δ 5.32 (1H, d, J = 8.3), 4.33 (1H, dt, J = 8.8, 2.7), 4.02 (1H, dd, J = 10.1, 2.6), 3.80 (1H, dd, J = 9.8, 3.1), 3.72 (3H, s), 1.43 (9H, s), 0.85 (9H, s), 0.0 (6H, s).

Preparation of Intermediate {1-(1-Acetyl-2-oxo-pyrrolidin-3-ylidenemethyl)-2-(t-butyldimethylsilanyloxy)-ethyl}-carbamic acid t-butyl ester

2-t-Butoxycarbonyl-3-(t-butyldimethylsilanoxy)-propionic acid methyl ester (12.7 g, 38.0 mmol) in toluene (190 mL) was cooled to -78°C and treated with a solution of diisobutylaluminum hydride (15.6 mL, 87.4 mmol) in toluene (175 mL). The internal temperature was kept below -70°C. The solution was held at -78°C for an additional 90 min., and then methanol (7.7 mL, 190 mmol) was added. 1-Acetyl-3-(triphenylphosphanylidine)-pyrrolidin-2-one (11.1 g, 28.6 mmol) in CH_2Cl_2 (50 mL) was added at -78°C, and the resulting solution was allowed to warm to room temperature and held for 30 minutes. A solution of sodium potassium tartrate (150 g) in water (600 mL) was added, and stirred vigorously for 30 minutes. The mixture was extracted with ethyl acetate (4 x 250 mL), dried ($MgSO_4$), and evaporated. Purification by silica gel chromatography yielded 7.04 g (60%) of {1-(1-acetyl-2-

oxo-pyrrolidin-3-ylidenemethyl)-2-(t-butyldimethylsilanyloxy)-ethyl}-carbamic acid t-butyl ester as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.59 (1H, dt, J = 8.7, 2.9), 4.98 (1H, d, J = 6.8), 4.37-4.25 (1H, m), 3.77 (2H, t, J = 7.3), 3.70-3.58 (2H, m), 2.90-2.80 (1H, m), 2.75-2.60 (1H, m), 5.53 (3H, s), 1.41 (9H, s), 0.87 (9H, s), 0.04 (6H, s).

Preparation of Intermediate {2-Hydroxy-1-(2-oxo-pyrrolidin-3-ylidenemethyl)-ethyl}-carbamic acid t-butyl ester

{1-(1-Acetyl-2-oxo-pyrrolidin-3-ylidenemethyl)-2-(t-butyldimethylsilanyloxy)-ethyl}-carbamic acid t-butyl ester (9.18 g, 22.2 mmol) in THF (150 mL) was treated with TBAF (22.2 mL of a 1M solution in THF, 22.2 mmol) at 0°C, and held for 1 hour. A solution of saturated aqueous ammonium chloride was added and stirred for 10 min., and then the solution was extracted with ethyl acetate (2 x 200 mL). The organic layer was dried ($MgSO_4$) and then evaporated. Purification by silica gel chromatography yielded 4.82 g (73%) of a colorless oil. This material was taken up in methanol (160 mL), treated with potassium carbonate (223 mg, 1.62 mmol), and held for 1 h at rt. The mixture was then treated with solid citric acid (311 mg, 1.62 mmol), and ethyl acetate (800 mL) was added. The solution was filtered through silica gel. Evaporation yielded 4.30 g (73% overall) of {2-hydroxy-1-(2-oxo-pyrrolidin-3-ylidenemethyl)-ethyl}-carbamic acid t-butyl ester as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.03 (1H, br s), 6.35 (1H, dt, J = 8.6, 2.6), 5.37 (1H, d, J = 6.5), 4.40-4.20 (1H, m), 3.66 (br s, 3H), 3.4 (2H, t, J = 6.7), 3.10-2.80 (1H, m), 2.80-2.70 (1H, m), 1.41 (9H, s).

Preparation of Intermediate {2-Hydroxy-1-(2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester (mixture of diastereomers) (Q1)

{2-Hydroxy-1-(2-oxo-pyrrolidin-3-ylidenemethyl)-ethyl}-carbamic acid t-butyl ester (4.30 g, 16.8 mmol) in ethyl acetate (168 mL) was treated with 5% palladium on carbon (1.78 g), and hydrogenated at ambient pressure for 1 h. The mixture was filtered and then evaporated to yield 3.92 g (91 %) of {2-hydroxy-1-(2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester as a colorless oil (1.5:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, s), 5.49 (1H, d, J = 8.4), 3.70-3.50 (3H, m), 3.38-3.20 (2H, m), 2.60-2.20 (2H, m), 2.00-1.70 (2H, m), 1.65-1.45 (1H, m), 1.37 (9H, s).

Preparation of Intermediate {2-Hydroxy-1-(*R*-2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester (Q2)

{2-Hydroxy-1-(2-oxo-pyrrolidin-3-ylidenemethyl)-ethyl}-carbamic acid t-butyl ester (98 mg, 0.39 mmol) in methanol (5 mL) was treated with (*R*)-BINAP-RuCl (19 mg, 0.02

mmol), and then put under a hydrogen atmosphere (1200 psi) at 50°C for 48 h. The solution was evaporated and then filtered through silica gel (10% MeOH-EtOAc elutant). Evaporation yielded 75 mg (75%) of {2-hydroxy-1-(*R*-2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester as a colorless oil (9:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 6.32 (1H, br s), 5.40(1H, d, J = 7.5), 3.82 (1H, br s), 3.71-3.63 (2H, m), 3.34-3.31 (2H, m), 2.45-2.30 (2H, m), 2.09-1.86 (2H, m), 1.70-1.63 (1H, m), 1.42 (9H, s).

Preparation of Intermediate {2-Hydroxy-1-(*S*-2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester (Q3)

{2-Hydroxy-1-(2-oxo-pyrrolidin-3-ylidenemethyl)-ethyl}-carbamic acid t-butyl ester (0.10 g, 0.39 mmol) in methanol (5 mL) was treated with (*S*)-BINAP-RuCl (19 mg, 0.02 mmol), and then put under a hydrogen atmosphere (1200 psi) at 50°C for 48 h. The solution was evaporated and then filtered through silica gel (10% MeOH-EtOAc elutant). Evaporation yielded 74 mg (74%) of {2-hydroxy-1-(*S*-2-oxy-pyrrolidin-3-ylmethyl)-ethyl}-carbamic acid t-butyl ester as a colorless oil (9:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 6.66 (1H, br s), 5.51 (1H, d, J = 8.2), 3.72-3.57 (3H, m), 3.34-3.31 (2H, m), 2.52-2.33 (2H, m), 2.20-1.86 (1H, m), 1.86-1.70 (1H, m), 1.62-1.50 (1H, m), 1.40 (9H, s).

Results of biochemical and biological tests conducted using various compounds of the invention are described below.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Inhibition of Rhinovirus 3C Protease

Stock solutions (50 mM, in DMSO) of various compounds were prepared; dilutions were in the same solvent. Recombinant rhinovirus 3C proteases (see Birch et al., "Purification of recombinant human rhinovirus 14 3C protease expressed in Escherichia coli," *Protein Expr. Pur.* **1995**, 6(5), 609-618) from serotypes 14, 16, and 2 were prepared by the following standard chromatographic procedures: (1) ion exchange using Q Sepharose Fast Flow from Pharmacia; (2) affinity chromatography using Affi-Gel Blue from Biorad; and (3) sizing using Sephadex G-100 from Pharmacia. Each assay sample contained 2% DMSO, 50 mM tris pH 7.6, 1 mM EDTA, a test compound at the indicated concentration, approximately 1μM substrate, and 50-100 nM protease. The $k_{obs/I}$ values were obtained from reactions initiated by addition of enzyme rather than substrate. RVP activity was measured in the fluorescence resonance energy transfer assay. The substrate was (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Phe-Gln-Gly-Pro-Val-Gly)-EDANS. In the uncleaved peptide, the EDANS fluorescence was quenched by the proximal DABCYL moiety. When the peptide was cleaved, the quenching

was relieved, and activity was measured as an increase in fluorescence signal. Data were analyzed using standard non-linear fitting programs (Enzfit), and are shown in Tables 1 and 2 below. In Table 1, all data are for rhinovirus 3C protease from HRV serotype-14 (produced from the infectious cDNA clone constructed by Dr. Robert Rueckert, Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin). Table 2 shows protease-inhibiting activity of compounds against proteases from several rhinovirus of serotype other than RVP serotype-14. The data in the column designated $k_{obs}/[I]$ were measured from progress curves in enzyme start experiments.

Antirhinoviral H1-HeLa Cell Culture Assay

In this cell protection assay, the ability of compounds to protect cells against HRV infection was measured by the XTT dye reduction method, which is described in Weislow et al., *J. Natl. Cancer Inst.* **1989**, vol. 81, 577-586.

H1-HeLa cells were infected with HRV-14 at a multiplicity of infection (m.o.i.) of 0.13 (virus particles/cell) or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8×10^5 cells per mL, and incubated with appropriate concentrations of the compounds to be tested. Two days later, XTT/PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} value was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free, mock-infected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in compound-treated, mock-infected cells to 50% of that produced by compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} value by the EC_{50} value.

All strains of human rhinovirus (HRV) for use in this assay were purchased from American Type Culture Collection (ATCC), except for HRV serotype-14 (produced from the infectious cDNA clone constructed by Dr. Robert Rueckert, Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin). HRV stocks were propagated and viral assays were performed in H1-HeLa cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum, available from Life Technologies (Gaithersburg, MD).

The compounds were tested against control compounds WIN 51711, WIN 52084, and WIN 54954 (obtained from Sterling-Winthrop Pharmaceuticals), Pirodavir (obtained from Janssen Pharmaceuticals), and Pleconaril (prepared according to the method described in Diana et al., *J. Med. Chem* **1995**, vol. 38, 1355). Antiviral data obtained for the test compounds are

shown in Tables 1 and 3, where all data are for HRV serotype-14 unless otherwise noted in parentheses. The designation "ND" indicates that a value was not determined for that compound.

Table 1. Activity vs. HRV Serotype-14

Compound	Protease Inhibition $k_{obs}/[I]$ ($M^{-1}sec^{-1}$)	Cell Protection EC_{50} (μM)
Example 31 (Comparison Compound #2)	25,000	0.610
Example 35 (A-26)	239,000	0.030
Example 33 (A-24)	257,000	0.100
Example 36 (A-27)	18,000	1.600
Example 32 (Comparison Compound #3)	62,500	0.380
Example 34 (A-25)	500,000	0.030
Example 5 (A-4)	270,000	0.100
Example 8 (A-7)	980,000	0.004
Example 7 (A-6)	248,000	0.420
Example 9 (A-8)	900,000	ND
Example 6 (A-5)	1,500,000	0.005
Example 12 (C-1)	68,400	0.100
Example 18 (C-2)	270,000	0.002
Example 10 (B-1)	240,000	0.100
Example 20 (B-4)	500,000	<0.030
Example 17 (B-2)	1,090,000	0.005
Example 1 (Comparison Compound #1)	573	>320.000
Example 2 (A-1)	260,000	0.250
Example 3 (A-2)	46,900	1.600
Example 4 (A-3)	310,000	0.050
Example 11 (A-10)	108,000	0.14
Example 13 (A-11)	108,000	0.03
Example 14 (A-9)	66,000	1.80

Table 1. Activity vs. HRV Serotype-14

Compound	Protease Inhibition $k_{obs}/[I]$ ($M^{-1}sec^{-1}$)	Cell Protection EC_{50} (μM)
Example 15 (A-12)	59,300	0.40
Example 16 (A-13)	95,800	0.20
Example 19 (B-3)	465,000	0.18
Example 21 (A-14)	54,500	0.48
Example 22 (A-15)	237,100	0.22
Example 23 (A-16)	172,800	0.45
Example 24 (A-17)	167,000	0.06
Example 25 (A-18)	292,000	1.50
Example 26 (A-19)	27,750	25.10
Example 27 (A-20)	1,020	12.60
Example 28 (A-21)	17,800	2.50
Example 29 (A-22)	2,400	ND
Example 30 (A-23)	26,000	ND

Table 2. Activity vs. Other HRV Serotypes

Compound	Rhinovirus Serotype	kobs/I (M-1sec-1)
Comparison Compound #2	(16)	6,500
"	(89)	3,400
"	(2)	2,000
Comparison Compound #3	(2)	8,000
"	(16)	16,900
(A-24)	(2)	31,000

Table 3. Anti-Rhinovirus Activity

Number	HRV	EC50 (μM)	CC50 (μM)	TI
Comparison Compound #1		>320.000	>320	-
(A-1)		0.250	>100	>400
"	(2)	0.410	ND	>243
"	(1A)	1.000	ND	>100
"	(89)	0.220	ND	>450
(A-2)		1.600	>100	>63
(A-3)		0.050	>10	>200
(A-4)		0.100	>100	>1000
(A-5)		0.005	>10	>2000
"	(2)	0.010	ND	>1000
"	(16)	0.020	ND	>500
"	(39)	0.020	ND	>500
"	(89)	0.020	ND	>500
"	(10)	0.050	ND	>200
"	(1A)	0.030	ND	>333
"	(3)	0.050	ND	>200
"	(9)	0.040	ND	>250
"	(12)	0.060	ND	>166
"	(13)	0.020	ND	>500
"	(17)	0.020	ND	>500
"	(25)	0.180	ND	>55
"	(30)	0.060	ND	>166
"	(38)	0.130	ND	>76
"	(87)	0.210	ND	>47
(A-6)		0.420	>100	>237
(A-7)		0.004	>10	>2500
"	(2)	0.020	ND	>500

Table 3. Anti-Rhinovirus Activity

Number	HRV	EC50 (μM)	CC50 (μM)	TI
"	(16)	0.040	ND	>250
"	(39)	0.020	ND	>500
"	(89)	0.020	ND	>500
"	(10)	0.060	ND	>166
"	(1A)	0.030	ND	>333
"	(3)	0.020	ND	>500
"	(9)	0.040	ND	>250
"	(12)	0.070	ND	>143
"	(13)	0.030	ND	>333
"	(17)	0.020	ND	>500
"	(25)	0.200	ND	>50
"	(30)	0.090	ND	>111
"	(38)	0.170	ND	>58
"	(87)	0.590	ND	>16
(A-8)		ND	ND	ND
(B-1)		0.100	>100	>1000
"	(1A)	0.300	ND	>333
"	(10)	0.400	ND	>250
(A-10)		0.140	>100	>714
(C-1)		0.100	>10	>100
(A-11)		0.030	50	1667
(A-9)		1.800	>100	>55
(A-12)		0.400	>100	>250
(A-13)		0.200	>10	>50
(B-2)		0.005	>100	>20000
"	(2)	0.020	ND	>5000
"	(16)	0.010	ND	>10000
"	(39)	0.050	ND	>2000

Table 3. Anti-Rhinovirus Activity

Number	HRV	EC50 (μM)	CC50 (μM)	TI
"	(89)	0.009	ND	>11111
"	(10)	0.020	ND	>5000
"	(1A)	0.020	ND	>5000
"	(3)	0.020	ND	>5000
"	(9)	0.006	ND	>16666
"	(12)	0.050	ND	>2000
"	(13)	0.010	ND	>10000
"	(17)	0.010	ND	>10000
"	(25)	0.030	ND	>3333
"	(30)	0.040	ND	>2500
"	(38)	0.070	ND	>1428
"	(87)	0.060	ND	>1666
(C-2)		0.002	>10	>5000
"	(2)	0.004	ND	>2500
"	(16)	0.010	ND	>1000
"	(39)	0.010	ND	>1000
"	(89)	0.004	ND	>2500
"	(10)	0.020	ND	>500
"	(1A)	0.010	ND	>1000
"	(3)	0.020	ND	>500
"	(9)	0.010	ND	>1000
"	(12)	0.040	ND	>250
"	(13)	0.007	ND	>1428
"	(17)	0.007	ND	>1428
"	(25)	0.070	ND	>142
"	(30)	0.030	ND	>333
"	(38)	0.050	ND	>200
"	(87)	0.020	ND	>500

Table 3. Anti-Rhinovirus Activity

Number	HRV	EC50 (μM)	CC50 (μM)	TI
(B-3)		0.180	>100	>543
(B-4)		<0.030	>100	>3333
(A-14)		0.480	>100	>208
(A-15)		0.220	>100	>454
"	(1A)	7.100	ND	>14
"	(10)	2.700	ND	>37
(A-16)		0.45	>100	>222
"	(1A)	4.80	ND	>21
"	(10)	4.50	ND	>22
(A-17)		0.06	>100	>1786
"	(1A)	1.80	ND	>56
"	(10)	3.30	ND	>30
(A-18)		1.50	>100	>67
(A-19)		25.10	>100	>4
(A-20)		12.60	>100	>8
(A-21)		2.50	>100	>40
(A-22)		ND	ND	ND
(A-23)		ND	ND	ND
Comparison Compound #2		0.61	>320	>524
"	(16)	2.30	>320	>139
"	(89)	6.30	>320	>50
"	(10)	0.60	>320	>533
Comparison Compound #3		0.38	>320	>842
(A-24)		0.10	>100	>1000
(A-25)		0.03	>100	>3333
(A-26)		0.03	>100	>3333
(A-27)		1.60	>100	>62

Table 3. Anti-Rhinovirus Activity

Number	HRV	EC50 (μM)	CC50 (μM)	TI
WIN 51711		0.78	>60	>77
WIN 52084		0.07	>10	>143
WIN 54954		2.13	>63	>30
Pirodavir		0.03	>10	>300
Pleconaril		0.01	>10	>1000

Anticoxsackieviral Cell Culture Assay

Coxsackievirus types A-21 (CAV-21) and B3 (CVB-3) were purchased from American Type Culture Collection (ATCC, Rockville, MD). Virus stocks were propagated and antiviral assays were performed in H1-HeLa cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum (Life Technologies, Gaithersburg, MD).

The ability of compounds to protect cells against either CAV-21 or CVB-3 infection was measured by the XTT dye reduction method. This method is described in Weislow et al., *J. Natl. Cancer Inst.* **1989**, vol. 81, 577-586. H1-HeLa cells were infected with CAV-21 or CVB-3 at a multiplicity of infection (m.o.i.) of 0.025 or 0.075, respectively, or mock-infected with medium only. H1-HeLa cells were plated at 4×10^4 cells per well in a 96-well plate and incubated with appropriate concentrations of the test compound. One day (CVB-3) or two days (CAV-21) later, XTT /PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased formazan production in compound-treated, uninfected cells to 50% of that produced in compound-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

The compounds were tested against control compounds WIN 54954 (obtained from Sterling-Winthrop Pharmaceuticals), Pirodavir (obtained from Janssen Pharmaceuticals), and Pleconaril (prepared according to Diana et al., *J. Med. Chem.* **1995**, *38*, 1355). Antiviral data obtained for the test compounds against CAV-21 and CVB-3 are shown in Table 4.

Table 4. Anti-Coxsackievirus Activity

Compound	Strain	EC50 (μM)	CC50 (μM)	TI
(A-5)	CAV-21	0.23	>10	>43
"	CVB-3	1.00	ND	>10
(B-2)	CAV-21	0.16	>100	>625
"	CVB-3	0.18	ND	>555
WIN 54954	CAV-21	>100.00	>100	ND
"	CVB-3	>100.00	ND	ND
Pirodavir	CAV-21	>100.00	>100	ND
"	CVB-3	>100.00	ND	ND
Pleconaril	CAV-21	0.09	>10	>107
"	CVB-3	>10.00	ND	ND

Anti-Echoviral and -Enteroviral Cell Culture Assays

Echovirus type 11 (EV 11) and enterovirus type 70 (EV 70) were purchased from ATCC (Rockville, MD). Virus stocks were propagated and antiviral assays were performed in MRC-5 cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum (Life Technologies, Gaithersburg, MD).

The ability of compounds to protect cells against either EV 11 or EV 70 infection was measured by the XTT dye reduction method (Weislow et al., *J. Natl. Cancer Inst.* **1989**, vol. 81, 577-586). MRC-5 cells were infected with EV 11 or EV 70 at an m.o.i. of 0.003 or 0.004, respectively, or mock-infected with medium only. Infected or uninfected cells were added at 1 x 10^4 cells per well and incubated with appropriate concentrations of compound. Four days later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased formazan production in compound-treated, uninfected cells to 50% of that produced in compound-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

The compounds were tested against control compounds Pirodavir (obtained from Janssen Pharmaceuticals) and Pleconaril (prepared according to Diana et al., *J. Med. Chem.* **1995**, vol. 38, 1355). Antiviral data obtained for the test compounds against strain EV 11 and EV 70 are shown below in Table 5.

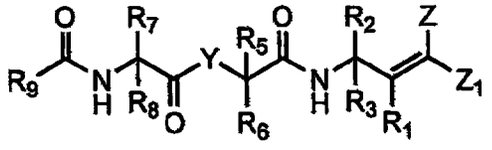
Table 5. Anti-Echovirus and Anti-Enterovirus Activity

Compound	Strain	EC50 (μM)	CC50 (μM)	TI
(A-5)	EV-11	0.080	>10	>125
"	EV-70	0.040	ND	>250
(B-2)	EV-11	0.010	>100	>10000
"	EV-70	0.003	ND	>33333
Pirodavir	EV-11	3.700	>10	>3
"	EV-70	0.060	ND	>167
Pleconaril	EV-11	0.160	>10	>62
"	EV-70	ND	ND	ND

While the invention has been described in terms of preferred embodiments and specific examples, those skilled in the art will recognize that various changes and modifications can be made without departing from the spirit and scope of the invention. Thus, the invention should be understood as not being limited by the foregoing detailed description, but as being defined by the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of the formula I:

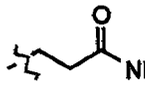
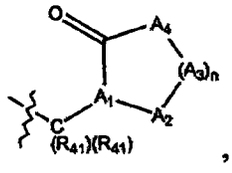
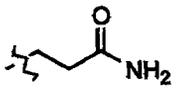
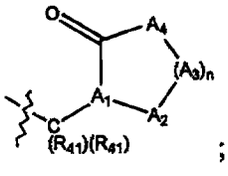


(I),

wherein:

Y is $-N(R_y)-$, $-C(R_y)(R_y)-$, or -O-, where each R_y is independently H or lower alkyl;

R_1 is H, F, an alkyl group, OH, SH, or an O-alkyl group;

R_2 and R_3 are each independently H; ; or , where n is an integer from 0 to 5, A_1 is CH or N, A_2 and each A_3 are independently selected from $C(R_{41})(R_{41})$, $N(R_{41})$, S, S(O), $S(O)_2$, and O, and A_4 is NH or NR_{41}, where each R_{41} is independently H or lower alkyl, provided that no more than 2 heteroatoms occur consecutively in the ring formed by A_1, A_2, $(A_3)_n$, A_4 and C=O; and provided that at least one of R_2 and R_3 is  or ;

R_5 and R_6 are each independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$, where R_{17}, R_{18}, and R_{19} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

R_9 is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S; and

Z and Z_1 are each independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, -CN, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

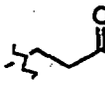
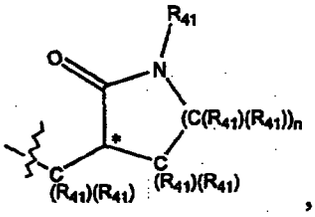
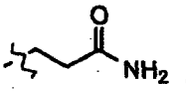
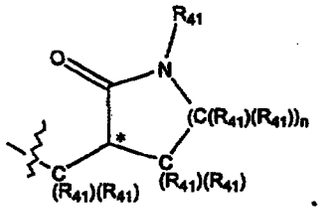
where R_{21}, R_{22}, R_{23}, and R_{24} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or a prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate thereof.

2. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 1, wherein R_2 and R_3 are each independently H;


; or

, where n is an integer from 0 to 5, each R_{41} is independently H or lower alkyl, and the stereochemistry at the carbon denoted with an asterisk (*) may be R or S; provided that at least one of R_2 and R_3 is

or


3. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 1, wherein Y is $-N(R_y)-$, where R_y is H or lower alkyl.

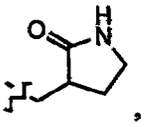
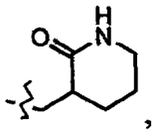
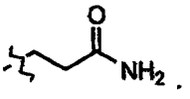
4. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein: Z and Z_1 are each independently selected from H, F, lower alkyl, $-CO_2R_{21}$, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

This Sheet Has Been Replaced

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group.

5. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein R_1 is H, F, or methyl.

6. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein at least one of R_2 or R_3 is , , or .

7. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 7, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

8. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

9. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein one of R_5 and R_6 is H and the other is unsubstituted or substituted phenylmethyl.

10. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group.

11. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein one of R_7 and R_8 is H and the other is alkyl or aryl.

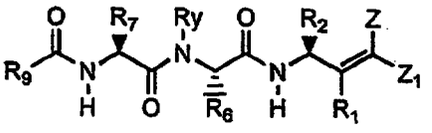
12. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein one of R_7 and R_8 is H and the other is 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, or naphthylmethyl.

13. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein R_9 is a five-membered heterocycle having at least one nitrogen heteroatom and one oxygen heteroatom.

14. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein R_9 is selected from substituted and unsubstituted 1,2-oxazolyl, 1,3-oxazolyl, and 1,2,4-oxadiazolyl..

15. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 3, wherein R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

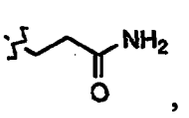
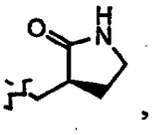
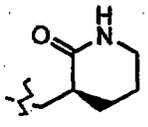
16. A compound according to claim 3 of the formula I-A'':



(I-A'')

wherein R_1, R_2, R_6, R_7, R_9, R_y, Z, and Z_1 are as defined in claim 3,

or a prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate thereof.

17. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 16, wherein R_2 is , ,  or .

18. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 16, wherein:

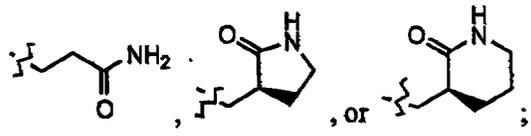
R_y is H or methyl;

R_1 is H, F, or methyl;

Z and Z_1 are each independently selected from H, F, $-CO_2R_{21}$, -CN, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

R_2 is ;

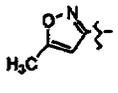
R_6 is unsubstituted or substituted phenylmethyl;

R_7 is alkyl or aryl; and

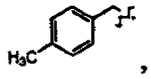
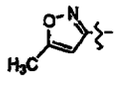
R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

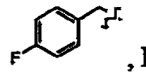
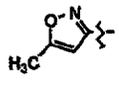
19. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 18, wherein R_7 is selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, and naphthylmethyl.

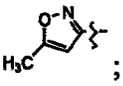
20. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 16, wherein R_y, R_1, and Z are each H, and:

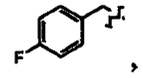
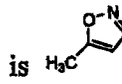
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

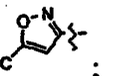
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

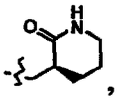
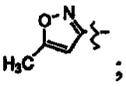
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

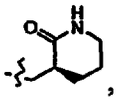
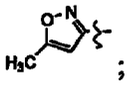
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

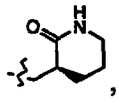
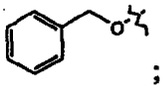
R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

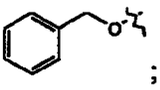
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

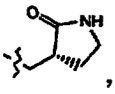
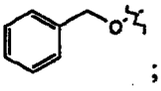
R_2 is , R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

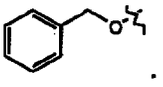
R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

R_2 is , R_6 is , R_7 is $C(CH_3)_3$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

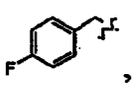
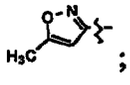
R_2 is , R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

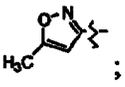
R_2 is , R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

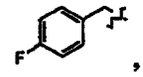
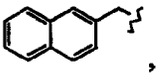
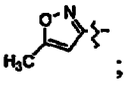
R_2 is , R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ; or

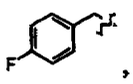
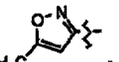
R_2 is , R_6 is CH_2Ph, R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

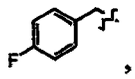
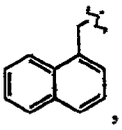
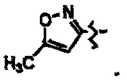
21. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 16, wherein R_y is CH_3, R_1 and Z are each H, and:

R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

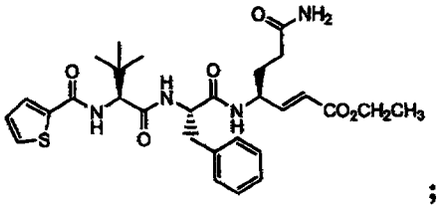
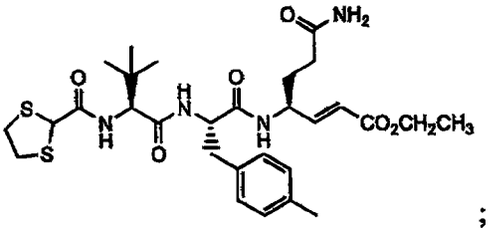
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is CH_2Ph, R_7 is $CH_2CH(CH_3)_2$, and R_9 is ;

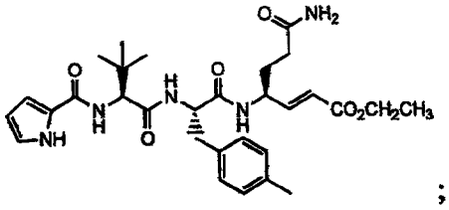
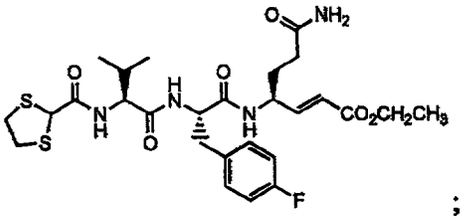
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , and R_9 is ;

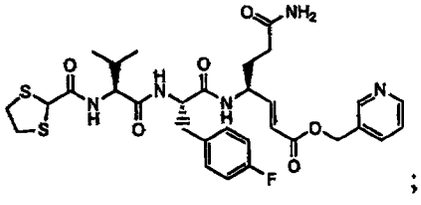
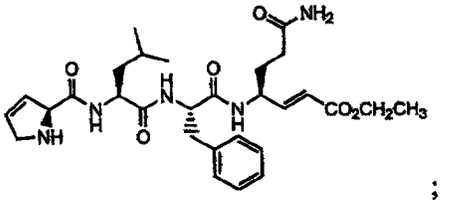
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH_2CH(CH_3)_2$, and R_9 is ; or

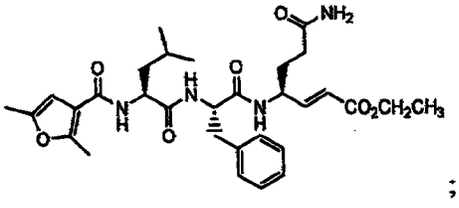
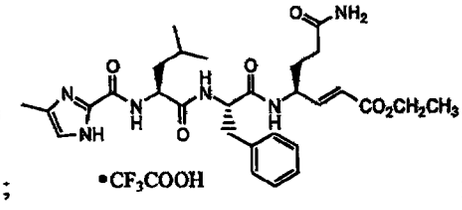
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is , and R_9 is .

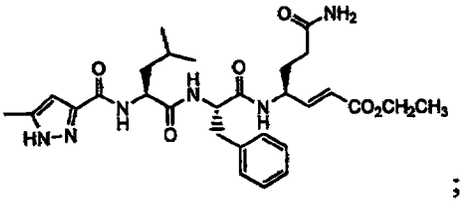
22. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 16 selected from the group consisting of:

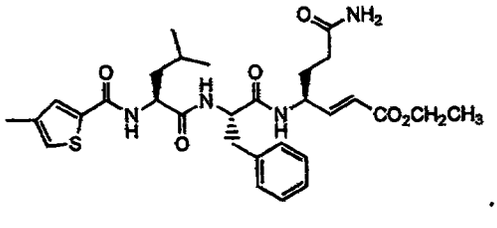
; ;

; ;

; ;

; ;

; •CF_3COOH ;

; 

; and

23. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 1, wherein Y is $-CH_2-$.

24. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein Z and Z_1 are each independently

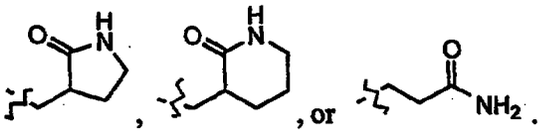
selected from H, F, lower alkyl, $-CO_2R_{21}$, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group.

25. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein R_1 is H, F, or methyl.

26. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein at least one of R_2 and R_3 is



, or .

27. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 26, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

28. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

29. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein one of R_5 and R_6 is H and the other is unsubstituted or substituted phenylmethyl.

30. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group.

31. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein one of R_7 and R_8 is H and the other is alkyl or aryl.

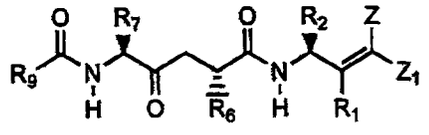
32. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein one of R_7 and R_8 is H and the other is 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, or naphthylmethyl.

33. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 23, wherein R_9 is a five-membered heterocycle having at least one nitrogen heteroatom and one oxygen heteroatom.

34. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 33, wherein R_9 is unsubstituted or substituted 1,2-oxazolyl, 1,3-oxazolyl, or 1,2,4-oxadiazolyl.

35. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 34, wherein R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

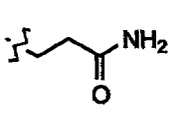
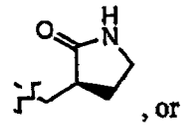
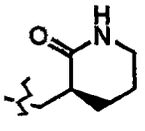
36. A compound according to claim 23 of the formula I-B'':



(I-B'')

wherein R_1, R_2, R_6, R_7, R_9, Z, and Z_1 are as defined in claim 23,

or a prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate thereof.

37. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 36, wherein R_2 is , , or .

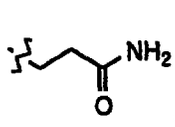
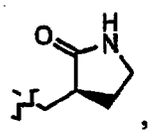
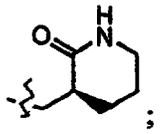
38. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 36, wherein:

R_1 is H, F, or methyl;

Z and Z_1 are each independently selected from H, F, $-CO_2R_{21}$, -CN, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

R_2 is selected from , , and ;

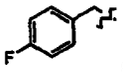
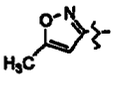
R_6 is unsubstituted or substituted phenylmethyl;

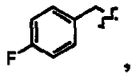
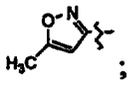
R_7 is alkyl or aryl; and

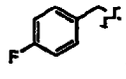
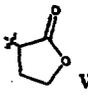
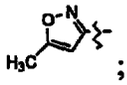
R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

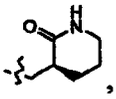
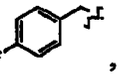
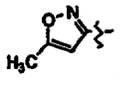
39. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 38, wherein R_7 is selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, and naphthylmethyl.

40. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 36, wherein R_1 is H and:

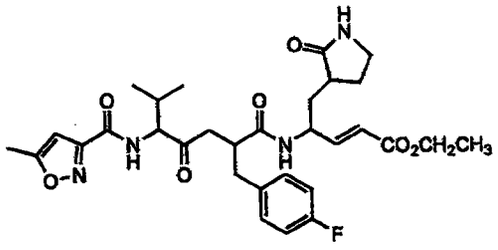
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is ;

R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z and Z_1 together are  where the carbonyl group is cis to the R_1 hydrogen, and R_9 is ; or

R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

41. A compound according to claim 1 of the formula:



or a prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate thereof.

42. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 1, wherein Y is -O-.

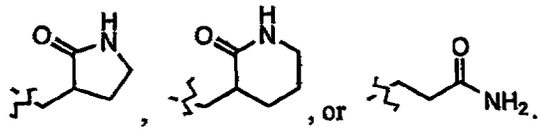
43. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein Z and Z_1 are each independently selected from H, F, lower alkyl, $-CO_2R_{21}$, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group.

44. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein R_1 is H, F, or methyl.

45. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein at least one of R_2 and R_3 is



46. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 45, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

47. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein one of R_5 and R_6 is H and the other is alkyl or aryl.

48. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein one of R_5 and R_6 is H and the other is unsubstituted or substituted phenylmethyl.

49. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein R_7 and R_8 are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group.

50. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein one of R_7 and R_8 is H and the other is alkyl or aryl.

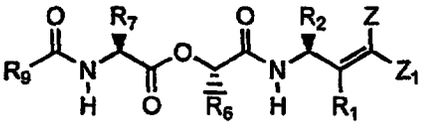
51. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein one of R_7 and R_8 is H and the other is 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, or naphthylmethyl.

52. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein R_9 is a five-membered heterocycle having at least one nitrogen heteroatom and one oxygen heteroatom.

53. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein R_9 is selected from substituted and unsubstituted 1,2-oxazolyl, 1,3-oxazolyl, and 1,2,4-oxadiazolyl.

54. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 42, wherein R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

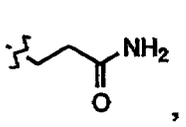
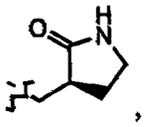
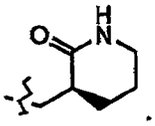
55. A compound according to claim 42, of the formula I-C'':



(I-C'')

wherein R_1, R_2, R_6, R_7, R_9, Z, and Z_1 are as defined in claim 42,

or a prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate thereof.

56. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 55, wherein R_2 is , ,  or .

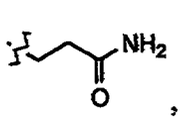
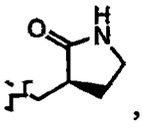
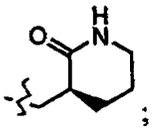
57. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 55, wherein:

R_1 is H, F, or methyl;

Z and Z_1 are each independently selected from H, F, $-CO_2R_{21}$, -CN, and $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, provided that Z and Z_1 are not both H;

or Z_1 and R_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z_1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

R_2 is selected from , , and ;

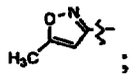
R_6 is unsubstituted or substituted phenylmethyl;

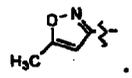
R_7 is alkyl or aryl; and

R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens.

58. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 57, wherein R_7 is selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, phenylmethyl, and naphthylmethyl.

59. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 55, wherein R_1 is H, Z is H, and:

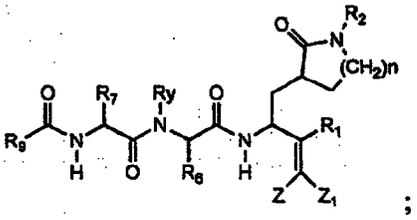
R_2 is $CH_2CH_2C(O)NH_2$, R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is ; or

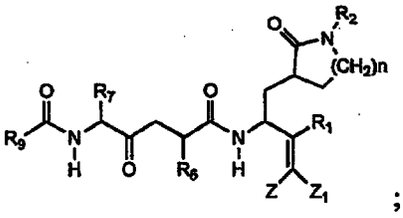
R_2 is , R_6 is , R_7 is $CH(CH_3)_2$, Z_1 is $CO_2CH_2CH_3$, and R_9 is .

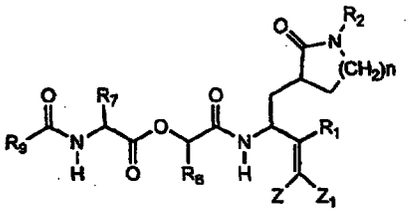
60. A compound, pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate according to claim 1, having an antipicornaviral activity corresponding to an EC_{50} less than or equal to 100 μM in an H1-HeLa cell culture assay.

61. A compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate according to claim 1, having an antirhinoviral activity corresponding to an EC_{50} less than or equal to 10 μM in an H1-HeLa cell culture assay.

62. A compound having a formula selected from the group consisting of:

;

; and



wherein:

R_1, R_2, Z, and Z_1 are as defined in claim 1,

n is 1 or 2;

R_y is H or lower alkyl,

R_6 is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R_7 is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$, where R_{17}, R_{18}, and R_{19} are each independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or acyl; and

R_9 is a five-membered heterocycle having one to three heteroatoms selected from O, N, and S;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate thereof.

63. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate according to claim 62, wherein:

R_1 is H, F, or alkyl;

R_y is H or methyl;

R_6 is an alkyl group optionally substituted with one or more substituents selected from alkyl and aryl;

R_7 is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R_9 is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S, where at least one of the heteroatoms is nitrogen, that is unsubstituted or substituted with one or two substituents selected from lower alkyl groups and halogens;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate thereof.

64. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate according to claim 62, wherein:

R_6 is arylmethyl or arylthiomethyl;

R_7 is an alkyl group;

R_9 is 3-isoxazolyl or 5-isoxazolyl unsubstituted or substituted with one or two substituents selected from methyl and halogens; and

Z is H and Z_1 is $-CO_2R_{21}$, -CN, or $-C(O)NR_{21}R_{22}$, where R_{21} and R_{22} are each independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or R_{21} and R_{22} together with the atom(s) to which they are bonded form a heterocycloalkyl group, or Z and Z_1 together form a cyclic ester or amide.

65. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate according to claim 64, wherein:

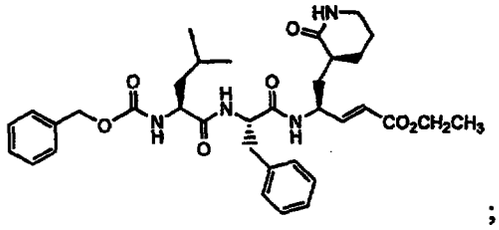
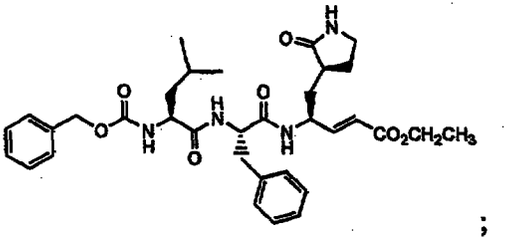
R_1 is H or F;

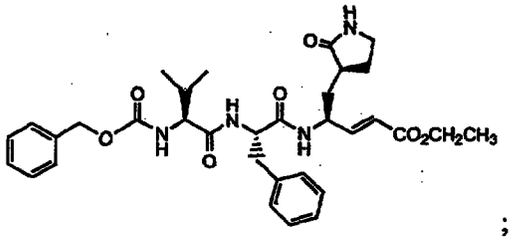
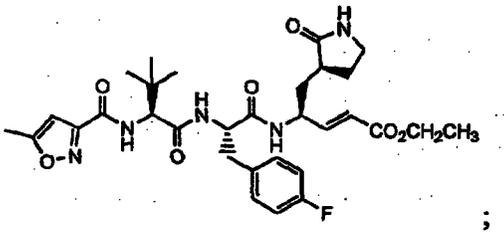
R_6 is arylmethyl or arylthiomethyl; and

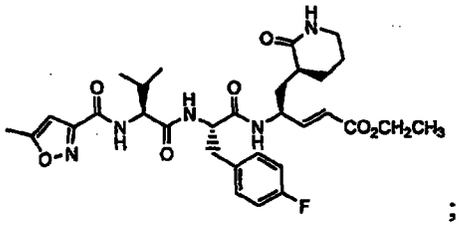
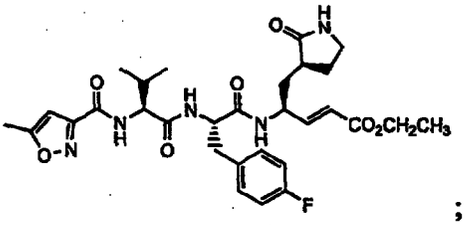
R_7 is selected from 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, and arylmethyl.

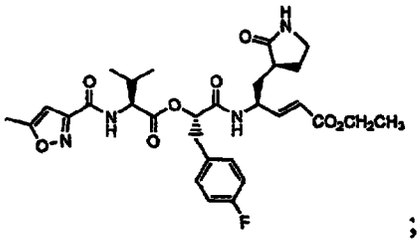
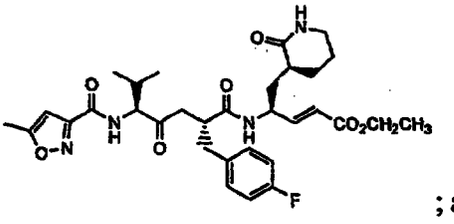
66. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate according to claim 65, wherein R_{11} is phenylmethyl, where the phenyl moiety optionally has one to three substituents selected from halogen, lower alkyl, and lower alkoxy.

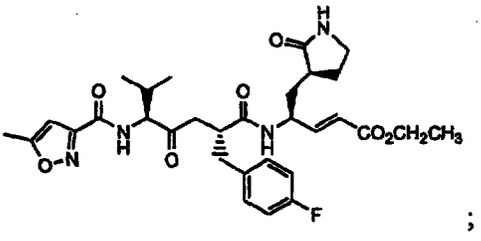
67. A compound according to claim 62, selected from the group consisting of:


;

;


;

;


;

;


;

; and


;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or solvate thereof.

68. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of at least one antipicornaviral agent that is a compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate as defined in claim 1; and

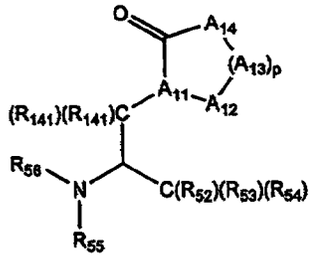
(b) a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

69. A method of treating a mammalian disease condition mediated by picornaviral protease activity, comprising: administering to a mammal in need thereof a therapeutically effective amount of at least one compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate as defined in claim 1.

70. A method of inhibiting the activity of a picornaviral 3C protease, comprising: contacting the picornaviral 3C protease with an effective amount of at least one compound, prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, or solvate as defined in claim 1.

71. A method as defined in claim 70, wherein the picornaviral 3C protease is a rhinoviral protease.

72. A compound of formula:



wherein:

p is an integer of from 0 to 5;

A_{11} is CH or N, A_{12} and each A_{13} are independently selected from $C(R_{61})(R_{61})$, $N(R_{61})$, S, S(O), $S(O)_2$, and O, and A_4 is NH or NR_{61}, where each R_{61} is independently H, alkyl, acyl, or aryl, provided that no more than two heteroatoms occur consecutively in the ring formed by A_{11}, A_{12}, $(A_{13})_n$, A_{14}, and C=O;

each R_{141} is independently H or lower alkyl;

R_{51} is H, alkyl, acyl, or aryl;

R_{52}, R_{53}, and R_{54} are each independently selected from H, hydroxyl, alkyl, acyl, and aryl, or any two of R_{52}, R_{53}, and R_{54} together form =O or $=C(R_{57})(R_{58})$, where R_{57} and R_{58} are

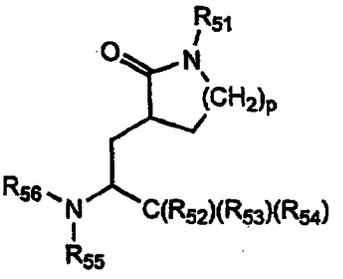
This Sheet Has Been Replaced

each independently selected from H, alkyl, $CO_2(C_1\text{-}C_6)$alkyl, $CO_2N(C_1\text{-}C_6)$alkyl, and CO_2(aryl); and

R_{55} and R_{56} are each independently H or a suitable protecting group for nitrogen;

or a pharmaceutically acceptable salt of said compound.

73. A compound of formula:



wherein:

p is an integer of from 0 to 5;

R_{51} is H, alkyl, acyl, or aryl;

R_{52}, R_{53}, and R_{54} are each independently selected from H, hydroxy, alkyl, acyl, and aryl, or any two of R_{52}, R_{53}, and R_{54} together form =O or $=C(R_{57})(R_{58})$, where R_{57} and R_{58} are each independently selected from H, alkyl, $CO_2(C_1\text{-}C_6)$alkyl, $CO_2N(C_1\text{-}C_6)$alkyl, and CO_2(aryl); and

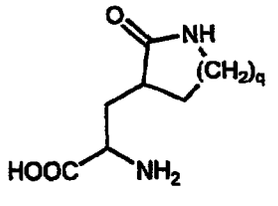
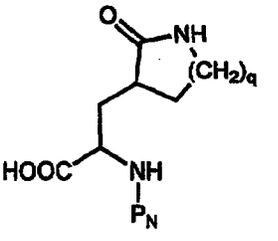
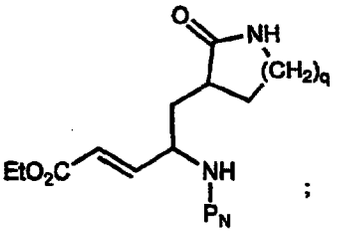
R_{55} and R_{56} are each independently H or a suitable protecting group for nitrogen;

or a pharmaceutically acceptable salt of said compound.

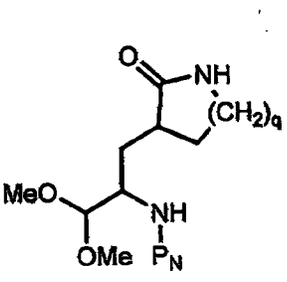
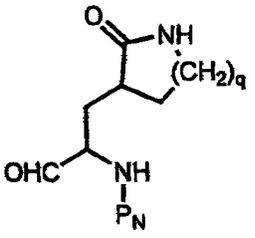
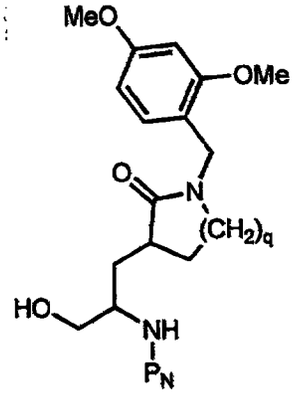
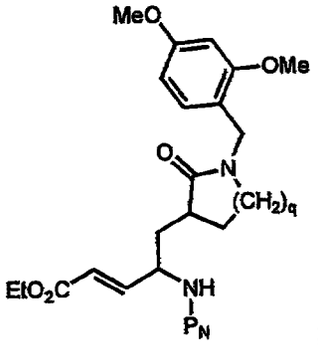
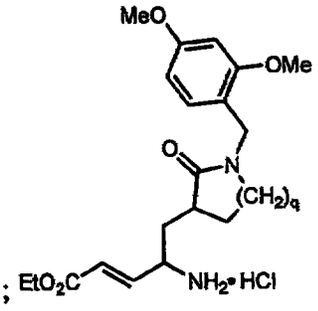
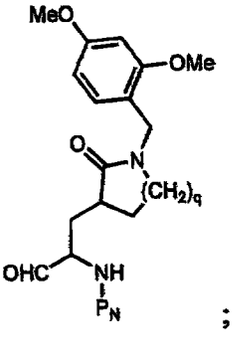
74. A compound or pharmaceutically acceptable salt according to claim 73, wherein n is 1 or 2.

75. A compound or pharmaceutically acceptable salt according to claim 74, wherein R_{52}, R_{53}, and R_{54} are each independently selected from H, alkoxy, hydroxy, and carbonyl.

76. A compound according to claim 73, selected from the group consisting of:


;

;

;

This Sheet Has Been Replaced

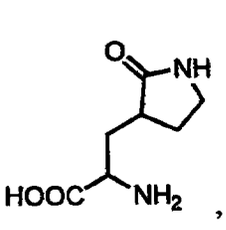
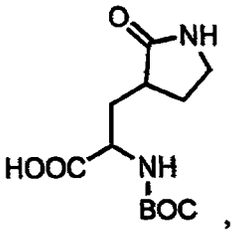
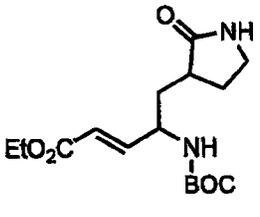
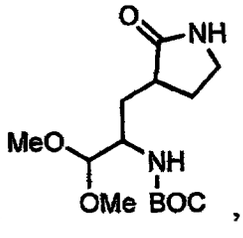
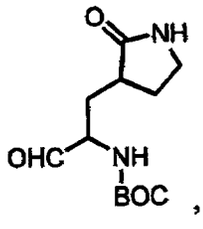
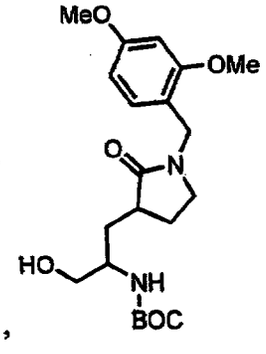
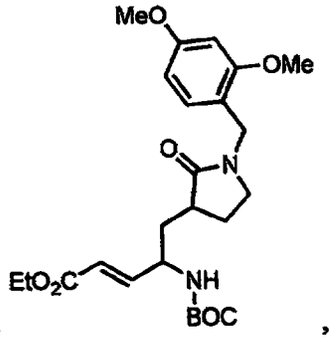







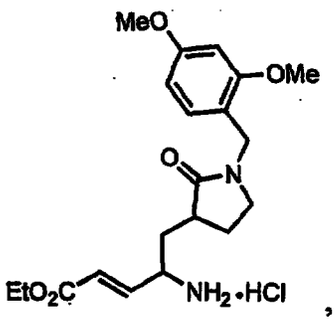
wherein:

P_N is a suitable protecting group for nitrogen and q is 1 or 2;

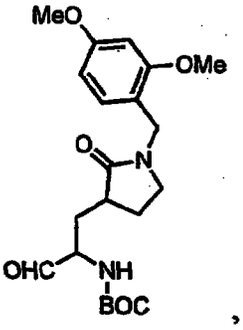
or a pharmaceutically acceptable salt of said compound.

77. A compound according to claim 73, selected from the group consisting of:



, and



,

where BOC is t-butyloxycarbonyl; or a pharmaceutically acceptable salt of said compound.