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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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APORTACION DE NUEVA DOCUMENTACION A
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MODELO DE UTILIDAD O DISEÑO INDUSTRIAL

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Otros ☐
NUEVA DOCUMENTACION APORTADA ☒

☒ PATENTE ☐ MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL

TITULO: **COMPUESTOS ANTIPICORNAVIRALES Y COMPOSICIONES, SUS USOS FARMACEUTICOS Y MATERIALES PARA SU SINTESIS**

SOLICITANTE: **AGOURON PHARMACEUTICALS, INC.**

INDICE DE DOCUMENTOS QUE SE ACOMPAÑAN

☒	1 Copias certificadas por la Oficina de Patentes	☐	
☐	de Estados Unidos de las dos primeras solicitu-	☐	
☐	des presentadas para la misma invención, de las	☐	
☐	cuales REIVINDICAMOS PRIORIDAD, junto con sus	☐	
☐	correspondientes traducciones al castellano.	☐	
☐		☐	

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FIRMA:

NUMERO DE HOJAS 713

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THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

October 19, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/168,986***
FILING DATE: ***December 03, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. Williams

N. WILLIAMS
Certifying Officer

12-06-99

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12/03/99 JC490 U.S. PTO

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

DOCKET NUMBER	2321.194 PVL	Type a plus sign (+) inside this box.	+

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09/160986 U.S. PTO 12/03/99

TITLE OF THE INVENTION (280 characters max)

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

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ENCLOSED APPLICATION PARTS (check all that apply)

- [X] Specification — Number of Pages 150
- [ ] Small Entity Statement
- [ ] Drawing(s) — Number of Sheets
- [ ] Other (specify)

METHOD OF PAYMENT (check one)

- [X] A check or money order is enclosed to cover the Provisional filing fees
- [X] The Commissioner is hereby authorized to charge any deficiencies in the payment of the filing fees and credit any overpayment to Deposit Account Number: 06-1206

PROVISIONAL FILING FEE AMOUNT ($): $150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- [X] No.
- [ ] Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Kathryn L. Sieburth

TYPED or PRINTED NAME Kathryn L. Sieburth

DATE December 3, 1999

REGISTRATION NO. 40,072 (If appropriate)

- [ ] Additional inventors are being named on separately numbered sheets attached hereto.

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Jose Adames
(Signature of person mailing paper or fee)

PROVISIONAL APPLICATION FILING ONLY

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UNITED STATES PROVISIONAL APPLICATION FOR PATENT

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TITLE

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

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TITLE

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

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BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to pyridone-containing 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 these compounds in pharmaceutical compositions, methods of treatment of rhinoviral infections using these compounds and compositions, and processes for the synthesis of these compounds and compounds useful in the syntheses thereof.

Related Background Art

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 picornaviral 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 viral 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.

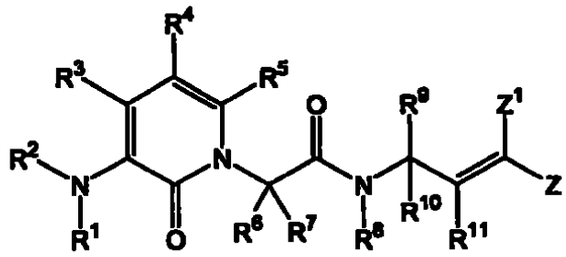
Some small-molecule inhibitors of the enzymatic activity of picornaviral 3C proteases (i.e., antipicornaviral compounds) have been recently discovered. See, for example: U.S. Patent No. 5,856,530; U.S Patent No. 5,962,487; U.S. Patent Application No. 08/991,282, filed December 16, 1997, by Dragovich et al.; and U.S. Patent Application No. 09/301,977, filed April 29, 1999, by Dragovich et al. See also: Dragovich et al., "Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ," *J. Med. Chem.* (1999), Vol. 42, No. 7, 1203-1212, 1213-1224; and Dragovich et al., "Solid-phase Synthesis of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ," *Bioorg. & Med. Chem.* (1999), Vol. 7, 589-598. There is still a desire, however, to discover small-molecule compounds that are especially potent antipicornaviral agents.

Inhibitors of other related cysteine proteases such as cathepsins have been described in, e.g., U.S. Patent No. 5,374,623; U.S. Patent No. 5,498,616; and WIPO International Publication Nos. WO 94/04172, WO 95/15749, WO 97/19231, and WO

97/49668. There yet remains a need for inhibitors targeting the picornaviral 3C cysteine protease with desirable pharmaceutical properties, such as high specificity.

SUMMARY OF THE INVENTION

This invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the general Formula I:



(I)

wherein:

R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group;

R^3 is a suitable substituent; or

R^1 together with R^2 form a suitable nitrogen protecting group; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is a suitable substituent;

R^5 is a suitable substituent;

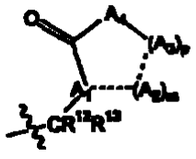
R^6 is a substituted or unsubstituted alkyl group; or

R^5 together with R^6 form a heterocycloalkyl group, which may be optionally substituted;

R^7 and R^{10} are independently H, halogen or a substituted or unsubstituted lower alkyl group;

R^8 is H or a substituted or unsubstituted lower alkyl group;

R^{11} is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

R^9 is a substituent having the formula: 

wherein,

R^{12} and R^{13} are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, and $O(R^{18})$, where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, each R^{17} is H, alkyl, aryl, or acyl, and each R^{18} is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0); and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group,

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$-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted.

In addition to compounds of the Formula I, antipicornaviral agents of the invention include prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates of such compounds.

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DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

Preferably, in the compounds of Formula I:

R^1, R^7, R^8, R^{10} and R^{11} are independently H or a substituted or unsubstituted lower alkyl group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

R^3 is a suitable substituent; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is a suitable substituent;

R^5 is a suitable substituent;

R^6 is an unsubstituted alkyl group or a lower alkyl group optionally substituted with a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkoxyl group, an aryloxy group, an alkylthio group, an

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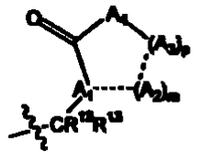
arylthio group, wherein each alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety thereof may be optionally substituted; or

R^5 together with R^6 form a substituted or unsubstituted five- or six-membered heterocycloalkyl group;

wherein when R^4, R^5 and R^6 are suitable substituents, said suitable substituents may be independently selected from H, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio and heteroarylthio, wherein any of the alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted;

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R^9 is an aminocarbonylalkyl group, an alkylcarbonylaminoalkyl group, an alkylaminocarbonylalkyl group or a substituent having the formula:



wherein:

R^{12} and R^{13} are independently H or lower alkyl;

m is 1;

p is 1 or 2;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O;

A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O ;

wherein each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, and each R^{17} is H, alkyl, aryl, or acyl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond; and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted.

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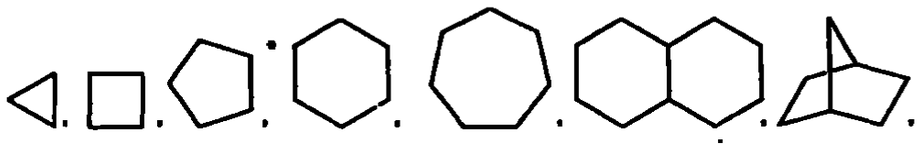
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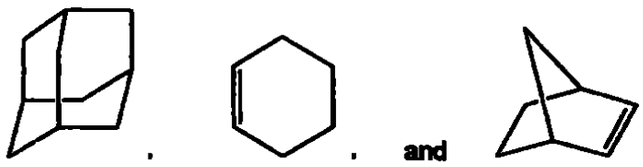
Preferably, R^4, R^5 and R^6 may be independantly selected from H, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, amino, halogen, hydroxyl, alkoxy, aryloxy, cycloalkoxy, heterocycloalkoxy, alkyloxycarbonyl, aryloxycarbonyl, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaryl carbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, alkylamino, arylamino, dialkylamino, alkylaminocarbonyl, alkylsulfonyl, or arylsulfonyl.

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.

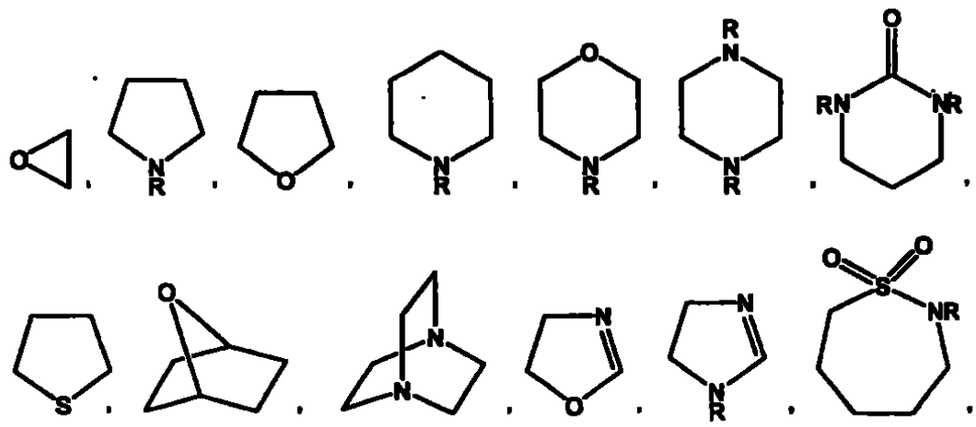
As used herein, the term "alkyl" represents a straight- or branched-chain saturated or unsaturated hydrocarbon, containing 1 to 10 carbon atoms. Exemplary alkyl substituents include, but are not limited to, methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, butynyl, propynyl, pentynyl, hexynyl and the like. The term "lower alkyl" refers to an alkyl group containing from 1 to 4 carbon atoms.

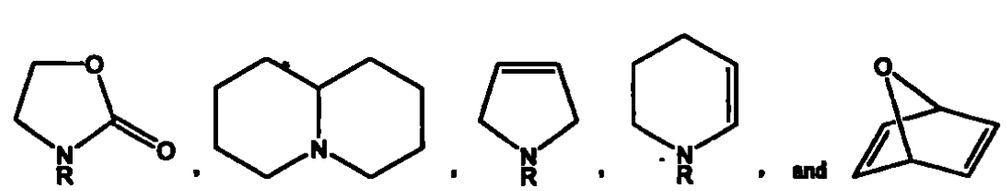
"Cycloalkyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms that may be saturated or partially unsaturated, mono- or poly-carbocyclic ring, preferably having 5-14 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, that may be fully saturated or partially unsaturated. Illustrative examples of cycloalkyl groups include the following:



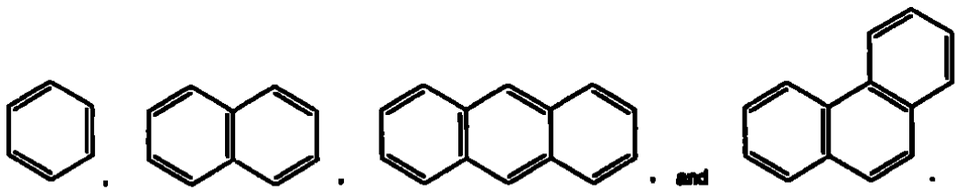


"Heterocycloalkyl" represents a group comprising a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or partially unsaturated, containing 3 to 18 ring atoms and which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and to which may be fused one or more cycloalkyl groups, aryl groups, or heteroaryl groups which may be unsubstituted or substituted by one ore more of the substituents described below. Illustrative examples of heterocycloalkyl groups include, but are not limited to, azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Illustrative examples of heterocycloalkyl groups include the following moieties:

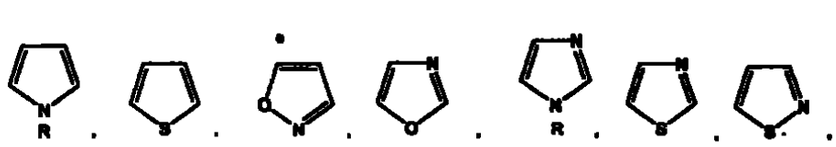




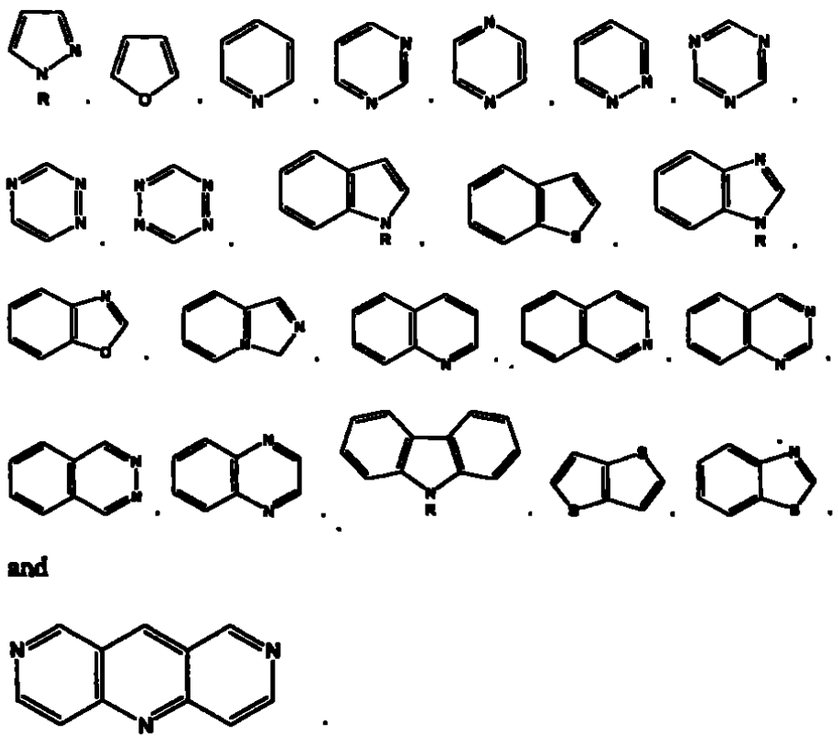
"Aryl" represents a group comprising an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing from 6 to 18 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of aryl groups include the following moieties:



"Heteroaryl" represents a group comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Further examples of heteroaryl groups include the following moieties:



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and

As indicated herein, the alkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl groups may be optionally substituted by one or more substituents. The term "optionally substituted" is intended to expressly indicate that the specified group is unsubstituted or substituted by one or more suitable substituents. Various groups may be unsubstituted or substituted (i.e., they are optionally substituted) as indicated. 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.

Exemplary "suitable substituents" that may be present on any of the above alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl groups are described herein and include alkyl (except for alkyl), aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl; cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy,

heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio, heteroarylthio, wherein any of the alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. Preferred "suitable substituents" include alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halogen, hydroxyl, alkoxy, aryloxy, cycloalkoxy, heteroaryloxy, and carboxyl. The alkyl, cyloalkyl, heterocycloalkyl, aryl, and heteroaryl and moieties of any of the above substituents may be optionally be substituted by one or more of alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some

instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the compounds of this invention, R^1 and R^2, independently or taken together, may be a suitable nitrogen protecting group. As indicated above, nitrogen protecting groups are well known in the art and any nitrogen protecting group that is useful in the methods of preparing the compounds of this invention or may be useful in the antipicornaviral compounds of this invention may be used. Exemplary nitrogen protecting groups include alkyl, substituted alkyl, carbamate, urea, amide, imide, enamine, sulfenyl, sulfonyl, nitro, nitroso, oxide, phosphinyl, phosphoryl, silyl, organiometallic, borinic acid and boronic acid groups. Examples of each of these groups, methods for protecting nitrogen moieties using these groups and methods for removing these groups from nitrogen moieties are disclosed in T. Greene and P. Wuts, *supra*. Preferably, when R^1 and/or R^2 are independently suitable nitrogen protecting groups, suitable R^1 and R^2 substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc: t-butyloxycarbonyl) and aryloxycarbonyl (e.g., Cbz: benzyloxycarbonyl, or FMOC: fluorene-9-methyloxycarbonyl), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl), and the like. When R^1 and R^2 taken together are a suitable nitrogen protecting group, suitable R^1/R^2 substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene).

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group. "Acyl" is intended to mean a -C(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Acyloxy" is intended to mean an -OC(O)-R radical, where R is a substituted or unsubstituted

alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Thioacyl" is intended to mean a -C(S)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Sulfonyl" is intended to mean an $-SO_2-$ biradical. "Sulfenyl" is intended to mean an -SO- biradical. "Sulfo" is intended to mean an $-SO_2H$ radical. "Hydroxy" is intended to mean the radical -OH. "Amine" or "amino" is intended to mean the radical $-NH_2$. "Alkylamino" is intended to mean the radical $-NHR_a$, where R_a is an alkyl group. "Dialkylamino" is intended to mean the radical $-NR_aR_b$, where R_a and R_b are each independently an alkyl group, and is intended to include heterocycloalkyl groups, wherein R_a and R_b, taken together, form a heterocyclic ring that includes the amine nitrogen. "Alkoxy" 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. "Lower alkoxy" groups have alkyl moieties having from 1 to 4 carbons. "Alkoxycarbonyl" is intended to mean the radical $-C(O)OR_a$, where R_a is an alkyl group. "Alkylsulfonyl" is intended to mean the radical $-SO_2R_a$, where R_a is an alkyl group. "Alkylaminocarbonyl" is intended to mean the radical $-C(O)NHR_a$, where R_a is an alkyl group. "Dialkylaminocarbonyl" is intended to mean the radical $-C(O)NR_aR_b$, where R_a and R_b are each independently an alkyl group. "Mercapto" is intended to mean the radical -SH. "Alkylthio" is intended to mean the radical $-SR_a$, where R_a is an alkyl group. "Carboxy" is intended to mean the radical -C(O)OH. "Carbamoyl" is intended to mean the radical $-C(O)NH_2$. "Cycloalkylalkyl" is intended to mean the radical –alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined as above, and is represented by the bonding arrangement present in the groups $-CH_2$-cyclohexane or $-CH_2$-cyclohexene. "Arylalkyl" is intended to mean the radical –alkylaryl, wherein alkyl and aryl are defined as above, and is represented by the bonding arrangement present in a benzyl group. "Aminocarbonylalkyl" is intended to mean the radical –alkylC(O) NH_2 and is represented by the bonding arrangement present in the group $-CH_2CH_2C(O)NH_2$. "Alkylaminocarbonylalkyl" is intended to mean the radical –alkylC(O)NHR_a, where R_a is an alkyl group and is represented by the bonding arrangement present in the group $-CH_2CH_2C(O)NHCH_3$. "Alkylcarbonylaminoalkyl is intended to mean the radical –alkylNHC(O)-alkyl and is

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represented by the bonding arrangement present in the group $-CH_2NHC(O)CH_3$. "Dialkylaminocarbonylalkyl" is intended to mean the radical -alkylC(O)NR_aR_b, where R_a and R_b are each independently an alkyl group. "Aryloxy" is intended to mean the radical $-OR_c$, where R_c is an aryl group. "Heteroaryloxy" is intended to mean the radical $-OR_d$, where R_d is a heteroaryl group. "Arylthio" is intended to mean the radical $-SR_c$, where R_c is an aryl group. "Heteroarylthio" is intended to mean the radical $-SR_d$, where R_d is a heteroaryl group.

If an inventive compound is a base, a desired salt may be prepared by any suitable method known in 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.

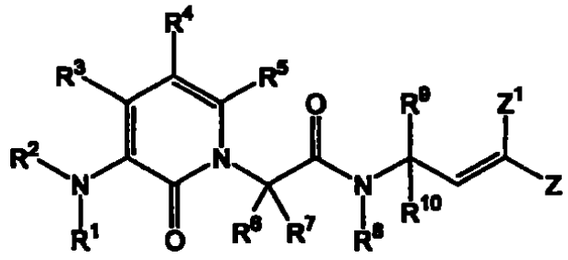
If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative 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.

The inventive compounds may exist as single stereoisomers and/or diastereomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All

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such single stereoisomers, diastereomers, racemates, and mixtures thereof are intended to be encompassed within the broad scope of the present invention. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral carbon. Preferably, however, the inventive compounds are used in optically pure form. When used describe a particular compound, the term "optically pure" is used herein to that the compound is substantially enantiomerically or diastereomerically pure. Compounds that are substantially enatiomerically pure contain at least 90% of a single isomer and preferably contain at least 95% of a single isomer. Compounds that are substantially diastereomerically pure contain at least 90% of a single isomer of each chiral carbon center present in the diastereomer, and preferably contain at least 95% of a single isomer of each chiral carbon. More preferably, the optically active compounds in this invention contain at least 97.5% of a single isomer and most preferably contain at least 99% of a single isomer. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least 90% of a single isomer. The term "racemic" or "racemic mixture" refers to a mixture of equal amounts of enantiomeric compounds, which encompasses mixtures of enantiomers and mixtures of enantiomeric diastereomers.

One preferred embodiment of this invention comprises the compounds depicted by Formula I-a:



I-a

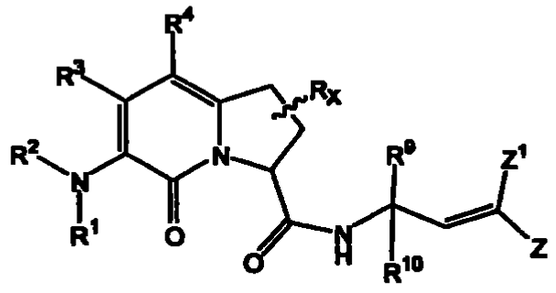
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

R^3, R^4, R^5 are suitable substituents described above, and

R^1, R^6, R^7, R^8, R^9, R^{10}, Z and Z^1, and the variables contained therein, are as defined above.

Another preferred embodiment of this invention comprises the compounds depicted by Formula I-b:



I-b

wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

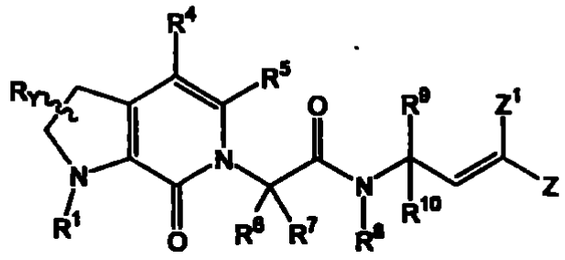
R_X represents one or more suitable substituents;

R^3 and R^4 are suitable substituents described above; and

R^1, R^9, R^{10}, Z and Z^1, and the variables contained therein, are as defined above.

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Yet another preferred embodiment of this invention comprises the compounds depicted by Formula I-c:



I-c

wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R_Y represents one or more suitable substituents;

R^4 and R^5 are the suitable substituents described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined above.

In preferred embodiments of Formulas I-a and I-b, R^2 is a substituted alkyloxycarbonyl group or a substituted or unsubstituted arylcarbonyl or heteroarylcarbonyl group. Preferably, R^2 is an unsubstituted or substituted arylalkyloxycarbonyl or a substituted or unsubstituted arylcarbonyl or heteroarylcarbonyl group. More preferably, R^2 is a substituted or unsubstituted benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl group. Even more preferably, R^2 is an unsubstituted or substituted benzyloxycarbonyl or heteroarylcarbonyl group, wherein the heteroaryl moiety 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

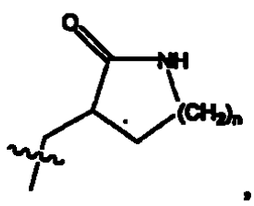
1,2,5-oxadiazolyl). When the heteroaryl moiety is oxadiazolyl, unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl are preferred. In especially preferred embodiments, the heteroaryl moiety is 3-isoxazolyl or 5-isoxazolyl, either unsubstituted or substituted with one or two methyl groups and/or halogens (F, Cl, Br or I), with chlorine and fluorine being preferred.

In especially preferred embodiments of Formulas I-a and I-c, R^6 is an unsubstituted alkyl group or an optionally substituted lower alkyl group, wherein these groups are comprised of a straight- or branched-chain saturated hydrocarbon group, a straight- or branched-chain substituted saturated hydrocarbon group, or group comprised of a straight- or branched-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety. In each case, the point of attachment of R^6 is via a saturated hydrocarbon moiety. When R^6 is a substituted saturated hydrocarbon group, the saturated hydrocarbon group may be optionally substituted with a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkoxy group, an aryloxy group, an alkylthio group, an arylthio group, wherein each alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety thereof may be optionally substituted. When R^6 is comprised of a saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety, the saturated hydrocarbon moiety may be bound to an unsaturated hydrocarbon moiety containing one or more double-bonds or triple-bonds, the terminal positions of which may be substituted by the substituents described above, or may contain additional straight- or branched-chain saturated hydrocarbon moieties. Preferably, the unsaturated hydrocarbon moiety contains one double-bond or one triple-bond, the terminal position(s) of which may optionally contain a straight- or branched-chain saturated hydrocarbon moiety. Preferably, if the unsaturated hydrocarbon moiety contains a double-bond, both terminal positions of the double bond contain a straight- or branched-chain saturated hydrocarbon moiety. In especially preferred embodiments R^6 is a substituted or unsubstituted lower alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl group, or a group comprised of a straight-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety.

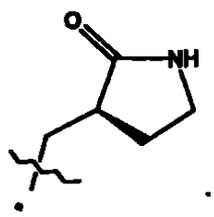
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Preferably, R^6 is methyl, substituted methyl, ethyl, propyl, butyl, sec-butyl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, substituted or unsubstituted -methylthienyl or substituted or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino or halogen and the thienyl moiety of the substituted -methylthienyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino or halogen. When R^6 is substituted methyl, the methyl (methylene) moiety may be substituted with an alkoxy group, an aryloxy group, an alkylthio group or an arylthio group. Most preferably, R^6 is ethyl, 2-propyn-1-yl, -methylcyclohexyl, or substituted or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy and halogen.

In especially preferred embodiments of Formulas I-a, I-b and I-c, R^9 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alkyl; $-CH_2NHC(O)CH_3$; and



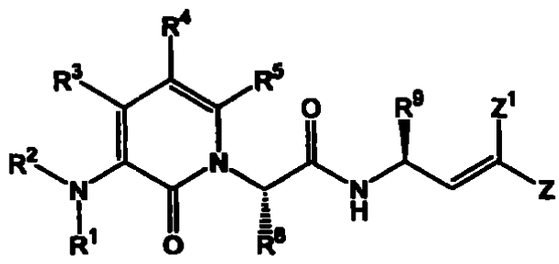
, where n is 1 or 2.

More preferably, R^9 is 

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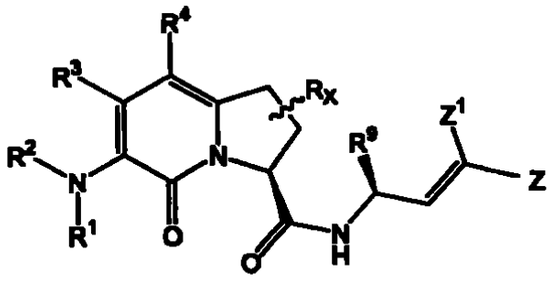
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Especially preferred embodiments of this invention comprise compounds of Formulas I-a', I-b' and I-c' as follows:



I-a'

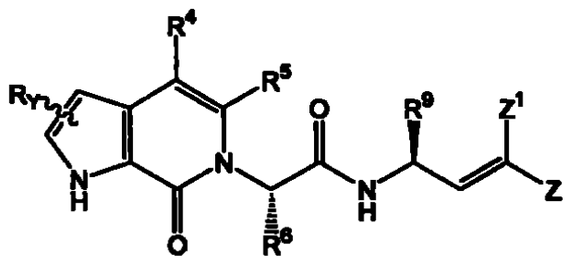
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z and Z^1 are as defined previously;



I-b'

wherein R^1, R^2, R^3, R^4, R^9, R_x, Z and Z^1 are as previously defined;

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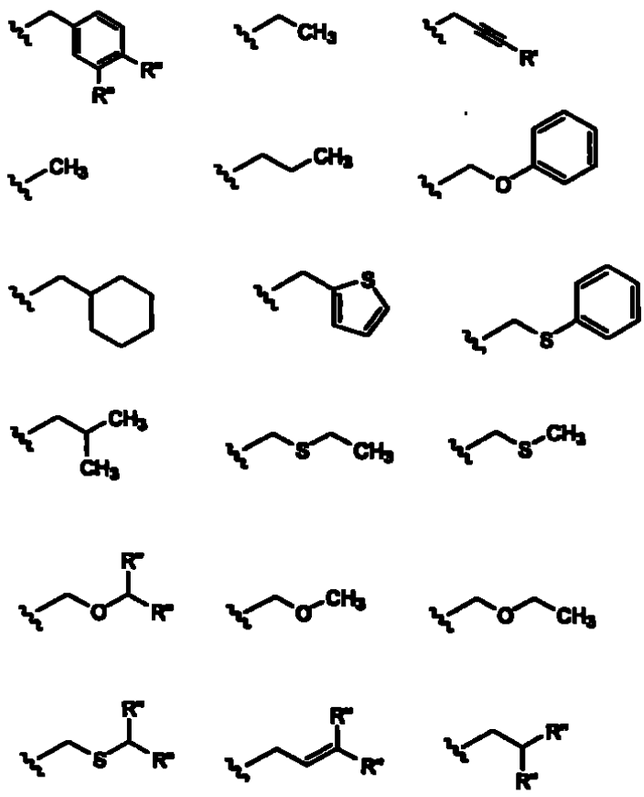
I-c'

wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as previously defined.

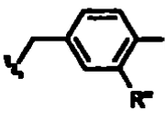
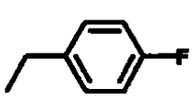
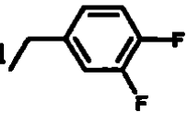
In especially preferred embodiments of Formulas I-a' and I-b', R^2 is unsubstituted or substituted benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl, more preferably heteroarylcarbonyl, where the heteroaryl moiety is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S. More preferably R^2 is heteroarylcarbonyl wherein the heteroaryl moiety is 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); preferred oxadiazolyls are unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl. In especially preferred embodiments, the heteroaryl moiety is 3-isoxazolyl or 5-isoxazolyl, either unsubstituted or substituted with one or two substituents selected from methyl and halogen, with chloro and fluoro being preferred halogen substituents.

In the especially preferred embodiments of Formulas I-a' and I-c', R^6 is selected from:

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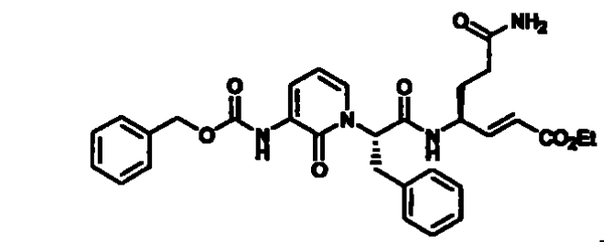


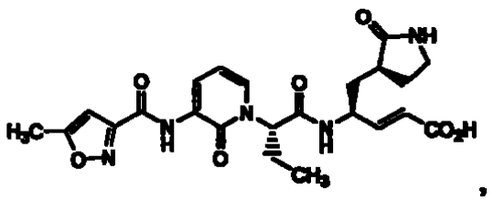
wherein R' may be H or alkyl and R" may one or two substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino, and halogen.

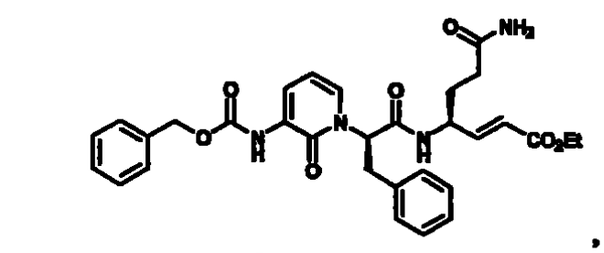
Preferred  groups are  and  .

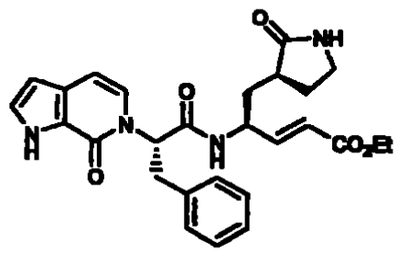
Preferred specific compounds include those of the Examples below, especially:

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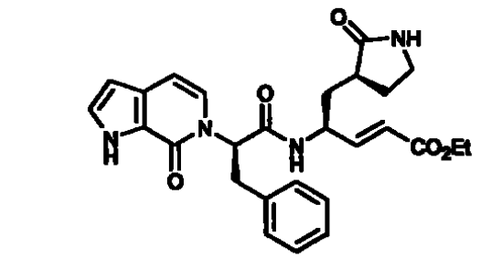


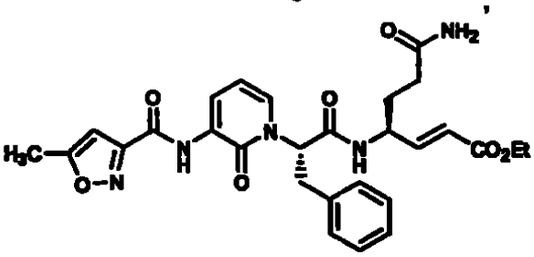


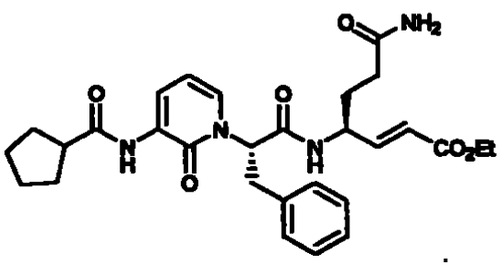


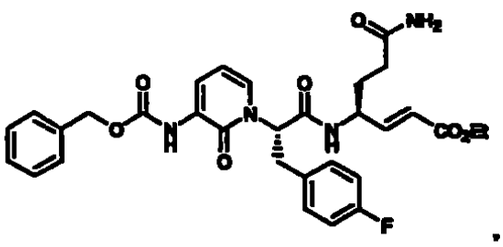


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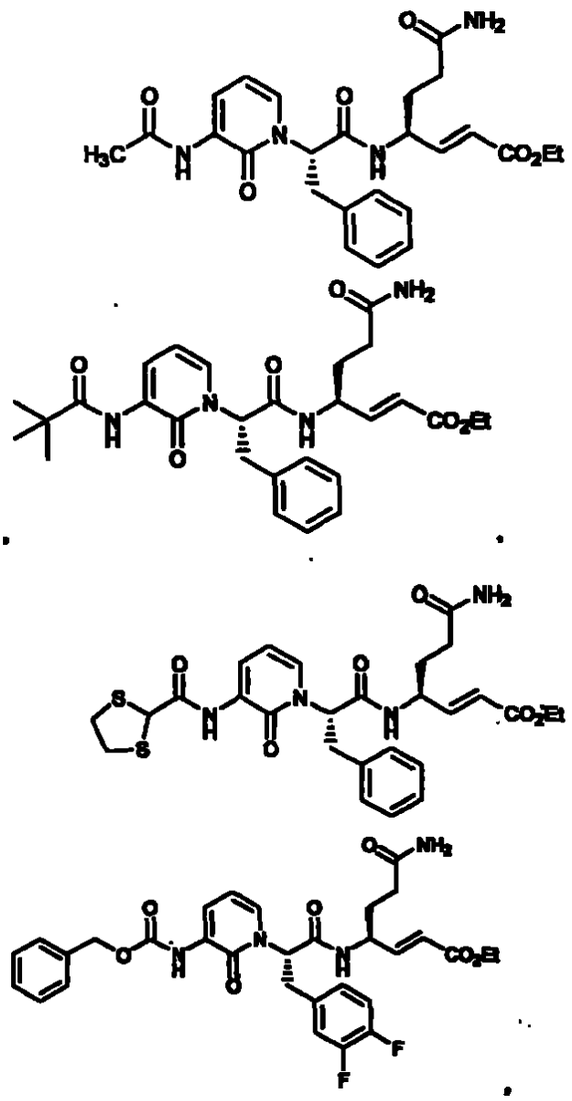






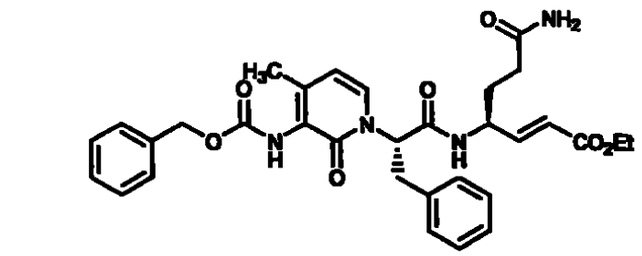
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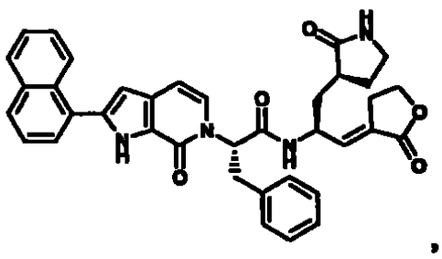
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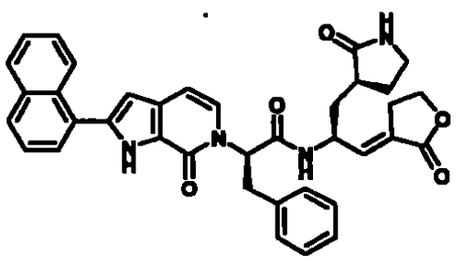


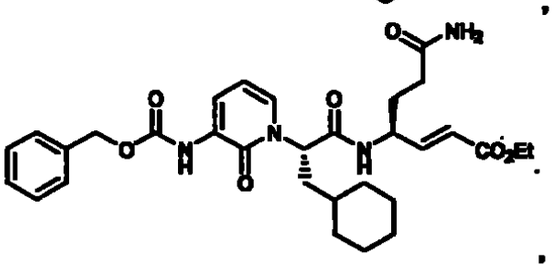
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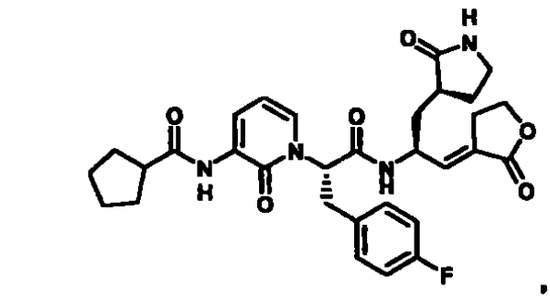


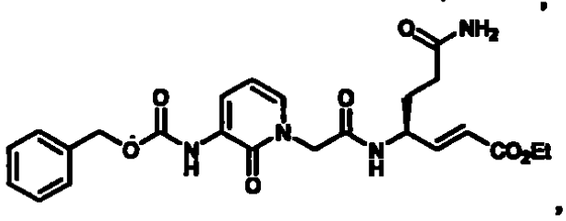


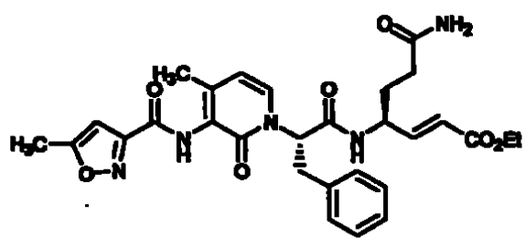


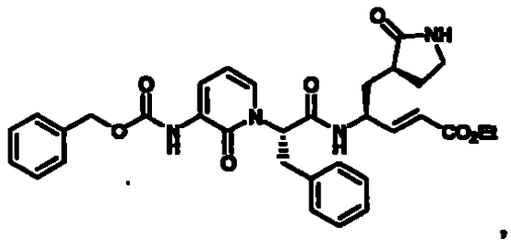
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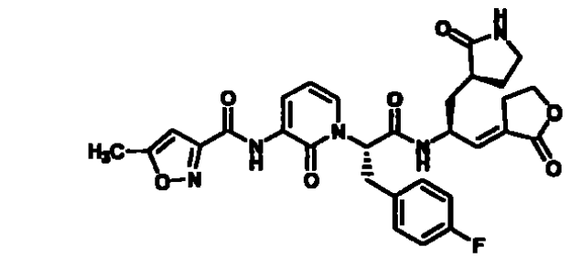


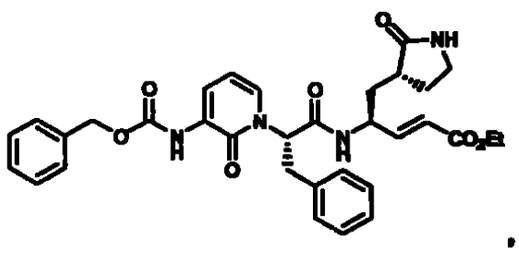


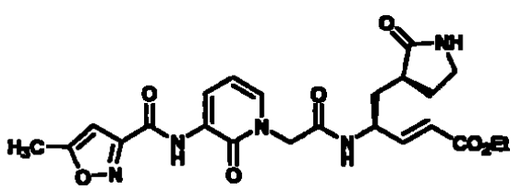


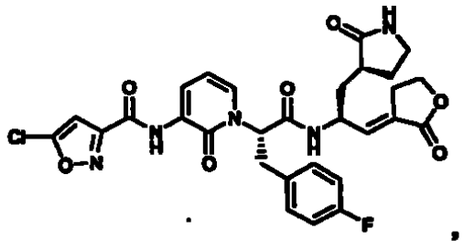
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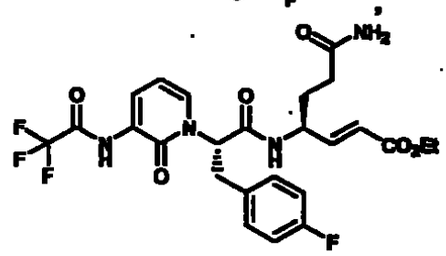
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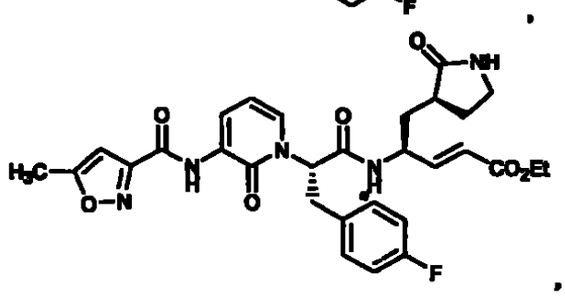


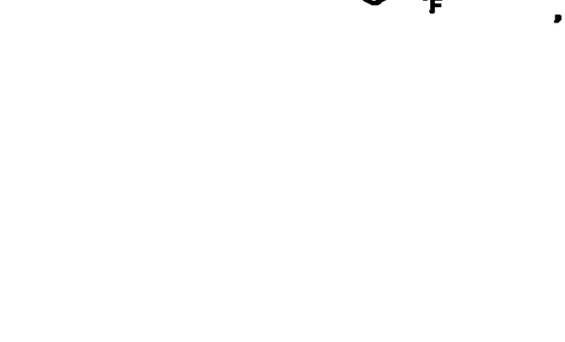






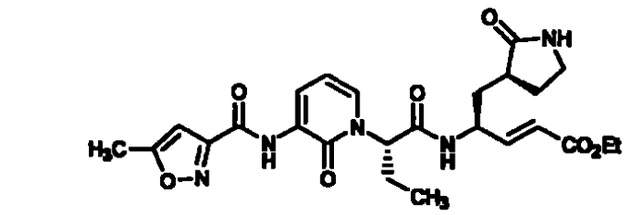


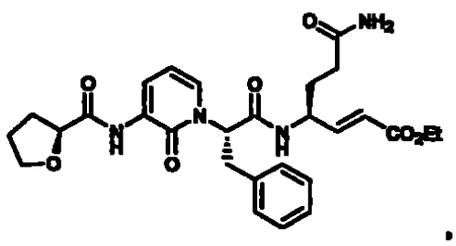


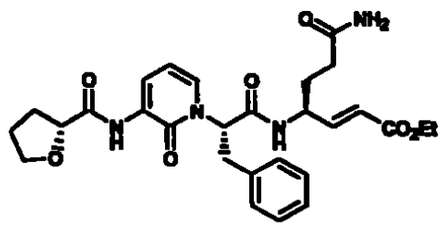


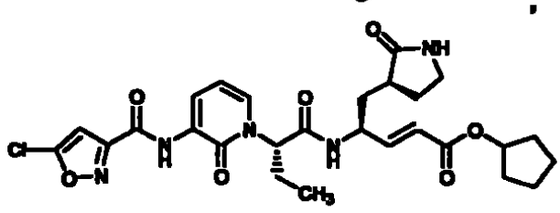
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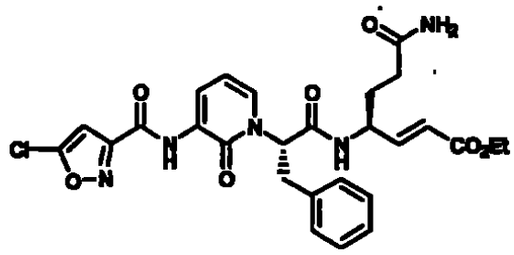
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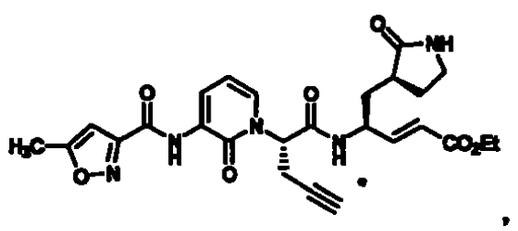






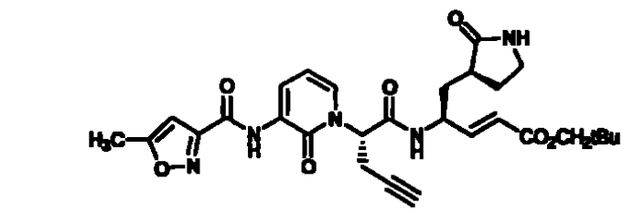


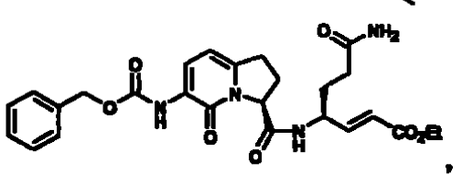


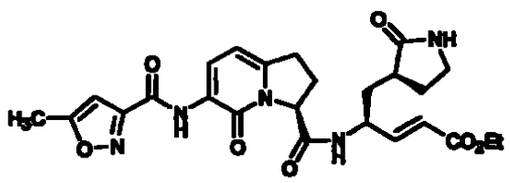


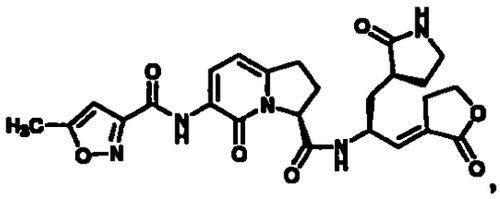
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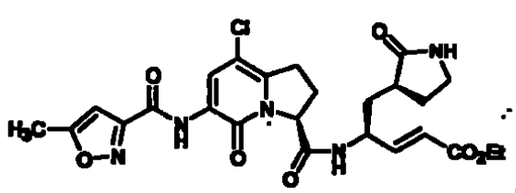
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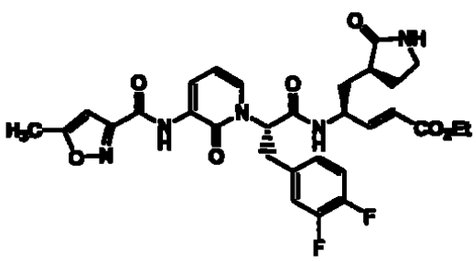




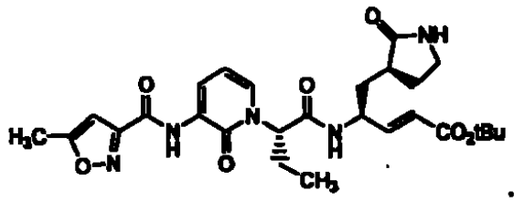




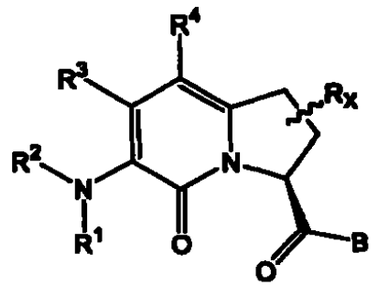




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and 

The invention is also directed to the intermediates of Formula II, which are useful in the synthesis of certain compounds of Formula I:



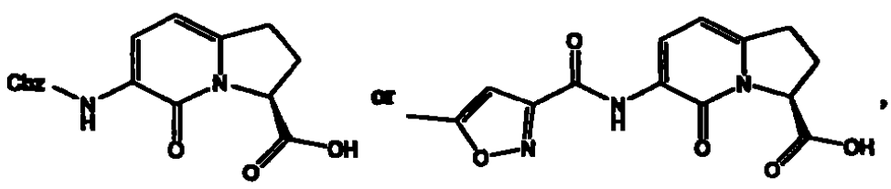
II

wherein the variables R^1, R^2, R^3, R^4 and R_X are as defined above, and B is H, $-OR^{24}$. When R^1 and/or R^2 are independently suitable nitrogen protecting groups, any suitable nitrogen-protecting group known in the art may be used (see, e.g., Greene & Wuts, *supra*). Suitable R^1 and R^2 substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc) and aryloxycarbonyl (e.g., Cbz or FMOC), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl) and the like. Preferably, when R^1 and R^2 are independently suitable nitrogen protecting groups, suitable R^1 and R^2 substituents include, but are not limited to, Boc, Cbz, FMOC, methyloxycarbonyl and trityl. When R^1 and R^2 taken together are a suitable nitrogen protecting group, suitable R^1/R^2 substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene). R^{24} may be H or a suitable protecting group for a carboxyl moiety. Suitable carboxyl protecting groups are

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also well known in the art, examples of which may be found in Greene and Wuts, *supra*, and include, but are not limited to, protecting groups where R^{24} is alkyl, substituted or unsubstituted aryl, alkyl and/or aryl substituted silyl (e.g., t-butyldimethylsilyl (TBS)), and the like.

The invention is also directed to pharmaceutically acceptable salts of the compounds of Formula II. Preferred examples of the Formula II useful as intermediates include the following:



and pharmaceutically acceptable salts thereof.

The antipicornaviral compounds of this invention include prodrugs, the pharmaceutically active metabolites, and the pharmaceutically acceptable salts and solvates thereof. In preferred embodiments, the compounds of Formula I, prodrugs, pharmaceutically acceptable salts, and pharmaceutically active metabolites and solvates thereof have an 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.

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 compound produced through metabolism in the body of a specified compound. A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of a 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. 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. 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 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, including, but not limited to human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, meningitis virus, and hepatitis A virus. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for

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example, as a prophylactic. 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 generally 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.

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 or mode of administration. In preferred embodiments, the inventive pharmaceutical compositions are delivered orally, or intranasally in the form of suspensions. Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions 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

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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 agent 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.

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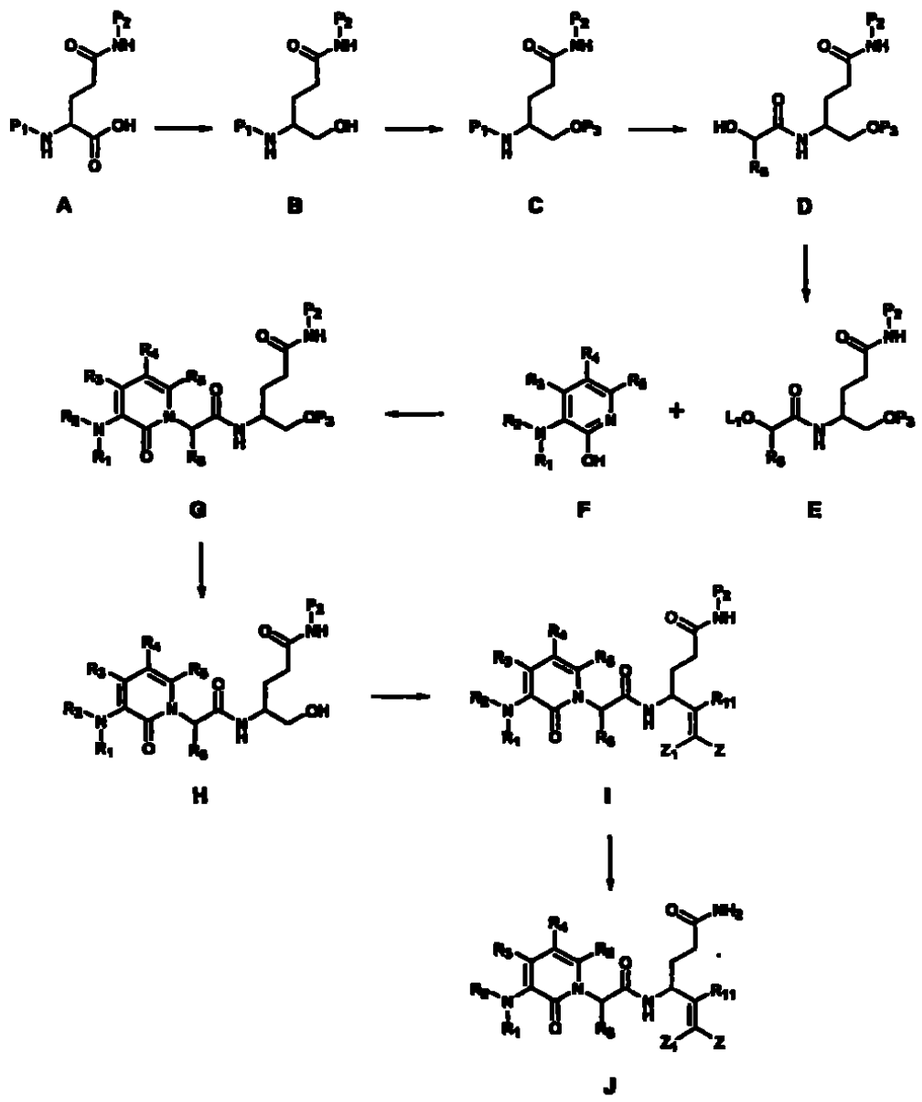
GENERAL SYNTHETIC METHODS

Preferably, the inventive compounds of Formulas I and II are prepared by the methods of the present invention, including the General Methods shown below. When stereochemistry is not specified in chemical structures, either stereocenter may be utilized.

Although several intermediates are described and depicted as 2-hydroxypyridines, it is understood that such entities may also exist as the corresponding 2-pyridone tautomers. The following abbreviations also apply: Boc (*tert*-butoxycarbonyl), Ac (acetyl), Cbz (benzyloxycarbonyl), DMB (2,4-dimethoxybenzyl), TBS (*tert*-butyldimethylsilyl), TBDPS (*tert*-butyldiphenylsilyl), Ms (methanesulfonate), Ts (toluenesulfonate), Bn (benzyl), and Tr (triphenylmethyl).

General Method 1

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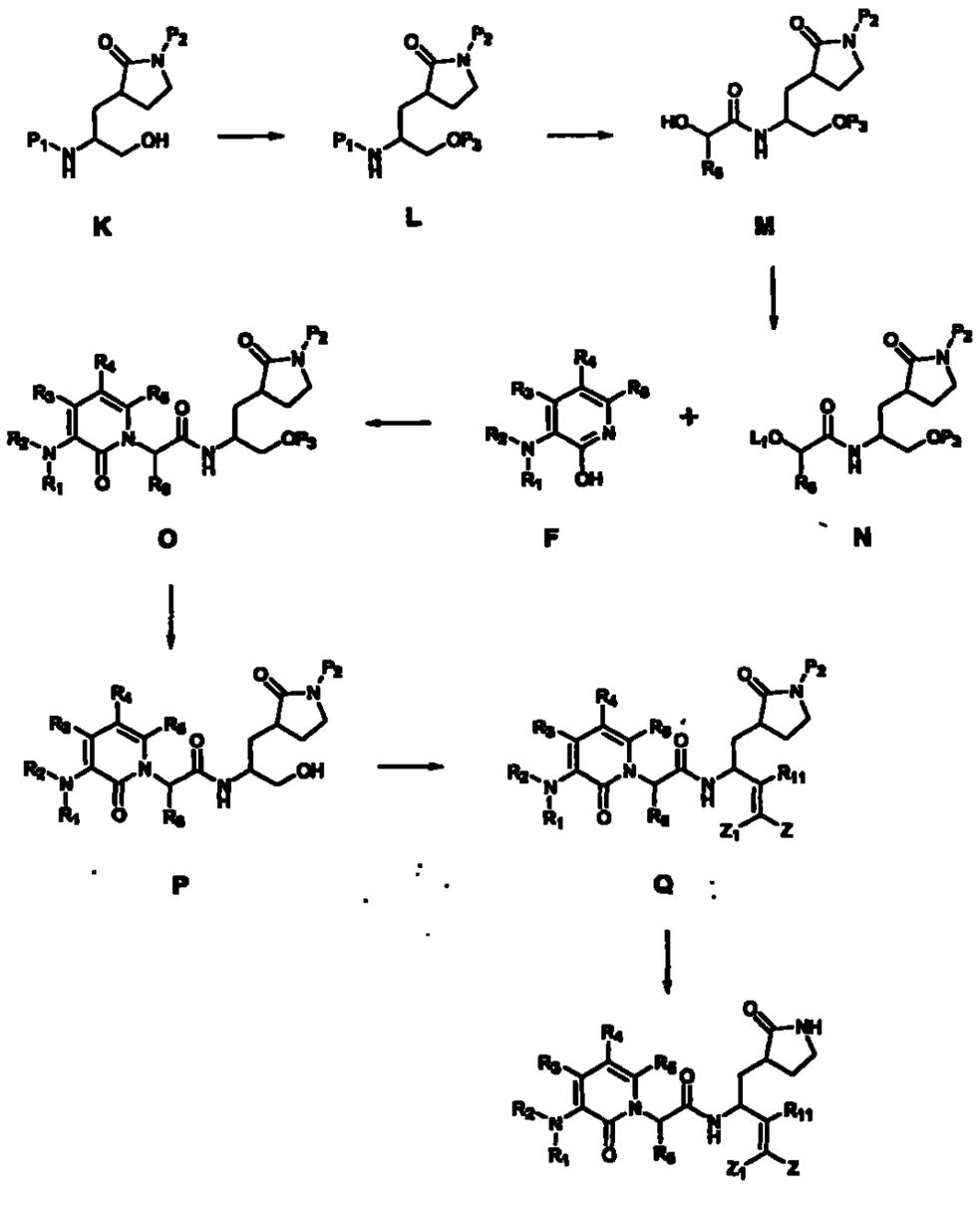


In General Method 1, an amino acid A (commercially available or prepared by methods described in the chemical literature) where P_1 is an appropriate protecting group for the amine functionality (e.g, Cbz, Boc, or Ac), and P_2 is an appropriate protecting group for the amide nitrogen (e.g, Tr), is reductively transformed into alcohol B. Compound B is subsequently converted to compound C where P_3 is an appropriate protecting group for the alcohol functionality (e.g., TBS). At this point, the P_1 protecting group present in C is removed and the resulting amine or salt thereof (not shown) is subjected to an amide bond

forming reaction with an appropriate α-hydroxycarboxylic acid (which incorporates R_6 and in which R_7 is H; also not shown) to provide intermediate D. The alcohol functionality present in D is then converted to an appropriate leaving group (e.g., mesylate, tosylate) E and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate G. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting groups for the amine functionality. The P_3 protecting group is subsequently removed from G and the resulting alcohol (H) is oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to afford intermediate I (which incorporates R_{11}, Z, and Z_1). The P_2 protecting group present in I is then removed to give product J. If R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates G, H, or I or product J and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates G, H, or I or products J.

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General Method 2

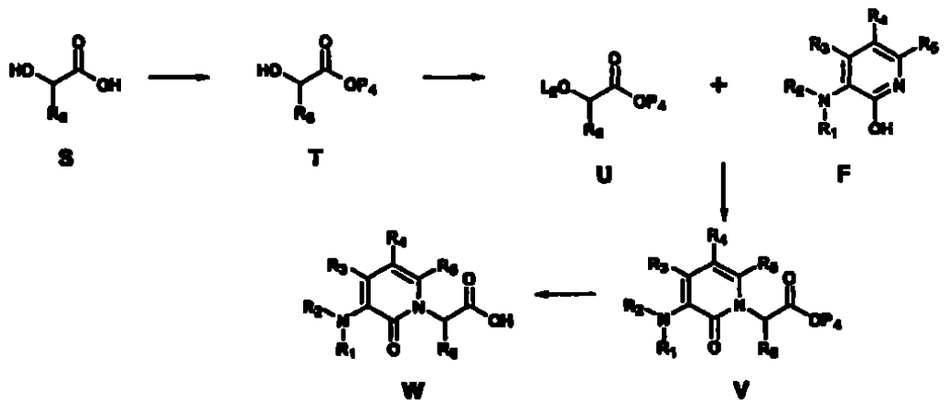


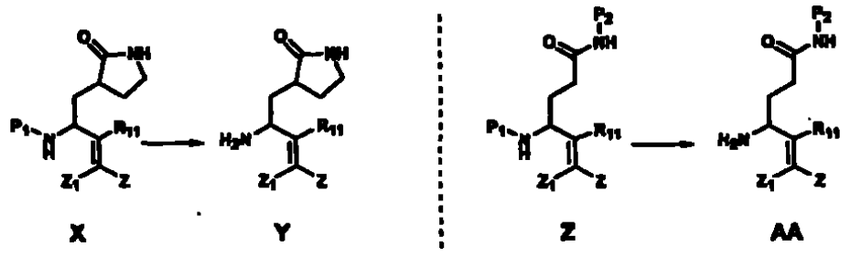
In General Method 2, amino alcohol K (prepared by methods described in the chemical literature), which incorporates R_9 and in which R_{10} is H, P_1 is an appropriate protecting group for amine functionality (e.g, Cbz, Boc, or Ac), and P_2 is an appropriate protecting group for the amide nitrogen (e.g, DMB), is converted to compound L where P_3 is

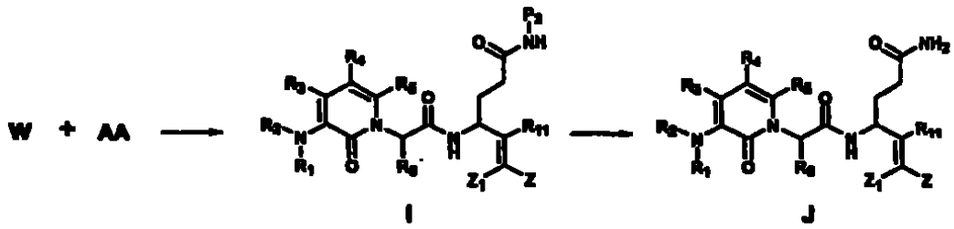
an appropriate protecting group for the alcohol functionality (e.g., TBDPS). The P_1 protecting group present in L is then removed and the resulting amine or salt thereof (not shown) is subjected to an amide bond forming reaction with an appropriate α-hydroxycarboxylic acid (which incorporates R_6 and in which R_7 is H; also not shown) to provide intermediate M. The alcohol functionality present in M is then converted to an appropriate leaving group (e.g., mesylate, tosylate) N and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate O. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting group for the amine functionality. The P_3 protecting group is subsequently removed from O and the resulting alcohol (P) is oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to afford intermediate Q (which incorporates R_{11}, Z, and Z_1). The P_2 protecting group present in Q is then removed to give product R. If R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates O, P, or Q or product R and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates O, P, or Q or products R.

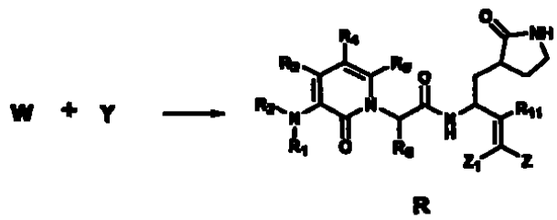
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General Method 3









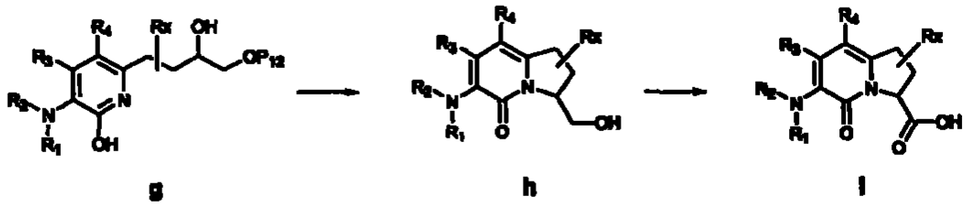
An alternate method for preparing either product J or product R is illustrated in General Method 3. An α-hydroxycarboxylic acid S (either commercially available or

prepared by methods described in the chemical literature) which incorporates R_6 and in which R_7 is H is converted to α-hydroxyester T where P_4 is an appropriate protecting group for the carboxylic acid functional group (e.g, methyl, benzyl, or *tert*-butyl). The alcohol functionality present in T is then converted to an appropriate leaving group (e.g., mesylate, tosylate, triflate) U and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate V. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting group for the amine functionality. The P_4 protecting group is subsequently removed from V to afford carboxylic acid W. Independently, intermediates X and Z (prepared by methods described in the chemical literature) which incorporate R_{11}, Z, and Z_1 and in which P_1 is an appropriate protecting group for the amine functionality (e.g., Cbz, Boc, or Ac) and P_2 is an appropriate protecting group for the amide nitrogen (e.g., Tr), are converted to their corresponding amines Y and AA (or salts thereof), respectively. Amines AA and Y are then independently coupled with carboxylic acid W to afford intermediate I and product R, respectively. The P_2 protecting group present in intermediate I is subsequently removed to afford product J. Note that, although not depicted in General Method 3, the lactam nitrogen present in intermediate X may be protected with a suitable protecting group (e.g., DMB). If such a moiety is present in X, it may be removed after coupling of W with Y to afford product R.

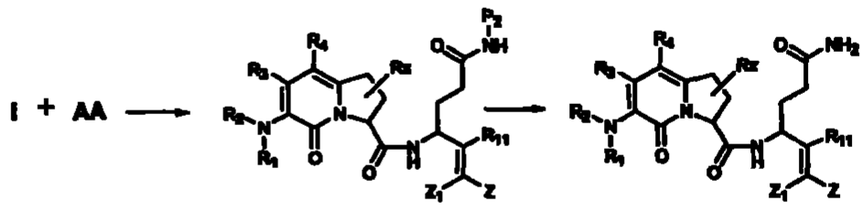
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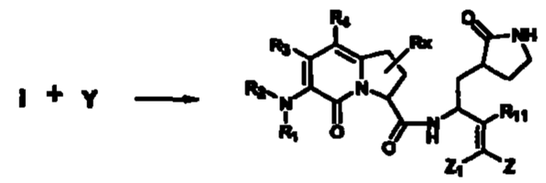
General Method 4



g h i



j k



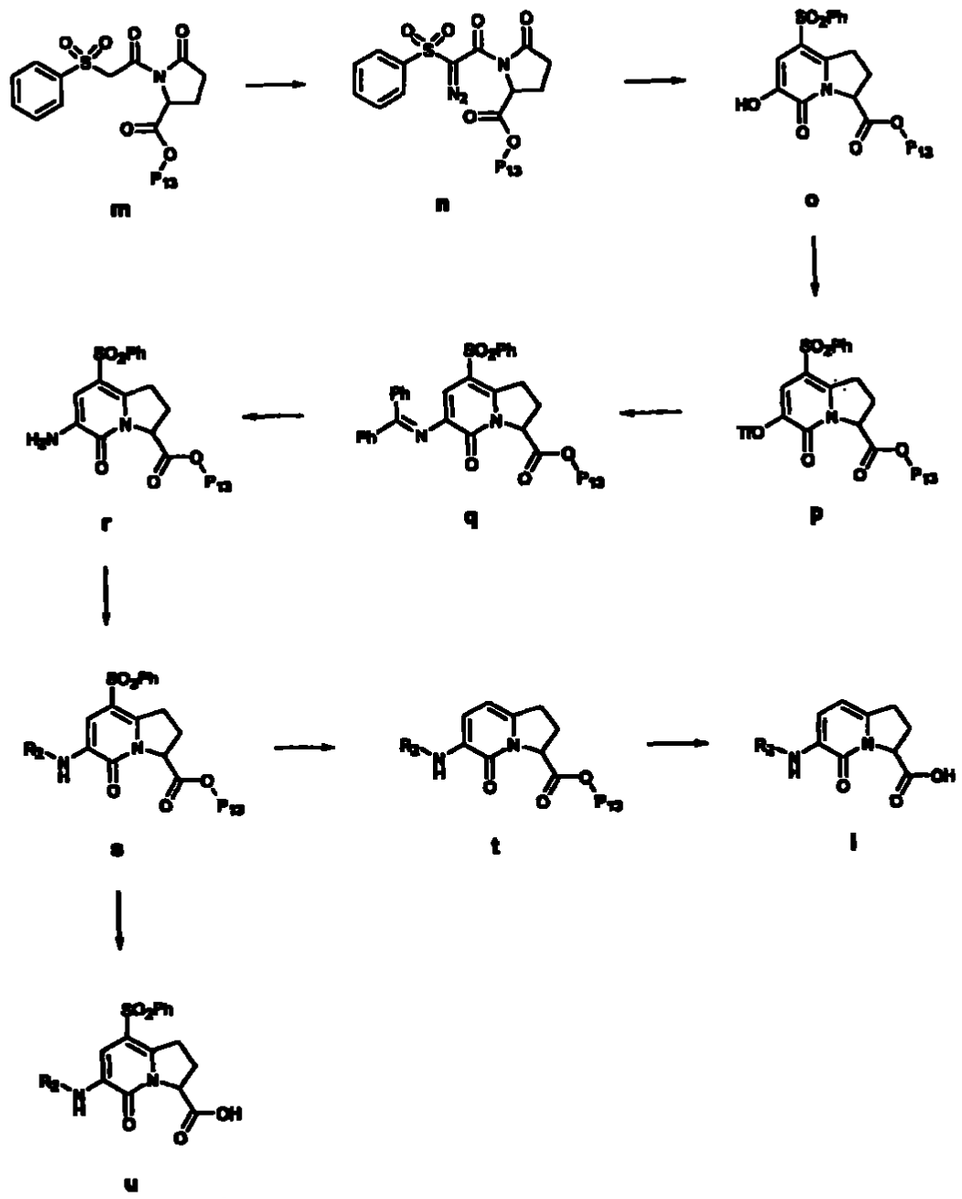
l

A method for preparing bicyclic products k and l is illustrated in General Method 4. Thus, an appropriate pyridine g (which incorporates R_1, R_2, R_3, and R_4, and which may be optionally substituted with R_x as shown) (an example of which may prepared as described in Specific Method 7 below) in which P_{11} and P_{12} are protecting groups for the alcohol functionality (e.g., silyl ether, methyl) is subjected to an intramolecular cyclization/deprotection protocol in which both P_{11} and P_{12} are removed to give pyridone h. Note that the R_1 and R_2 moieties present in g may be an appropriate protecting group for the amine functionality (e.g., Cbz). The alcohol moiety present in h is then oxidized to the corresponding carboxylic acid i. This oxidation may be accomplished via an aldehyde intermediate (not shown). Carboxylic acid i is then independently coupled with amines AA and Y (or salts thereof) (prepared as described in General Method 3 above) to afford

intermediate j and product l, respectively. The P_2 protecting group present in intermediate j is subsequently removed to afford product k. Note that, although not depicted in General Method 4, the lactam nitrogen present in intermediate Y may be protected with a suitable protecting group (e.g., DMB). If such a moiety is present in Y, it may be removed after coupling of i with Y to afford product l. In addition, if R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates g, h, i, or j or products k or l and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates g, h, i, or j or products k or l.

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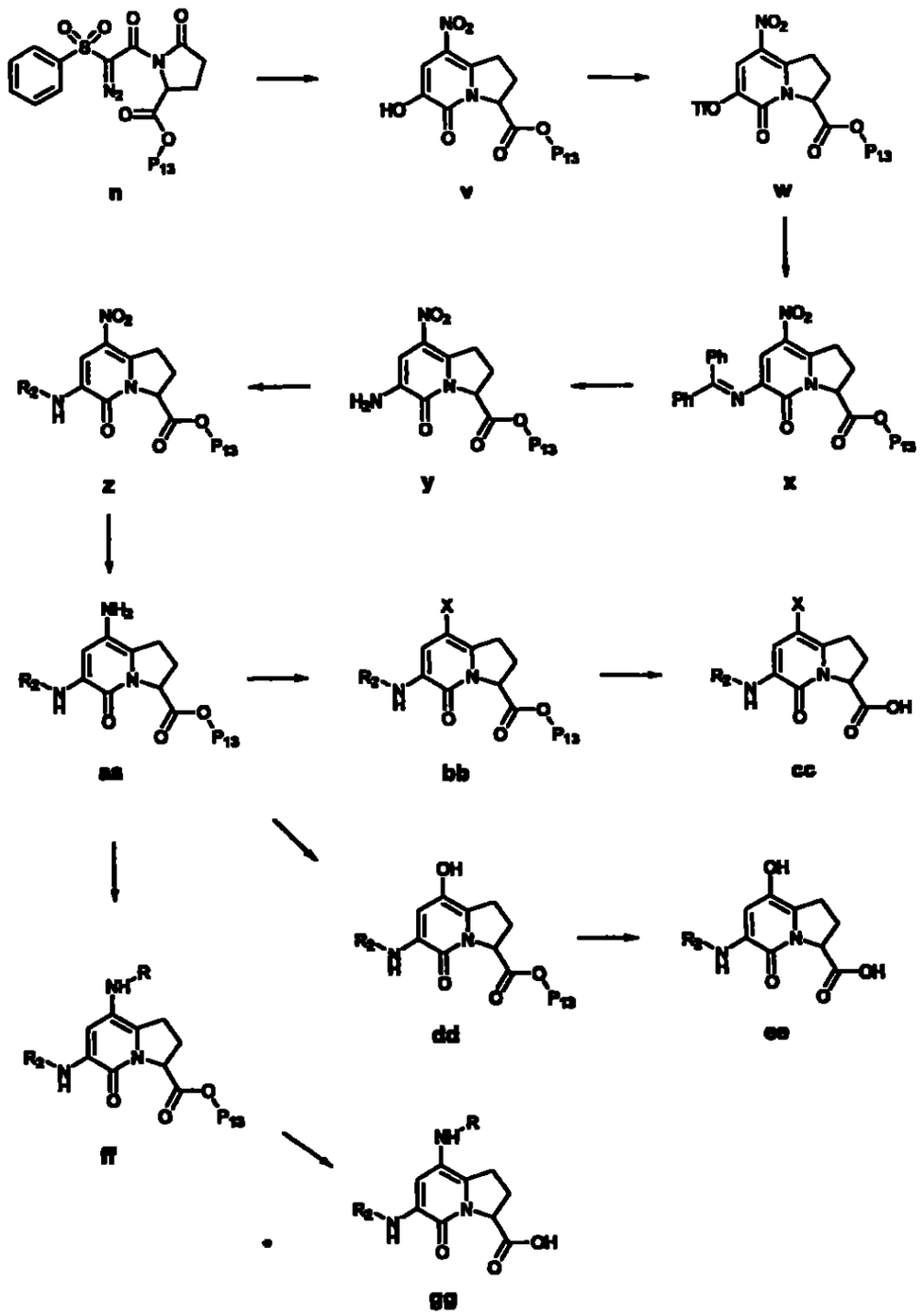
General Method 5



An alternate method for preparing a particular type of intermediate i is illustrated in General Method 5. Thus, the sulfone m (which may be prepared by the method described in *Org. Lett.* 1999, *1*, 83) in which R_X is/are H and P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is transformed

into diazo compound n. This intermediate is subjected to a rhodium-catalyzed cyclization reaction involving phenylvinyl sulfone to give intermediate o (in which R_3 is H). The hydroxyl group present in o is converted to the corresponding trifluoromethane sulfonate (OTf) p, and this intermediate is further transformed to the amine r via imnine q. The amine present in r is derivatized with an appropriate moiety to afford intermediate s (which contains the R_2 functional group and in which R_1 is H). Intermediate s is subjected to a desulfurization reaction to give intermediate t and this entity is deprotected to give carboxylic acid i (in which R_1, R_3, R_4, and R_x are H). Alternatively, intermediate s may be deprotected to give carboxylic acid u (in which R_1, R_3, and R_x are H) which may be utilized in place of i in General Method 4 above.

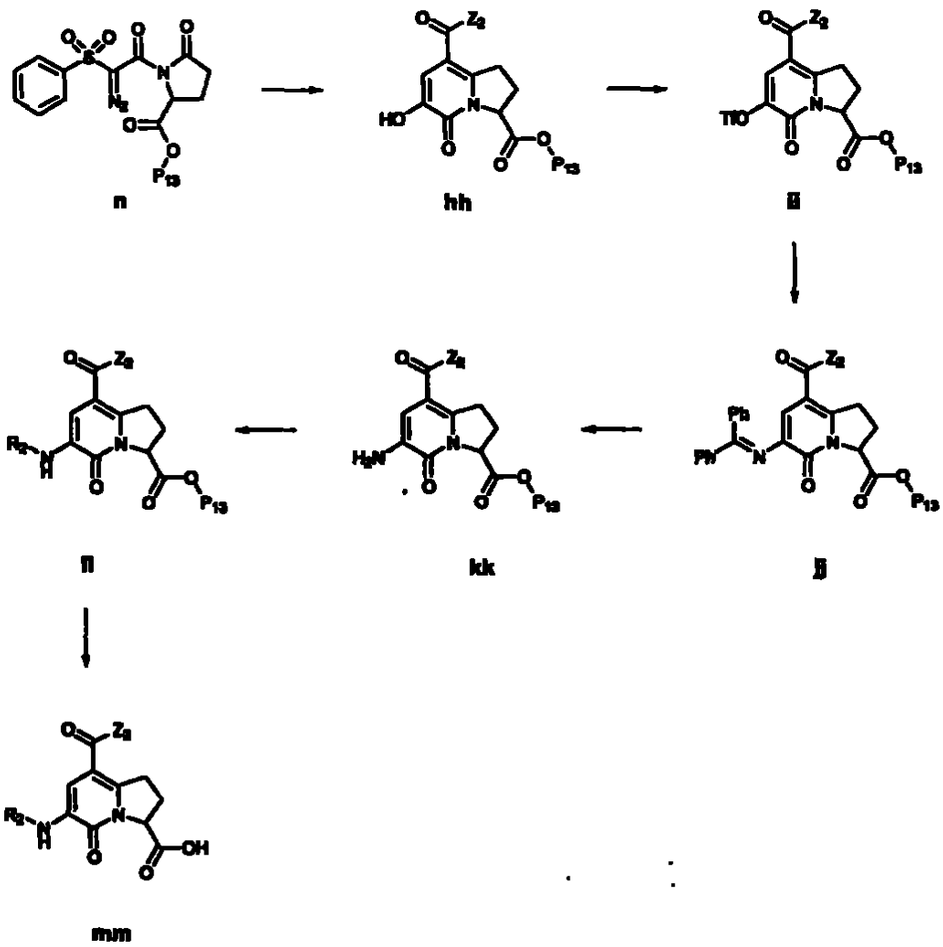
General Method 6



An additional method for preparing intermediates related to i is illustrated in General Method 6. Thus, the diazo compound n (prepared in General Method 5 above) in which R_x is/are H and in which P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is subjected to a rhodium-catalyzed cyclization reaction involving nitroethylene to give intermediate v (in which R_3 is H). The hydroxyl group present in v is converted to the corresponding trifluoromethane sulfonate (OTf) w, and this intermediate is further transformed to the amine y via immine x. The amine present in y is derivatized with an appropriate moiety to afford intermediate z (which contains the R_2 functional group and in which R_1 is H). Intermediate z is reduced to give intermediate aa and this entity is transformed to intermediate bb in which X is a halogen. Intermediate bb is subsequently deprotected to give carboxylic acid cc. If desired, intermediate aa may also be transformed into intermediate t (General Method 5 above). Alternatively, intermediate aa is transformed to intermediate dd which is subsequently deprotected to give carboxylic acid ee. Alternatively, intermediate aa is transformed to intermediate ff in which R is alkyl, acyl, sulfonyl, or acyloxy. Intermediate ff is subsequently deprotected to give carboxylic acid gg. Carboxylic acids cc, ee, and gg may each be utilized in place of i in General Method 4 above.

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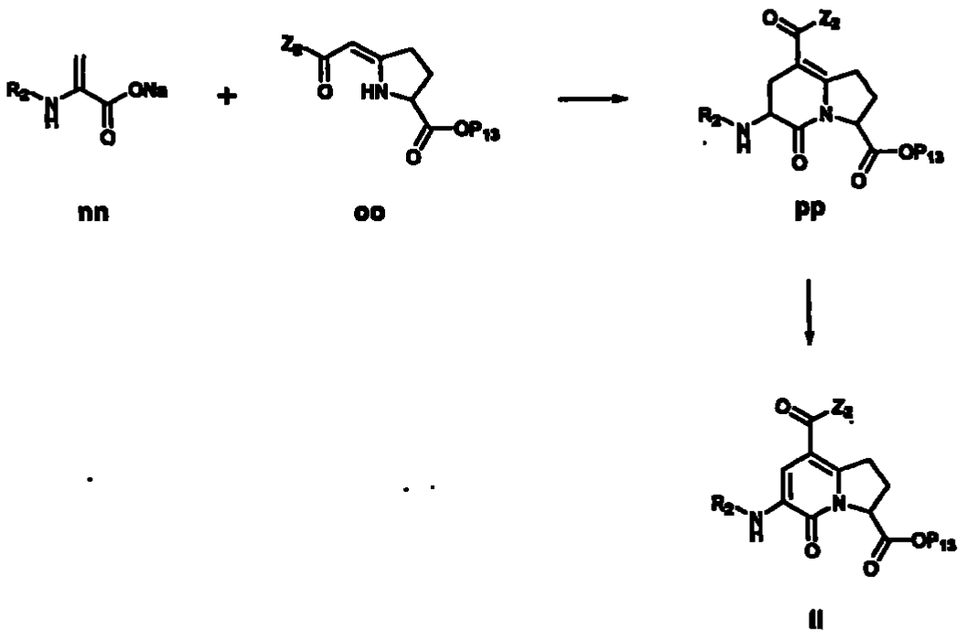
General Method 7



An additional method for preparing intermediates related to i is illustrated in General Method 7. Thus, the diazo compound n (prepared in General Method 5 above) in which R_X is/are H and in which P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is subjected to a rhodium-catalyzed cyclization reaction involving acrylate esters or vinyl ketones to give intermediate hh (in which R_3 is H and Z_2 is alkyl, aryl, alkoxy, and benzyloxy). The hydroxyl group present in hh is converted to the corresponding trifluoromethane sulfonate (OTf) ii, and this intermediate is further transformed to the amine kk via immine jj. The amine present in kk is derivatized with an appropriate moiety to afford intermediate ll (which

contains the R_2 functional group and in which R_1 is H). Intermediate ll is subsequently deprotected to give carboxylic acid mm which may be utilized in place of i in General Method 4 above. At any point in the above sequence, if Z_2 is alkoxy or benzyloxy it may be replaced with a hydroxyl functionality. The resulting carboxylic acid may subsequently be rearranged to the corresponding amine using established methods and the amine-containing intermediates may be utilized as depicted in General Method 6. For example, intermediate ll (when Z_2 is OH) may be rearranged to intermediate aa (General Method 6).

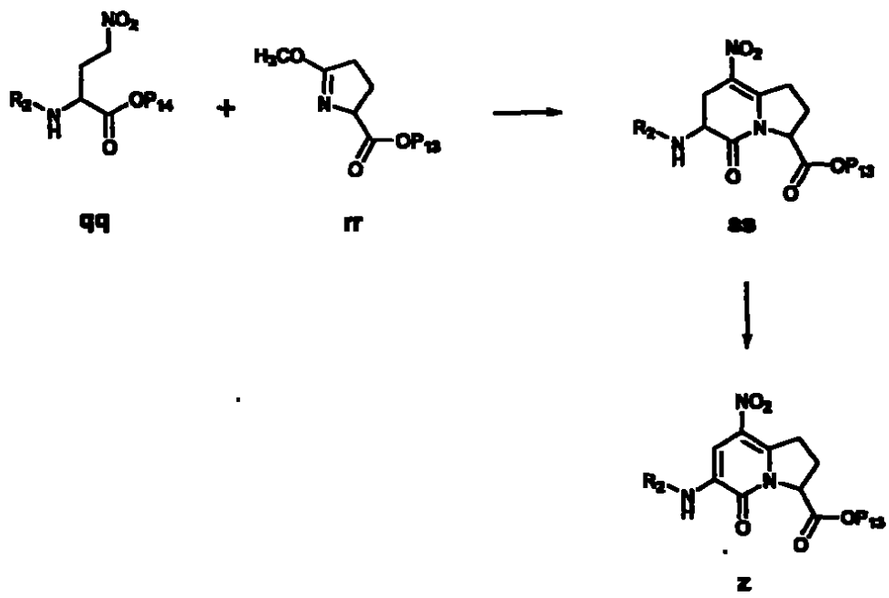
General Method 8



Yet another method for preparing intermediate ll is depicted in General Method 8. Thus the sodium salt of α-dehydroalanine derivative nn (which incorporates R_2 and in which R_1 is H) (which is either commercially available or may be prepared from serine by a variety of literature techniques) is condensed with intermediate oo (which may be prepared as described in *Tetrahedron Lett.* 1989, *30*, 3621) in which R_x is/are H and P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) and in which Z_2 is alkyl, aryl, alkoxy, or benzyloxy to give intermediate pp.

Intermediate pp is subsequently oxidized (by a variety of literature methods) to afford intermediate ll which may be utilized as described above in General Method 7.

General Method 9



An alternate method for preparing intermediate z (from General Method 6 above) is depicted in General Method 9. Thus the nitro compound qq (prepared by analogy with the method described in: *J. Chem. Soc., Perkin Trans. 1* 1998, 1113) which incorporates R_2 and in which R_1 is H and P_{14} is a suitable protecting group for the carboxylic acid functionality (e.g., methyl or ethyl) is condensed with intermediate rr (prepared according to: *J. Heterocyclic Chem.* 1992, *29*, 1285) in which R_x is/are H and P_{13} is a suitable protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl) to give intermediate ss. Intermediate ss is subsequently oxidized (by a variety of literature methods) to afford intermediate z which may be utilized as described above in General Method 6.

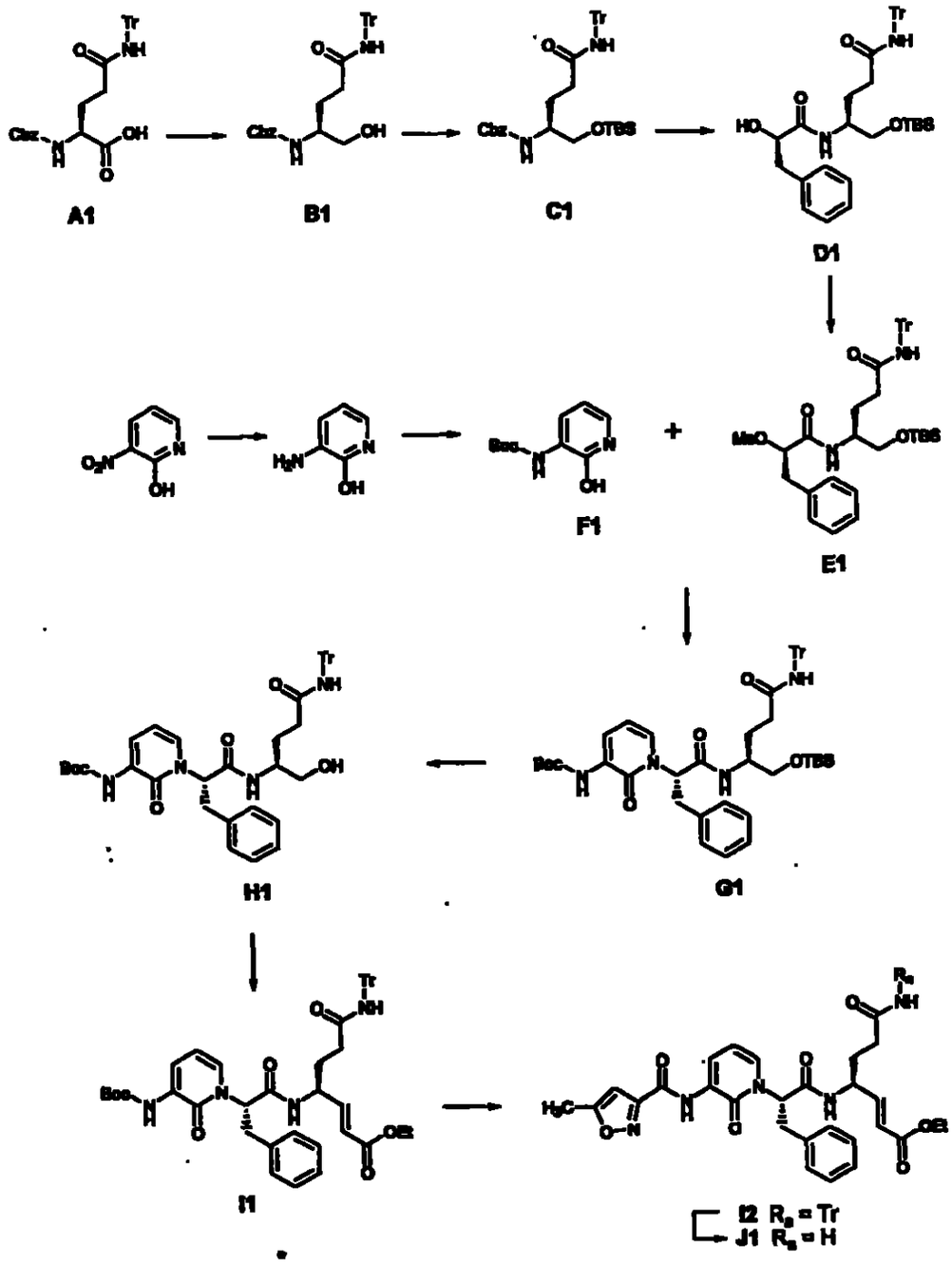
SPECIFIC METHODS

The following Specific Methods may also be utilized to prepare some of the compounds described in this invention.

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Specific Method 1

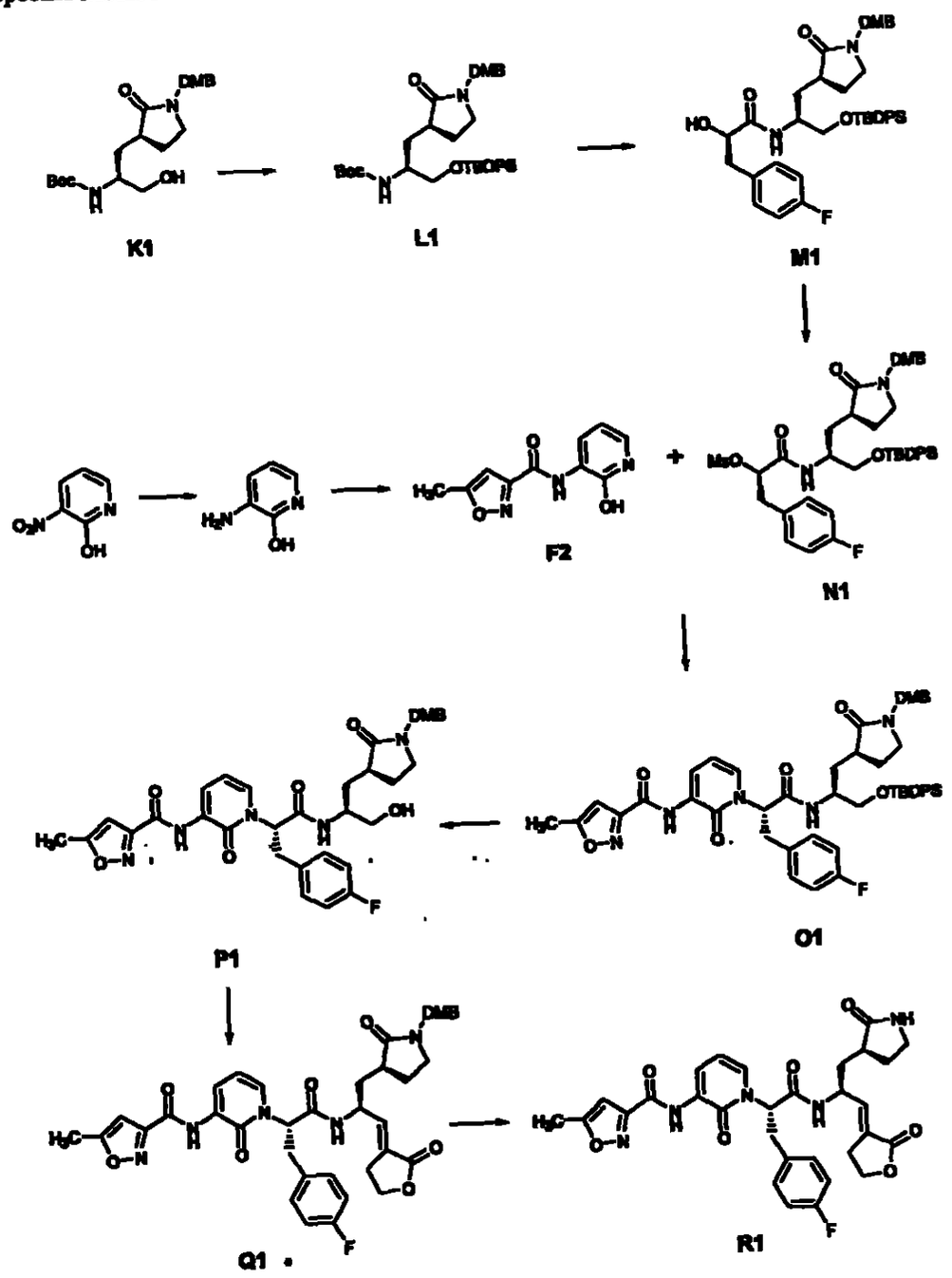


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Specific Method 1 describes the preparation of specific compound J1 (compound 5). Thus, commercially available amino acid A1 was reduced to alcohol B1 which, in turn, was transformed into compound C1. The Cbz moiety present in C1 was removed by hydrogenation and the resulting amine (not shown) was coupled with D-3-phenyllactic acid (commercially available) to afford intermediate D1. This latter entity was subsequently transformed to the corresponding methanesulfonate (mesylate) (E1) and was coupled with the sodium salt of 2-hydroxypyridine F1 to provide intermediate G1. The 2-hydroxypyridine F1 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent Boc protection of the resulting amine. The silyl protecting group present in G1 was removed and the alcohol thus obtained (H1) was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate I1. The Boc moiety contained in I1 was then thermally deprotected and the resulting amine (not shown) was derivatized with commercially available 5-methylisoxazole-3-carbonyl chloride to give intermediate I2. The trityl protecting group present in I2 was subsequently removed under acidic conditions to complete the preparation of specific compound J1 (compound 5).

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Specific Method 2

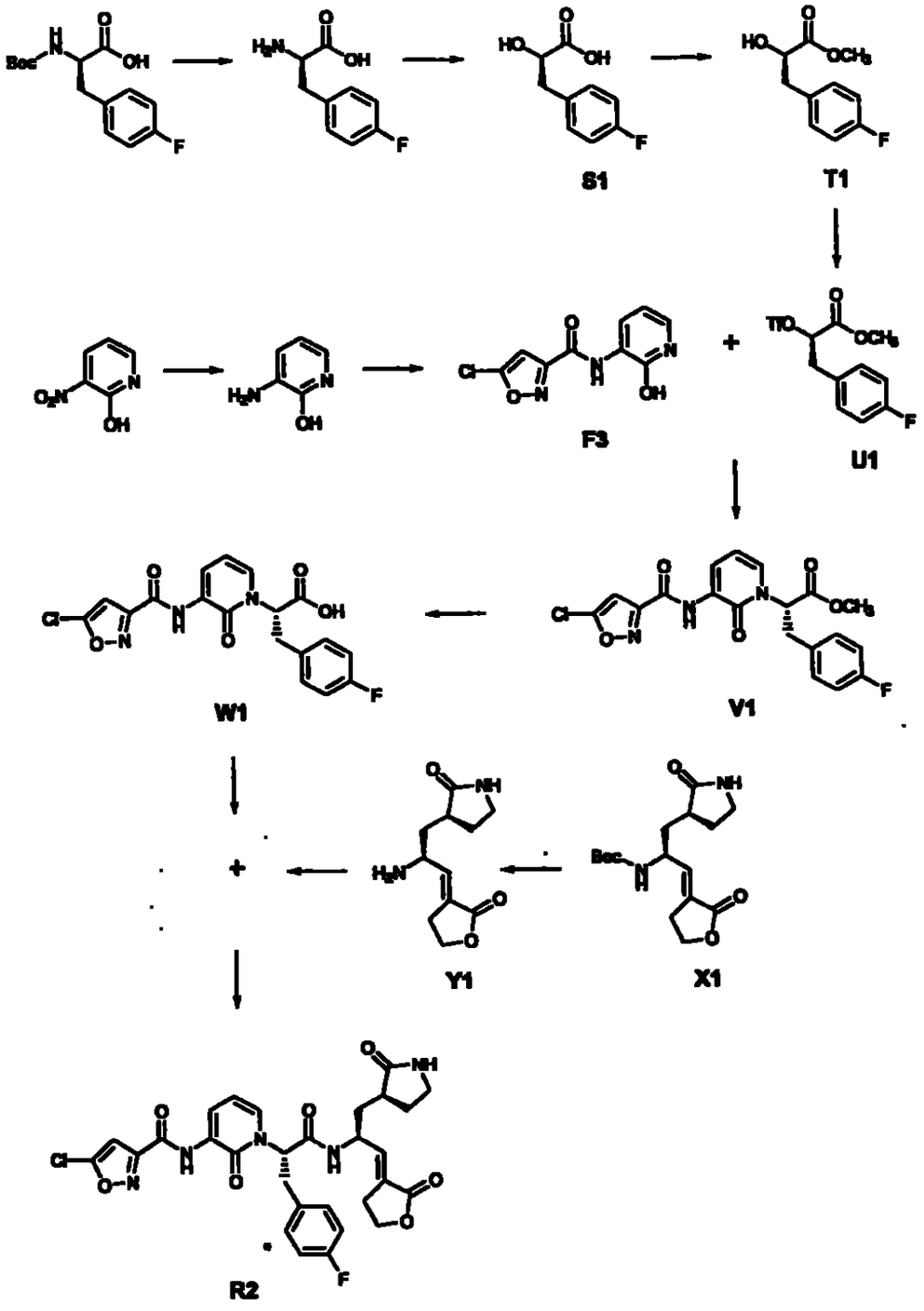


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Specific Method 2 describes the preparation of specific compound R1 (compound 20). Thus, alcohol K1 (prepared as described in Dragovich, et al., *J. Med Chem.* 1999, *42*, 1213) was protected to give intermediate L1. The Boc protecting group present in L1 was removed under acidic conditions and the resulting amine salt (not shown) was coupled with (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1, prepared as described in Specific Method 3 below) to afford intermediate M1. This latter entity was subsequently transformed to the corresponding methanesulfonate (mesylate) (N1) and was coupled with the sodium salt of 2-hydroxypyridine F2 to provide intermediate O1. The 2-hydroxypyridine F2 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with commercially available 5-methylisoxazole-3-carbonyl chloride. The silyl protecting group present in O1 was removed and the alcohol thus obtained (P1) was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate Q1. The DMB moiety contained in Q1 was then deprotected to complete the preparation of specific compound R1 (compound 20).

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Specific Method 3

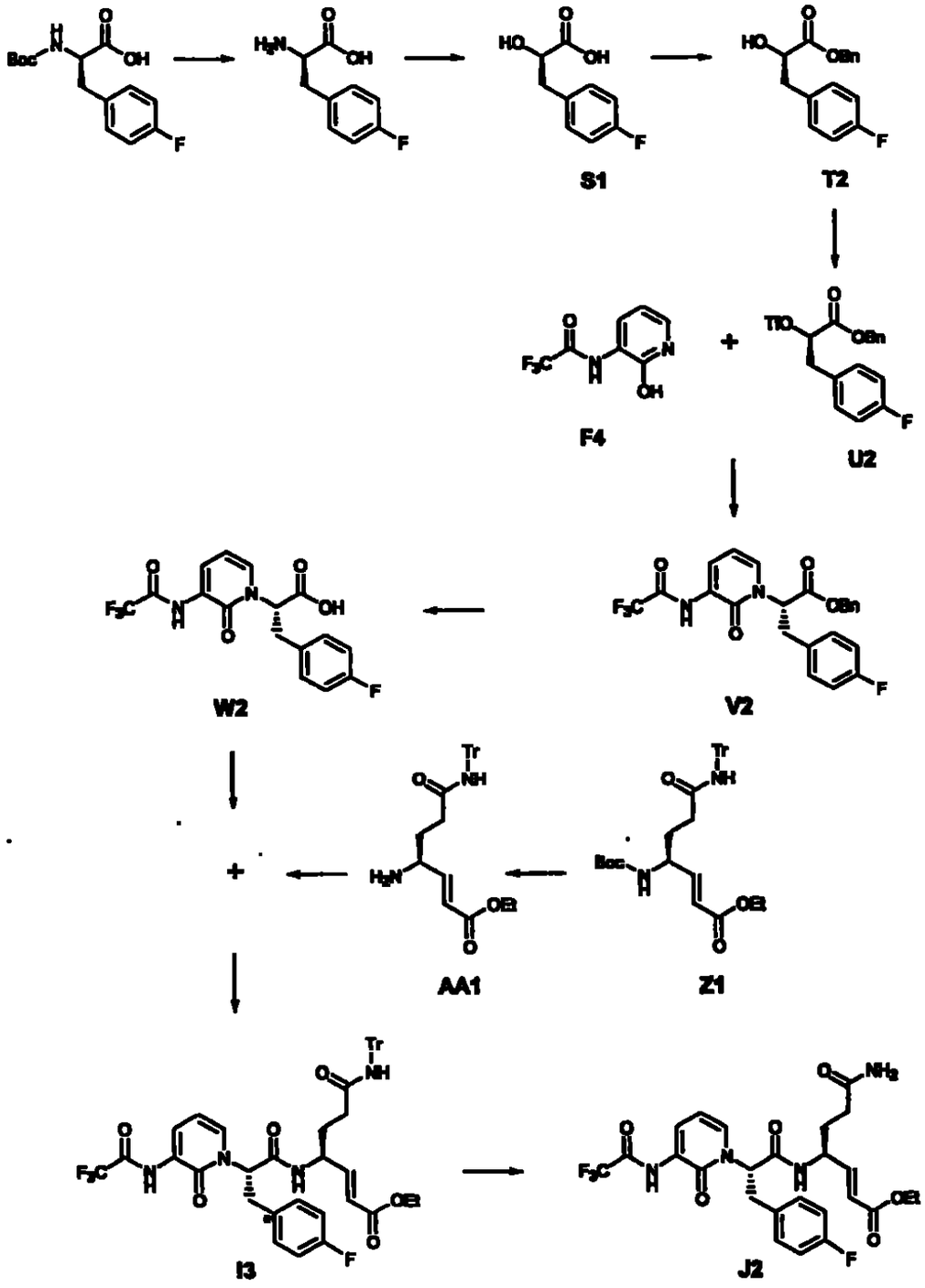


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Specific Method 3 describes the preparation of specific compound R2 (compound 23). Thus, commercially available Boc-D-(4-F)Phe-OH was deprotected under acidic conditions and the resulting amine salt was subjected to a diazotization/displacement protocol to provide (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1). This material was subsequently transformed into the corresponding trifluoromethane sulfonate (triflate) U1 via the methyl ester T1 and was coupled with the sodium salt of 2-hydroxypyridine F3 to provide intermediate V1. The 2-hydroxypyridine F3 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with 5-chloroisoxazole-3-carbonyl chloride (prepared as described in the Experimental Section of this work). The methyl ester present in V1 was subsequently hydrolyzed under basic conditions and the resulting carboxylic acid (W1) was coupled with amine Y1 (or salt thereof) to complete the preparation of specific compound R2 (compound 23). Amine Y1 (or salt thereof) was prepared by deprotection of intermediate X1 (prepared in a manner analogous to that described in Baldwin et al., *J. Org. Chem.* 1971, *36*, 1441).

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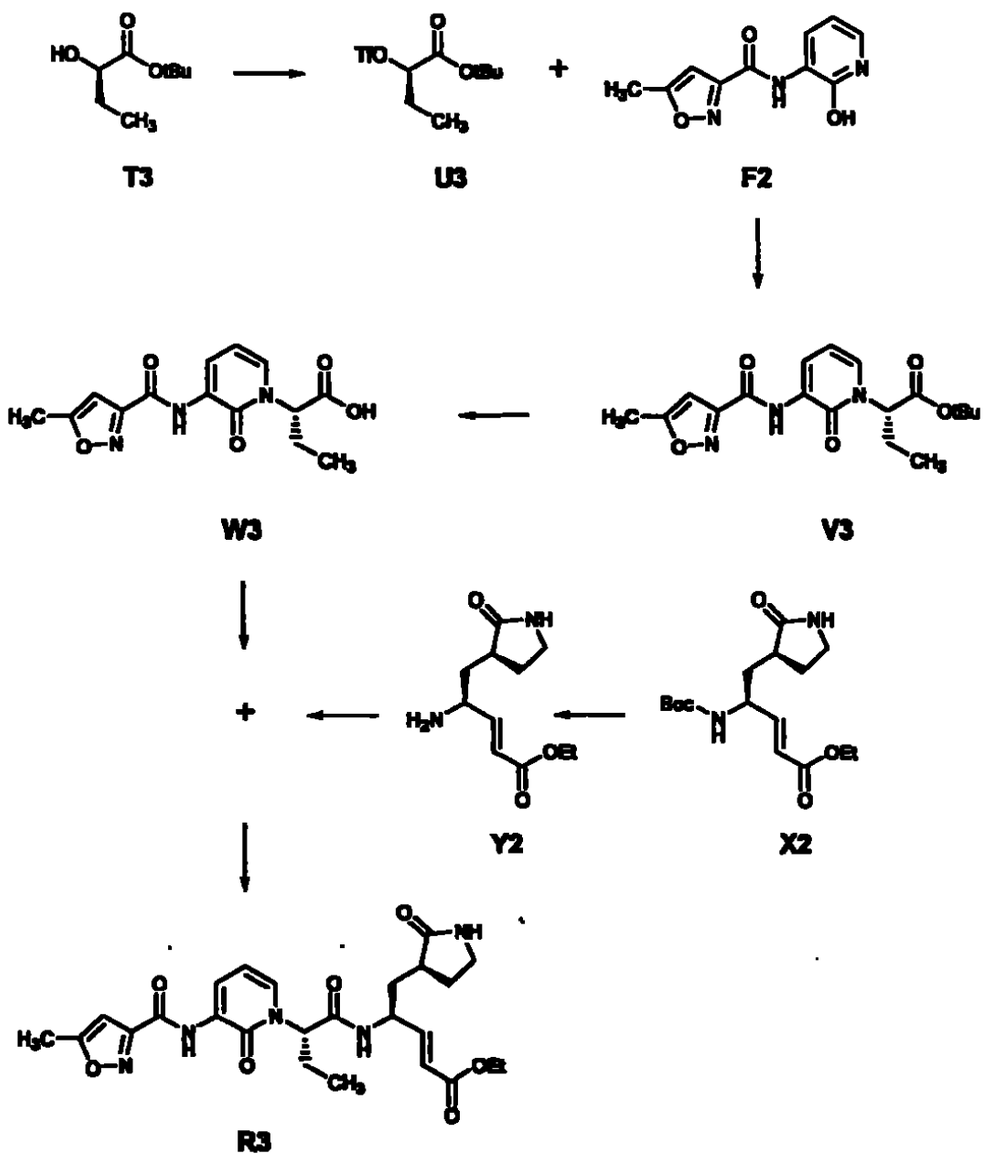
Specific Method 4



Specific Method 4 describes the preparation of specific compound J2 (compound 24). Thus, (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1, prepared as described above in Specific Method 3) was transformed into the corresponding trifluoromethane sulfonate (triflate) U2 via the benzyl ester T2 and was coupled with the sodium salt of 2-hydroxypyridine F4 to provide intermediate V2. The 2-hydroxypyridine F4 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with trifluoroacetic anhydride. The benzyl ester present in V2 was subsequently removed by hydrogenation and the resulting carboxylic acid (W2) was coupled with amine AA1 (or salt thereof) to give intermediate I3. The trityl protecting group present in I3 was then removed under acidic conditions to complete the preparation of specific compound J2 (compound 24). Amine AA1 (or salt thereof) was prepared by deprotection of intermediate Z1 (prepared as described in Dragovich, et al. *J. Med. Chem.* 1998, *41*, 2806).

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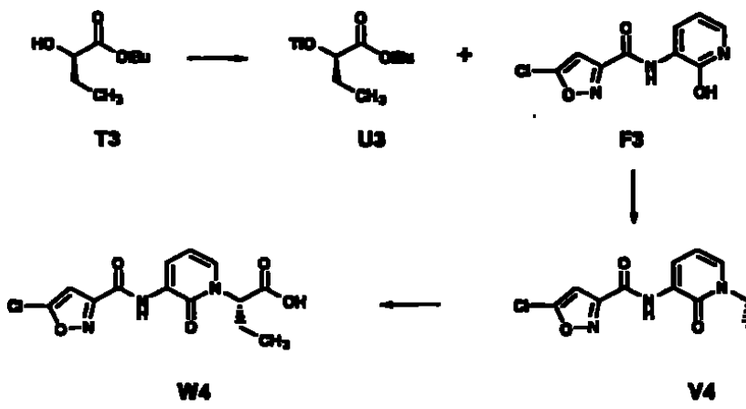
Specific Method 5

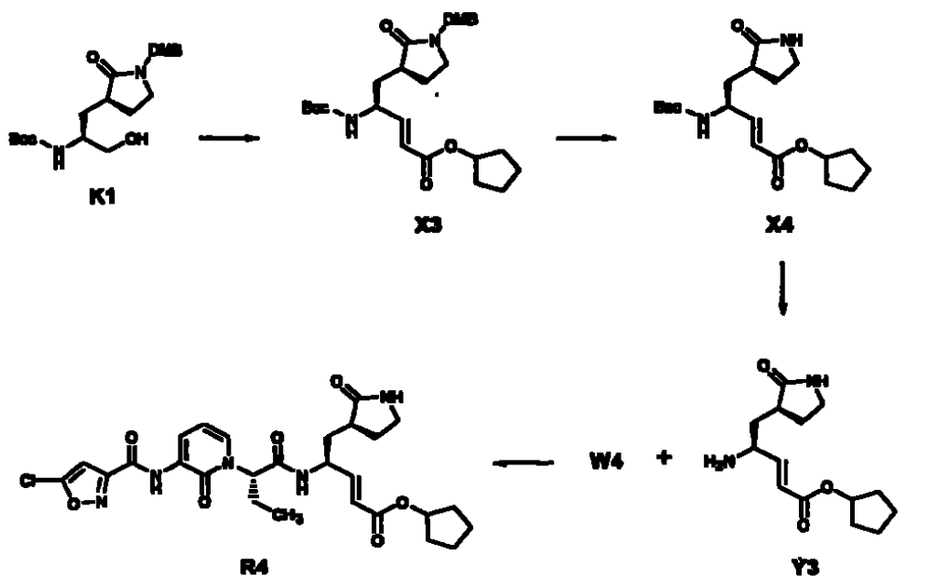


Specific Method 5 describes the preparation of specific compound R3 (compound 26). Thus, commercially available *tert*-butyl (*R*)-2-hydroxybutyrate (T3) was transformed into the corresponding trifluoromethane,sulfonate (triflate) U3 and was coupled with the sodium salt of 2-hydroxypyridine F2 (prepared as described in Specific Method 2 above) to provide intermediate V3. The *tert*-butyl ester present in V3 was subsequently hydrolyzed under

acidic conditions and the resulting carboxylic acid (W3) was coupled with amine Y2 (or salt thereof) to complete the preparation of specific compound R3 (compound 26). Amine Y2 (or salt thereof) was prepared by deprotection of intermediate X2, prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999, the disclosure of which is incorporated herein by reference.

Specific Method 6



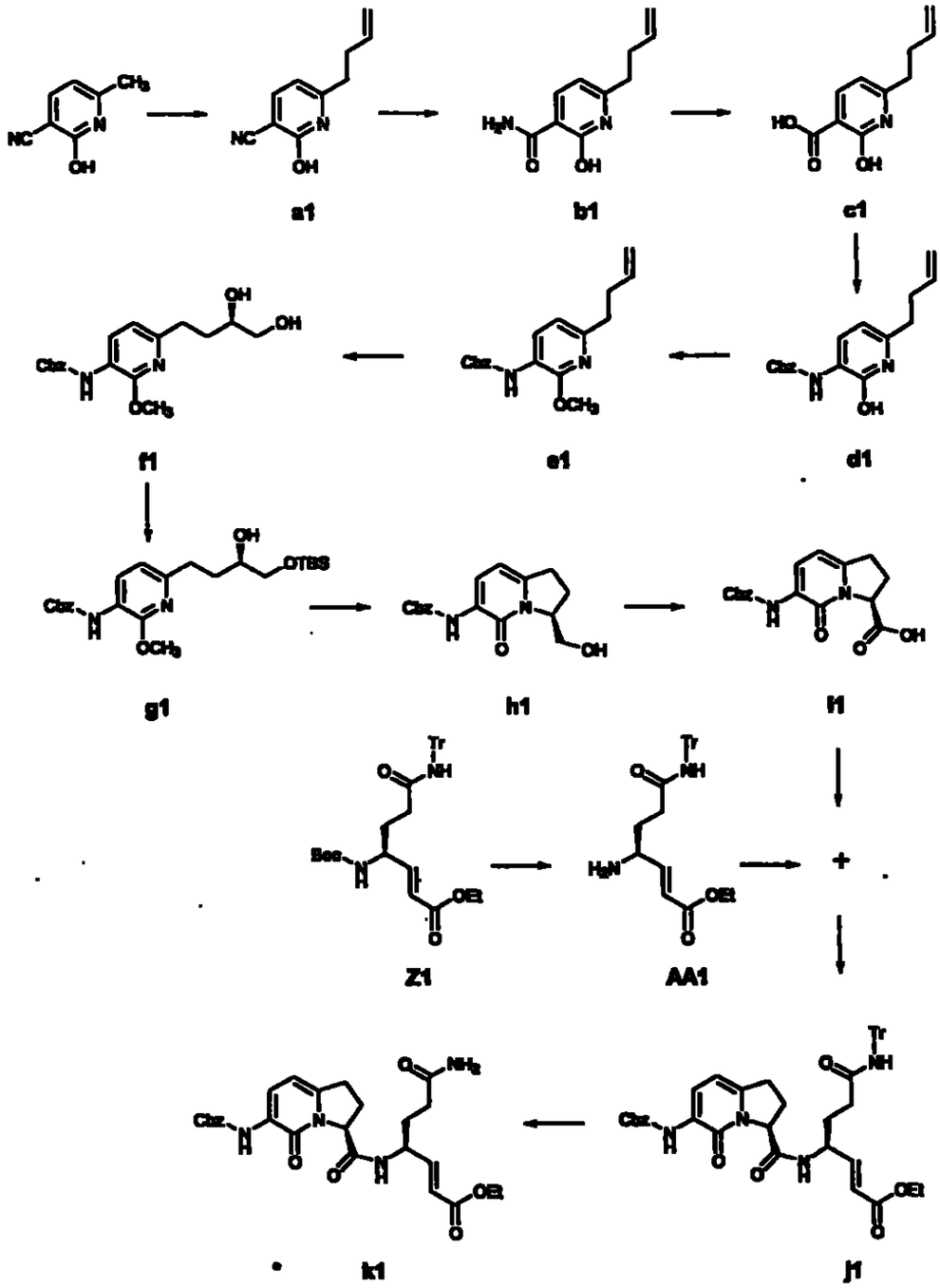


Specific Method 6 describes the preparation of specific compound R4 (compound 29). Thus, trifluoromethane sulfonate (triflate) U3 (prepared as described in Specific method 5 above) was coupled with the sodium salt of 2-hydroxypyridine F3 (prepared as described in Specific Method 3 above) to provide intermediate V4. The *tert*-butyl ester present in V4 was subsequently hydrolyzed under acidic conditions and the resulting carboxylic acid (W4) was coupled with amine Y3 (or salt thereof) to complete the preparation of specific compound R4 (compound 29). Amine Y3 (or salt thereof) was synthesized from alcohol K1 (prepared as described in Dragovich, et al., *J. Med Chem.* 1999, *42*, 1213) by the following method. Alcohol K1 was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate X3. The DMB moiety contained in X3 was then deprotected to provide intermediate X4, and this entity was deprotected under acidic conditions to afford amine Y3 (or salt thereof).

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Specific Method 7

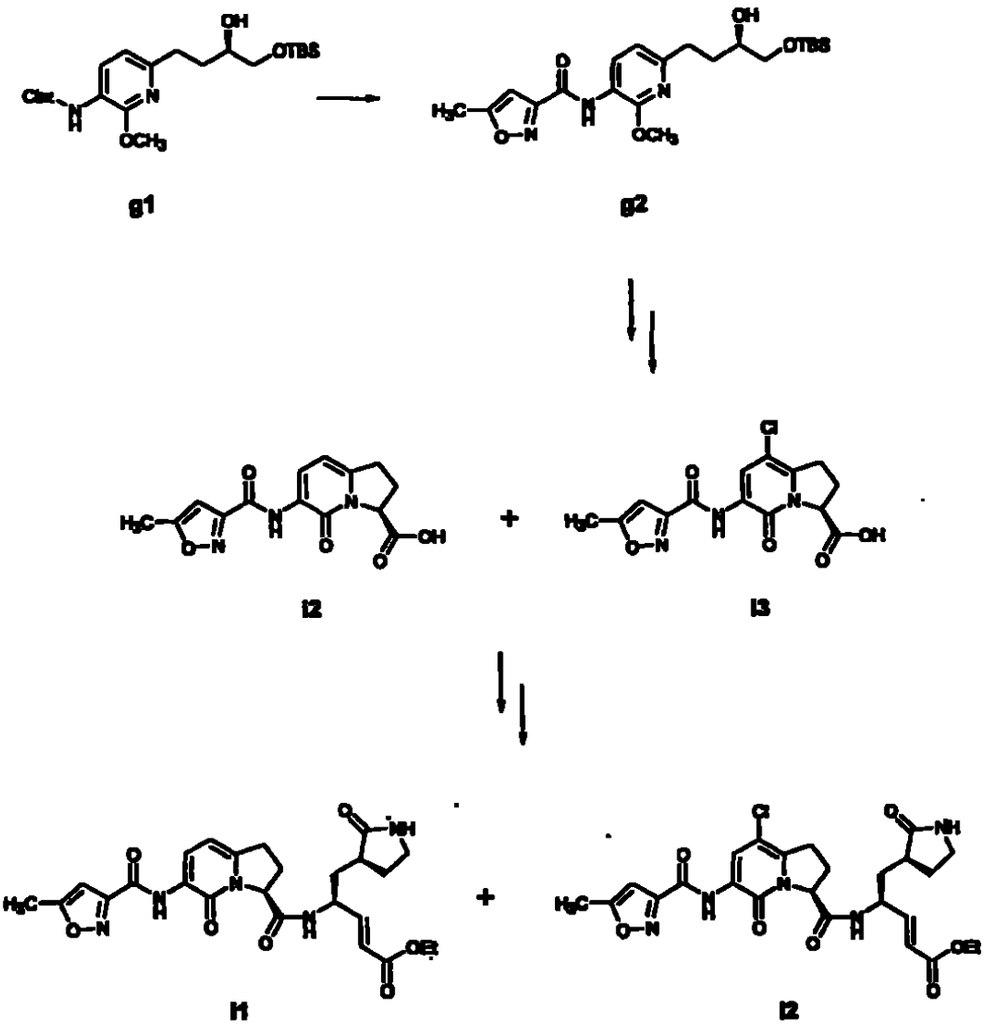


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Specific Method 7 describes the preparation of specific compound k1 (compound 36). Thus, the dianion of commercially available 2-hydroxy-6-methylnicotinonitrile was converted to intermediate a1 by methods related to those described in the literature (DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocyclic Chem.* 1983, *20*, 1295). The nitrile functionality present in this intermediate was then converted to the corresponding carboxylic acid c1 via the primary amide b1. Intermediate c1 was subjected to a Curtius rearrangement and the resulting isocyanate was trapped with benzyl alcohol to provide carbamate d1. The hydroxyl moiety contained in d1 was selectively methylated and the resulting methyl ether (e1) was subjected to an asymmetric dihydroxylation reaction to give diol f1. This asymmetric dihydroxylation reaction can be effected utilizing a variety of commercial and non-commercial chiral additives. The primary hydroxyl moiety contained in f1 was selectively protected as the corresponding *tert*-butyldimethylsilyl ether (g1). This intermediate was treated with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine at low temperature followed by exposure to tetrabutylammonium fluoride to effect (i) intramolecular cyclization and (ii) silyl ether deprotection and afford alcohol h1. Alcohol h1 was oxidized to the corresponding aldehyde (not shown), and this intermediate was further oxidized to the corresponding carboxylic acid i1. Acid i1 was coupled with amine AA1 (or salt thereof) to give intermediate j1. The trityl protecting group present in j1 was then removed under acidic conditions to complete the preparation of specific compound k1 (compound 36). Amine AA1 (or salt thereof) was prepared by deprotection of intermediate Z1 (prepared as described in Dragovich, et al. *J. Med. Chem.* 1998, *41*, 2806).

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Specific Method 8



Specific Method 8 describes the preparation of specific compounds I1 and I2 (compounds 37 and 39, respectively). Thus, the Cbz moiety present in intermediate g1 (prepared as described in Specific Method 7 above) was removed and the resulting amine (not shown) was derivatized with commercially available 5-methylisoxazole-3-carbonyl chloride to provide intermediate g2. This intermediate was converted to specific compound I1 (compound 37) by a process analogous to that described in Specific Method 7 for the conversion of intermediate g1 to intermediate j1 utilizing amine Y2 (Specific Method 5)

where appropriate. During this process, a small amount of intermediate i3 was also serendipitously generated. This intermediate was transformed to specific compound l2 (compound 39) by a process analogous to that described in Specific Method 7 for the conversion of intermediate g1 to intermediate j1 utilizing amine Y2 (Specific Method 5) where appropriate.

EXAMPLES

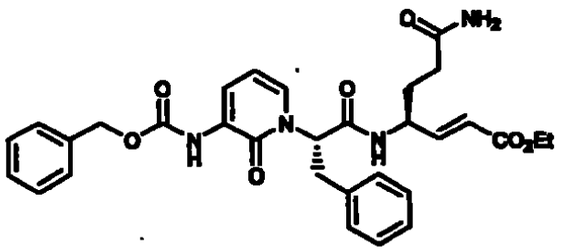
Examples of the processes used to make several of the compounds of Formulas I and II are set forth below. The structures of the compounds of the following examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis and melting point. Proton magnetic resonance (^{1}H NMR) spectra were determined using either a Varian UNITY*plus* 300 or a General Electric QE-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; 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 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. Et_2O refers to diethyl ether. DMF refers to *N,N*-dimethylformamide. DMSO refers to

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dimethylsulfoxide. 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), TMEDA (*N,N,N',N'*-tetramethylethylenediamine), AcOH (acetic acid), Ac_2O (acetic anhydride), NMM (4-methylmorpholine), HOBt (1-hydroxybenzotriazole hydrate), HATU [*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate], EDC [1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride], DCC (dicyclohexyl-carbodiimide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), DMAP (4-dimethylaminopyridine), Gln (glutamine), Leu (leucine), Phe (phenylalanine), Phe(4-F) (4-fluorophenylalanine), Val (valine), amino-Ala (2,3-diaminopropionic acid), and (*S*)-Pyrrol-Ala [(2*S*,3'*S*)-2-amino-3-(2'-oxopyrrolidin-3'-yl)-propionic acid]. Additionally, "L" represents the configuration of naturally occurring amino acids.

EXAMPLE 1

Preparation of Compound 1: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2-Hydroxypyridin-3-yl)carbamic Acid Benzyl Ester

A suspension of 10% palladium on carbon (0.20 g) and 2-hydroxy-3-nitropyridine (3.00 g, 21.4 mmol, 1 equiv) in EtOH (100 mL) was subjected to one atmosphere of hydrogen for 4 hours. After purging the reaction vessel with argon, the mixture was filtered and the filtrate evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was stirred in THF (70 mL) at 23 °C. Benzyl

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chloroformate (3.37 mL, 23.6 mmol, 1.1 equiv) and Na_2CO_3 (5.00 g, 47.2 mmol, 2.2 equiv) were added and the reaction mixture was stirred for 60 h then diluted with EtOAc (250 mL) and washed sequentially with saturated $NaHCO_3$ and brine (50 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (gradient elution, 3→5% CH_3OH in CH_2Cl_2) to provide the title intermediate (3.69 g, 71%) as a white solid: ^1H NMR ($CDCl_3$) δ 5.21 (s, 2H), 6.33 (t, 1H, *J* = 6.8), 7.00 (dd, 1H, *J* = 6.8, 1.6), 7.31-7.43 (m, 5H), 7.80 (s, 1H), 8.12-8.17 (m, 1H), 12.97 (s, 1H).

Preparation of Intermediate
5-(3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)-6-phenyl-4-[2-(tritylcarbamoyl)ethyl] hex-2-enoic Acid Ethyl Ester

(2-Hydroxypyridin-3-yl)carbamic acid benzyl ester was converted to the title intermediate via condensation with E1 (see Example 5) by a process analogous to that described in Example 5 for the conversion of F1 to intermediate I1: ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.2), 1.55-1.69 (m, 1H), 1.86-2.00 (m, 1H), 2.06-2.23 (m, 2H), 3.12 (dd, 1H, *J* = 13.6, 7.8), 3.46 (dd, 1H, *J* = 13.6, 8.2), 4.17 (q, 2H, *J* = 7.2), 4.43-4.54 (m, 1H), 5.14 (d, 1H, *J* = 12.1), 5.18 (d, 1H, *J* = 12.1), 5.49-5.57 (m, 1H), 5.62 (dd, 1H, *J* = 15.7, 1.7), 6.14 (t, 1H, *J* = 7.3), 6.59-6.75 (m, 3H), 7.08-7.41 (m, 26H), 7.73 (s, 1H), 7.93-7.98 (m, 1H).

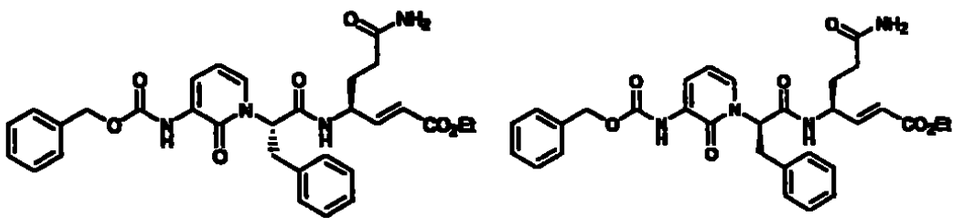
Preparation of Compound 1

The preceding intermediate was converted to compound 1 by a process analogous to that described in Example 5 for the conversion of I2 to product J1: IR (cm^{-1}) 3298, 1713, 1655, 1590, 1508, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.1), 1.65-1.96 (m, 2H), 2.02-2.19 (m, 2H), 3.15 (dd, 1H, *J* = 13.8, 7.6), 3.49 (dd, 1H, *J* = 13.8, 8.3), 4.18 (q, 2H, *J* = 7.1), 4.42-4.53 (m, 1H), 5.17 (s, 2H), 5.62-5.81 (m, 4H), 6.28 (t, 1H, *J* = 7.2), 6.66 (dd, 1H, *J* = 15.6, 5.4), 7.12-7.40 (m, 12H), 7.81 (s, 1H), 7.97-8.04 (m, 1H); Anal. $C_{31}H_{34}N_4O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 2

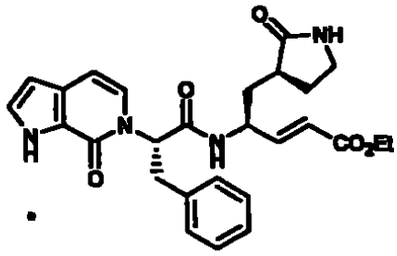
Preparation of a 1:1 mixture of Compound 1 (above) and Compound 2: *trans*-(2'*R*,4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



The title products were prepared from commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid by a process analogous to that described in Example 22 for the conversion of S1 to product R2 utilizing intermediates (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 1) and AA1 (Example 23) where appropriate: ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 1.20 (t, *J* = 7.0), 1.29 (t, *J* = 7.2), 1.64-2.25 (m), 3.08 (dd, *J* = 13.6, 6.4), 3.14 (dd, *J* = 13.6, 7.8), 3.41-3.52 (m), 4.09 (q, *J* = 7.2), 4.18 (q, *J* = 7.0), 4.39-4.50 (m), 5.16 (s), 5.18 (s), 5.59-5.82 (m), 6.12-6.22 (m), 6.25-6.34 (m), 6.65 (dd, *J* = 15.6, 5.6), 6.70 (dd, *J* = 15.6, 5.3), 7.10-7.41 (m), 7.47-7.58 (m), 7.79-7.86 (m), 7.97-8.07 (m).

EXAMPLE 3

Preparation of Compound 3: *trans*-(2'*S*,3'''*S*,4*S*)-4-[2'-(7''-Oxo-1'',7''-dihydropyrrolo[2'',3''-c-pyridin-6''-yl)-3'-phenyl propionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2*S*)-2-(2',2'-Diethyloxyethylamino)-3-phenylpropionic Acid Ethyl Ester

A solution of L-phenylalanine ethyl ester (8.37 g, 46.8 mmol, 1 equiv), bromoacetaldehyde diethyl acetal (10.6 mL, 70.1 mmol, 1.5 equiv), and DIEA (16.2 mL, 93.4 mmol, 2.0 equiv) in DMF (100 mL) was heated at 80 °C for 2 d. The resulting solution was cooled to 23 °C, taken up in chloroform (200 mL), washed with 10% aqueous potassium carbonate (3 x 50 mL), dried over potassium carbonate, and concentrated. Purification of the residue by silica gel chromatography yield 7.4 g (54%) of product. ^{1}H NMR ($CDCl_3$) δ 1.13-1.23 (m, 9H), 2.61 (dd, 1H, J = 11.8, 5.9), 2.78 (dd, 1H, J = 11.8, 5.9), 2.96-3.03 (m, 2H), 3.46-3.53 (m, 1H), 3.55-3.70 (m, 4H), 4.18 (q, 2H, J = 7.1), 4.57 (t, 1H, J = 5.5), 7.19-7.33 (m, 5H).

Preparation of Intermediate (2*S*)-2-[(2,2-Diethoxyethyl)-(1H-pyrrole-2-carbonyl)-amino]-3-phenylpropionic Acid Ethyl Ester

Pyrrole-2-carboxylic acid (0.82 g, 7.41 mmol, 1.42 equiv) in CH_2Cl_2 (30 mL) was treated with oxalyl chloride (1.0 mL, 11.1 mmol, 2.13 equiv), followed by DMF (1 drop). The reaction mixture was held at 23 °C overnight, then was concentrated under reduced pressure. The resulting solid was taken up in CH_2Cl_2 (30 mL), and was treated with the preceding intermediate (1.60 g, 5.2 mmol, 1 equiv), and collidine (1.96 mL, 14.8 mmol, 2.85 equiv). The resulting solution was held at 23 °C overnight, then was taken up in EtOAc (100 mL), and washed sequentially with saturated aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (2 x 20 mL). The organic layer was dried over $MgSO_4$, then was concentrated to yield 2.18 g of crude product. The product was purified by silica gel chromatography to give 1.42 g (68%) of product. ^{1}H NMR ($CDCl_3$) δ 1.15-1.30 (m, 9H), 3.24 (d, 2H, J = 5.8), 3.75-4.43 (m, 2H), 4.15-4.28 (m, 6H), 4.50-4.57 (m, 1H), 5.05 (dd, 1H, J = 13.6, 5.8), 6.22-6.24 (m, 1H), 6.56-6.59 (m, 1H), 6.94-6.96 (m, 1H), 7.19-7.33 (m, 5H), 9.76 (s, 1H).

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Preparation of Intermediate (2*S*)-(7-Oxo-1,7-dihydropyrrolo [2,3-c]pyridin-6-yl)-3-phenylpropionic Acid Ethyl Ester

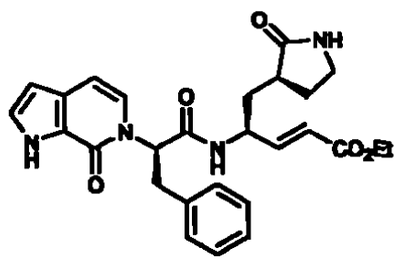
A solution of the preceding intermediate (1.04 g, 2.59 mmol) in toluene (30 mL) was treated with PTSA (5 mg), then heated to reflux for 1 h. The solution was taken up in EtOAc (100 mL), washed with saturated aqueous sodium bicarbonate (30 mL), then brine (30 mL), then concentrated. Purification of the residue by silica gel chromatography gave 0.14 g (18%) of product. ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, *J* = 7.1), 3.25 (dd, 1H, *J* = 14.2, 9.8), 3.49 (dd, 1H, *J* = 14.2, 5.7), 4.11 (q, 2H, *J* = 7.1), 5.57 (dd, 1H, *J* = 9.6, 5.7), 6.26 (t, 1H, *J* = 2.3), 6.42 (d, 1H, *J* = 7.2), 6.70 (d, 1H, *J* = 7.2), 7.00-7.20 (m, 6H), 10.33 (s, 1H),.

Preparation of Compound 3

A solution of the preceding intermediate (0.14 g, 0.45 mmol, 1 equiv) in 1:1 1,4-dioxane-water (5 mL) was treated with LiOH-hydrate (28 mg, 0.68 mmol, 1.42 equiv), and heated to reflux for 30 min. The resulting solution was taken up in ethyl acetate (50 mL), washed with saturated aqueous citric acid (10 mL), followed by brine (2 x 15 mL), dried over $MgSO_4$, then evaporated to yield 61 mg of the corresponding acid. This was taken up in DMF (5 mL), treated with intermediate Y2 (Example 25, 49 mg, 0.22 mmol, 0.48 equiv), DIEA (0.07 mL, 0.43 mmol, 0.95 equiv), and HATU (82 mg, 0.22 mmol, 0.49 equiv), then held at 23 °C overnight. The solution was taken up in ethyl acetate (30 mL), washed with brine (10 mL), then evaporated. Purification of the residue by silica gel chromatography yielded 0.12 g (56%) of product as a 2:1 mixture of 2*S* : 2*R* diastereomers (Compounds 3 and 4, respectively). The diastereomers were separated by preparative reverse phase HPLC (acetonitrile-H_2O gradient). Compound 3: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1), 1.42-1.65 (m, 2H), 1.90-2.10 (m, 2H), 2.20-2.35 (m, 1H), 2.82-2.95 (m, 1H), 3.05-3.25 (m, 2H), 3.53 (dd, 1H, *J* = 13.8, 7.8), 4.17 (q, 2H, *J* = 7.1), 4.45-4.58 (m, 1H), 5.76-5.90 (m, 2H), 6.32 (t, 1H, *J* = 2.1), 6.63 (d, 1H, *J* = 7.3), 6.69-6.78 (m, 2H), 7.08-7.35 (m, 7H), 8.11 (d, 1H, *J* = 7.1), 11.22 (s, 1H).

EXAMPLE 4

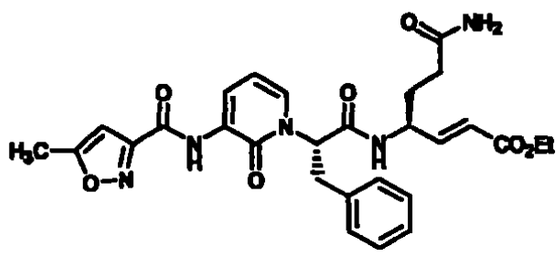
Preparation of Compound 4: *trans*-(2'*R*,3'''*S*,4*S*)-4-[2'-(7''-Oxo-1'',7''-dihydropyrrolo[2'',3''-c-pyridin-6''-yl)-3'-phenylpropionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester



See Preceding Example for preparation: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.1), 1.42-1.52 (m, 1H), 1.58-1.70 (m, 1H), 1.90-2.28 (m, 3H), 3.12 (dd, 1H, J = 13.3, 7.1), 3.20-3.28 (m, 2H), 3.57 (dd, 1H, J = 13.3, 9.0), 4.07 (q, 2H, J = 7.0), 4.45-4.58 (m, 1H), 5.80 (d, 1H, J = 15.7), 6.04 (t, 1H, J = 7.7), 6.37 (t, 1H, J = 2.3), 6.48 (s, br, 1H), 6.60-6.80 (m, 2H), 7.00-7.40 (m, 6H), 8.11 (d, 1H, J = 7.8), 10.61 (s, 1H).

EXAMPLE 5

Preparation of Compound 5: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3''-[(5'''-methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester (J1)



Preparation of Intermediate (1*S*)-[1-Hydroxymethyl-3-(tritylcarbamoyl)propyl]carbamic Acid Benzyl Ester (B1)

4-Methylmorpholine (1.89 mL, 17.2 mmol, 1 equiv) and ethyl chloroformate (1.65 mL, 17.3 mmol, 1 equiv) were added to a mixture of commercially available Cbz-Gln(Trt)-OH (9.00 g, 17.2 mmol, 1 equiv) in THF (23 mL) at -10 °C. After stirring 20 min, the reaction mixture was filtered and the filtrate was added dropwise to a suspension of $NaBH_4$ (1.47 g, 38.9 mmol, 2.25 equiv) in H_2O (10 mL) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 5 h. It was then cooled again to 0 °C, quenched by the careful addition of 1 N HCl (30 mL) and then partitioned between MTBE (500 mL) and brine (2 x 100 mL). The organic phase was dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (1*S*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-3-(tritylcarbamoyl)propyl]carbamic Acid Benzyl Ester (C1)

Intermediate B1, prepared above, was dissolved in DMF (10 mL). Imidazole (2.69 g, 39.5 mmol, 2.3 equiv) and *tert*-butyldimethylsilyl chloride (2.86 g, 19.0 mmol, 1.1 equiv) were added. The reaction mixture was stirred overnight, then diluted with MTBE (500 mL) and washed sequentially with 2.5% $KHSO_4$, H_2O, $NaHCO_3$, H_2O, and brine (100 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 25→40% EtOAc in hexanes) to provide the title intermediate (7.6 g, 71%) as a white amorphous solid: IR (cm^{-1}) 3307, 1708, 1660, 1496, 1249; ^1H NMR ($CDCl_3$) δ -0.01-0.05 (m, 6H), 0.89 (s, 9H), 1.76-1.93 (m, 2H), 2.29-2.40 (m, 2H), 3.56-3.77 (m, 3H), 5.03-5.16 (m, 3H), 7.00 (s, 1H), 7.18-7.39 (m, 20 H); Anal. $C_{38}H_{46}N_2O_4Si$: C, H, N.

Preparation of Intermediate (2'*R*,4*S*)-5-(*tert*-Butyldimethylsilanyloxy)-4-(2'-hydroxy-3'-phenylpropionylamino)pentanoic Acid Tritylamide (D1)

Intermediate C1 from above (7.6 g, 12 mmol, 1 equiv) and 10% palladium on carbon (0.45 g) were suspended in EtOH (140 mL) and hydrogenated at 50 psi overnight. The reaction mixture was filtered through Whatman #3 paper, the paper was washed with EtOH (120 mL) and the combined filtrates were evaporated. The residue was combined with

D-3-phenyllactic acid (1.42 g, 12.2 mmol, 1 equiv), iPr_2NEt (4.25 mL, 24.4 mmol, 2 equiv) and HATU (4.64 g, 12.2 mmol, 1 equiv) in DMF (35 mL) at 0 °C. After stirring 1 h, the reaction mixture was allowed to warm to 23 °C and stirred 20 min more. Then 5% $KHSO_4$ (80 mL) and MTBE (600 mL) were added and the phases were separated. The organic phase was washed with H_2O (80 mL) and brine (70 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to provide the title intermediate as a white foam (4.85 g, 62%): IR (cm^{-1}) 3394, 3295, 1666, 1649, 1519, 1255, 1114, 1085; ^1H NMR ($CDCl_3$) δ -0.03-0.02 (m, 6H), 0.85 (s, 9H), 1.70-1.89 (m, 2H), 2.18-2.42 (m, 3H), 2.83 (dd, 1H, J = 13.8, 8.1), 3.15 (dd, 1H, J = 13.8, 4.0), 3.40 (dd, 1H, J = 10.0, 4.7), 3.51 (dd, 1H, J = 10.0, 3.1), 3.83-3.94 (m, 1H), 4.17-4.23 (m, 1H), 6.79 (d, 1H, J = 8.7), 7.09 (s, 1H), 7.17-7.32 (m, 20H); Anal. $C_{39}H_{48}N_2O_4Si \cdot 0.30H_2O$: C, H, N.

Preparation of Intermediate (1'*S*,2*R*)-Methanesulfonic Acid 1-[1'-(*tert*-butyldimethylsilanyloxymethyl)-3'-(tritylcarbamoyl) propylcarbamoyl]-2-phenylethyl Ester (E1)

Intermediate D1 from above (1.96 g, 3.08 mmol, 1 equiv) and iPr_2NEt (0.752 mL, 4.32 mmol, 1.4 equiv) were dissolved in CH_2Cl_2 (30 mL) and cooled to –10 °C. Methanesulfonyl chloride (0.286 mL, 3.70 mmol, 1.2 equiv) was added dropwise, slowly, with vigorous stirring. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with brine (50 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (2-Hydroxypyridin-3-yl) carbamic acid *tert*-Butyl Ester (F1)

A suspension of 10% palladium on carbon (0.35 g) and 2-hydroxy-3-nitropyridine (5.00 g, 35.7 mmol, 1 equiv) in EtOH (170 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was stirred in THF (100 mL) at 23 °C. Di-*tert*-butyl dicarbonate (7.79 g, 35.7 mmol, 1 equiv) was added and the reaction mixture was heated to reflux for 4 h. More di-*tert*-butyl dicarbonate (6.0 g, 27 mmol, 0.8 equiv) was added and the reaction mixture was heated to

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reflux overnight. The solvent was evaporated and the residue was purified by flash column chromatography (gradient elution, 50→60% EtOAc in hexanes) to provide the title intermediate as a white solid (6.48 g, 83%): IR (cm^{-1}) 3225, 1725, 1649, 1514; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.33 (dd, 1H, J = 7.4, 6.6), 7.01 (dd, 1H, J = 6.6, 1.8), 7.56 (s, 1H), 8.11 (d, 1H, J = 7.1), 12.61 (s, 1H); Anal. $C_{10}H_{14}N_2O_3$: C, H, N.

Preparation of Intermediate (1''*S*,2'*S*)-(1-{1'-[1''-(*tert*-Butyldimethylsilanyloxymethyl)-3''-(tritylcarbamoyl)propylcarbamoyl]-2'-phenylethyl}-2-oxo-1,2-dihydropyridin-3-yl)-carbamic Acid *tert*-Butyl Ester (G1)

Intermediate F1 from above (0.838 g, 3.99 mmol, 1.3 equiv) was stirred in THF (20 mL). Sodium hydride (60% dispersion in mineral oil, 0.148 g, 3.70 mmol, 1.2 equiv) was added. After stirring 20 min, a solution of intermediate E1 from above (1 equiv based on D1) in THF (15 mL) was added. The resulting mixture was heated to reflux for 40 h, but thin layer chromatography showed the reaction to be only 50% complete. *In a separate flask*, more sodium hydride (60% dispersion in mineral oil, 0.111 g, 2.78 mmol, 0.9 equiv) was added to a suspension of F1 (0.647 g, 3.08 mmol, 1 equiv) in THF (10 mL). After stirring 20 min, this mixture was added to original reaction vessel and the resulting mixture was heated to reflux for 21 h. After stirring at 23 °C over the weekend, the crude reaction mixture was diluted with MTBE (600 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 80 mL) and brine (80 mL), then dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (gradient elution, 30→35% EtOAc in hexanes) to provide the desired intermediate G1 as a white foam (1.98 g, 77%): IR (cm^{-1}) 3389, 3307, 1725, 1678, 1649, 1590, 1502; ^1H NMR ($CDCl_3$) δ -0.02-0.04 (m, 6H), 0.86 (s, 9H), 1.52 (s, 9H), 1.55-1.88 (m, 2H), 2.08-2.14 (m, 2H), 3.19 (dd, 1H, J = 13.7, 8.1), 3.39-3.51 (m, 2H), 3.53 (dd, 1H, J = 14.2, 7.8), 3.82-3.93 (m, 1H), 5.60-5.67 (m, 1H), 6.17 (t, 1H, J = 7.3), 6.44 (d, 1H, J = 8.3), 7.04 (s, 1H), 7.12-7.36 (m, 21H), 7.59 (s, 1H), 7.94 (d, 1H, J = 7.1); Anal. $C_{49}H_{60}N_4O_6Si$: C, H, N.

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Preparation of Intermediate (1''*S*,2'*S*)-(1-{1'-[1''-Hydroxymethyl-3''-(tritylcarbamoyl)propylcarbamoyl]-2'-phenylethyl}-2-oxo-1,2-dihydropyridin-3-yl)carbamic Acid *tert*-Butyl Ester (H1)

Intermediate G1 from above (1.92 g, 2.32 mmol, 1 equiv) was dissolved in a mixture of CH_3CN (30 mL) and H_2O (3 mL) in a plastic tube. Triethylamine trihydrofluoride (21 drops) was added and the reaction solution was stirred overnight. It was then diluted with EtOAc (750 mL), washed with brine (3 x 80 mL), dried over $MgSO_4$ and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-[2'-(3''-*tert*-Butoxy carbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-6-(tritylcarbamoyl)-hex-2-enoic Acid Ethyl Ester (I1)

Intermediate H1 from above (1 equiv based on G1) was dissolved in CH_2Cl_2 (20 mL). Commercially available Dess-Martin periodinane (1.09 g, 2.55 mmol, 1.1 equiv) was added. After stirring 2 h, the solvent was evaporated and the residue was suspended in toluene and again evaporated (70 mL, then 2 x 20 mL) to give a yellow foam. One half of this material (1.16 mmol based on G1) was dissolved in THF (17 mL). (Carbethoxymethylene) triphenylphosphorane (0.563 g, 1.62 mmol, 1.4 equiv) was added and the reaction mixture was heated to reflux for 1 h and then stirred at 23 °C overnight. After evaporating the solvent, the residue was purified by flash column chromatography (gradient elution, 40→50% EtOAc in hexanes) to provide the title intermediate (0.710 g, 77%): IR (cm^{-1}) 3378, 3284, 1719, 1649, 1596, 1508, 1267; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.47 (s, 9H), 1.54-1.69 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.22 (m, 2H), 3.12 (dd, 1H, J = 13.7, 7.7), 3.47 (dd, 1H, J = 13.7, 8.1), 4.17 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.51-5.58 (m, 1H), 5.64 (dd, 1H, J = 15.7, 1.6), 6.12 (t, 1H, J = 7.2), 6.60-6.68 (m, 3H), 7.08-7.31 (m, 21H), 7.51 (s, 1H), 7.90 (d, 1H, J = 7.1); Anal. $C_{47}H_{50}N_4O_7 \cdot 0.50H_2O$: C, H, N.

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Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-(2'-{3''-[(5'''-Methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (I2)

Intermediate I1 from above (0.088 g, 0.11 mmol, 1 equiv) was heated (neat) to between 190 and 200 °C for 65 minutes, then allowed to cool providing the crude amine as a dark residue which was dissolved in CH_3CN (2 mL) and cooled to 0 °C. 5-Methylisoxazole-3-carbonyl chloride (0.033 g, 0.23 mmol, 2 equiv) and 4-methylmorpholine (0.025 mL, 0.23 mmol, 2 equiv) were added and the reaction mixture was allowed to warm to 23 °C. After stirring 40 min, a mixture of 10% $KHSO_4$ and brine (1:1, 15 mL) and EtOAc (70 mL) were added. The phases were separated and the organic phase was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to provide the title intermediate (0.049 g, 55%): IR (cm^{-1}) 3331, 1678 (br), 1590, 1525; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.58-1.72 (m, 1H), 1.87-2.03 (m, 1H), 2.10-2.26 (m, 2H), 2.48 (s, 3H), 3.15 (dd, 1H, J = 13.7, 7.8), 3.47 (dd, 1H, J = 13.7, 8.1), 4.17 (q, 2H, J = 7.1), 4.43-4.55 (m, 1H), 5.54-5.61 (m, 1H), 5.65 (dd, 1H, J = 15.8, 1.5), 6.17 (t, 1H, J = 7.3), 6.45 (s, 1H), 6.65 (dd, 1H, J = 15.8, 5.4), 6.72 (s, 1H), 6.84 (d, 1H, J = 8.0), 7.08-7.32 (m., 22 H), 8.35 (dd, 1H, J = 7.3, 1.5), 9.49 (s, 1H); Anal. $C_{47}H_{46}N_5O_7 \cdot 0.25H_2O$: C, H, N.

Preparation of Product J1 (Compound 5)

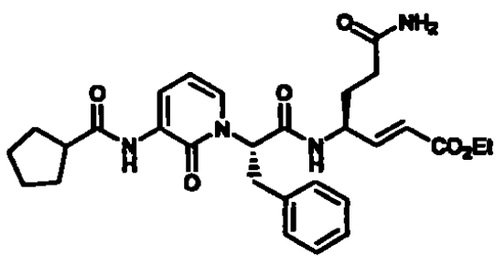
Intermediate I2 from above (0.047 g, 0.059 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 mL). Triisopropylsilane (0.036 mL, 0.176 mmol, 3 equiv) and TFA (2 mL) were added. The bright yellow solution was stirred 25 min, then diluted with CCl_4 (3 mL) and all the volatiles were evaporated. The residue was purified by flash column chromatography (3% CH_3OH in CH_2Cl_2) to give the desired product J1 (0.028 g, 85%): IR (cm^{-1}) 3342, 1666 (br), 1590, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.17-2.24 (m, 2H), 2.48 (s, 3H), 3.18 (dd, 1H, J = 13.7, 7.8), 3.50 (dd, 1H, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.68 (dd, 1H, J = 15.7, 1.3), 5.74-5.82 (m, 1H), 6.00 (s, 1H), 6.19 (s, 1H), 6.32 (t, 1H, J = 7.3), 6.46 (s, 1H), 6.69 (dd, 1H, J = 15.7, 5.5), 7.13-7.30

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(m, 5H), 7.48 (dd, 1H, J = 7.3, 1.6), 7.62 (d, 1H, J = 7.6), 8.39 (dd, 1H, J = 7.3, 1.6), 9.46 (s, 1H); Anal. $C_{28}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 6

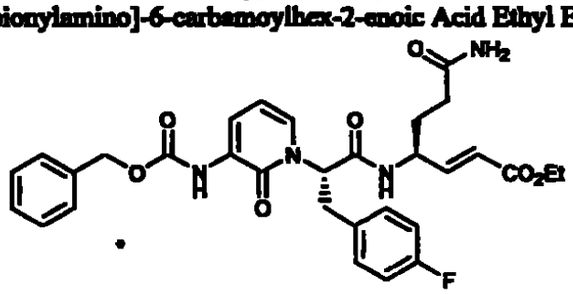
Preparation of Compound 6: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{2'-[3''-cyclopentanecarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl]-3'-phenylpropionylamino}hex-2-enoic Acid Ethyl Ester



The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate cyclopentanecarbonyl chloride where appropriate: IR (cm^{-1}) 3319, 1713, 1666, 1590, 1514; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 1.55-2.02 (m, 10H), 2.04-2.22 (m, 2H)2.68-2.80 (m, 1H), 3.16 (dd, 1H, J = 13.7, 7.7), 3.51 (dd, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.45-4.56 (m, 1H), 5.57-5.74 (m, 4H), 6.29 (t, 1H, J = 7.4), 6.68 (dd, 1H, J = 15.8, 5.5), 7.10-7.32 (m, 7H), 8.30 (s, 1H), 8.35 (dd, 1H, J = 7.4, 1.7); Anal. $C_{29}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 7

Preparation of Compound 7: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxy carbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-(4''''-fluorophenyl) propionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



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Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxycarbonyl amino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-(4'''-fluorophenyl)propionylamino]-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester

Intermediate C1 (Example 5) was converted to the title intermediate by a process analogous to that described in Example 5 for the conversion of C1 to intermediate I1 utilizing S1 (Example 22) where appropriate: IR (cm^{-1}) 3283, 1722, 1651, 1604, 1513; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 6.9), 1.62-1.71 (m, 1H), 1.94-2.01 (m, 1H), 2.17-2.24 (m, 2H), 3.06-3.13 (m, 1H), 3.43-3.50 (m, 1H), 4.21 (q, 2H, J = 6.9), 4.50-4.57 (m, 1H), 5.16-5.25 (m, 2H), 5.52 (t, 1H, J = 8.1), 5.63 (dd, 1H, J = 15.6, 1.5), 6.18 (t, 1H, J = 7.2), 6.65 (s, br. 1H), 6.69 (dd, 1H, J = 15.6, 5.4), 6.84 (d, 1H, J = 8.4), 6.96 (t, 2H, J = 8.4), 7.09-7.18 (m, 7H), 7.21-7.33 (m, 12H), 7.38-7.42 (m, 4H), 7.76 (s, br. 1H), 7.99 (d, 1H, J = 7.5); Anal. $C_{50}H_{47}N_4O_7 \cdot 0.50H_2O$: C, H, N.

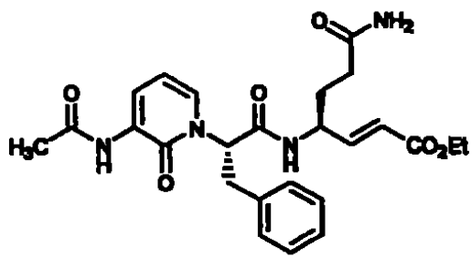
Preparation of Compound 7

The preceding intermediate was converted to compound 7 by a process analogous to that described in Example 5 for the conversion of I2 to product J1: mp = 99-101 °C; IR (cm^{-1}) 3308, 1714, 1650, 1511, 1199; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 6.9), 1.72 –1.82 (m, 1H), 1.86-1.96 (m, 1H), 2.10-2.18 (m, 2H), 3.10-3.17 (m, 2H), 3.10-3.17 (m, 2H), 3.46-3.53 (m, 1H), 3.63-3.74 (m, 2H), 4.22 (q, 2H, J = 6.9), 4.48-4.57 (m, 1H), 5.21 (s, 2H), 5.58-5.65.(m, 2H), 5.91-5.97 (m, 1H), 6.19-6.22 (m, 1H), 6.35 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.6, 5.1), 6.98 (t, 2H, J = 8.7), 7.13-7.18 (m, 2H), 7.36-7.40 (m, 5H), 7.85 (s, br. 1H), 8.06-8.09 (m, 1H); Anal. $C_{33}H_{33}N_4O_7 \cdot 1.25H_2O$: C, H, N.

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EXAMPLE 8

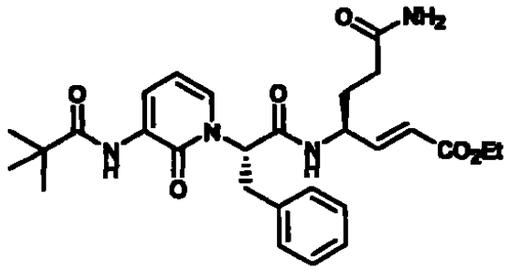
Preparation of Compound 8: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Acetylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenypropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate acetyl chloride where appropriate: IR (cm^{-1}) 3307, 1708, 1666, 1643, 1590, 1519; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.70-1.86 (m, 2H), 2.05-2.24 (m, 5H), 3.15 (dd, 1H, J = 13.7, 8.1), 3.50 (dd, 1H, J = 13.7, 7.8), 4.19 (q, 2H, J = 7.1), 4.45-4.56 (m, 1H), 5.66-5.77 (m, 2H), 5.82 (s, 1H), 5.94 (s, 1H), 6.28 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.7, 5.6), 7.10-7.29 (m, 5H), 7.32-7.45 (m, 2H), 8.28-8.36 (m, 2H); Anal. $C_{25}H_{30}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 9

Preparation of Compound 9: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{2'-[3''-(2''',2'''-dimethylpropionylamino)-2''-oxo-2''*H*-pyridin-1''-yl]-3'-phenylpropionylamino}hex-2-enoic Acid Ethyl Ester



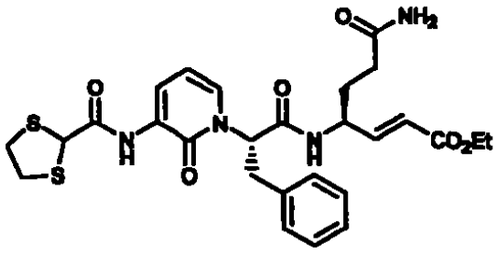
The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate 2,2-dimethylpropionyl chloride where appropriate: IR (cm^{-1}) 3378, 3307, 3213, 1713, 1666, 1643, 1590, 1514, 1273; ^1H NMR ($CDCl_3$) δ 1.18-1.37 (m, 12H), 1.67-1.98 (m, 2H),

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2.05-2.20 (m, 2H), 3.17 (dd, 1H, J = 13.6, 7.7), 3.50 (dd, 1H, J = 13.6, 8.2), 4.19 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.62-5.72 (m, 2H), 5.81-5.92 (m, 2H), 6.29 (t, 1H, J = 7.2), 6.66 (dd, 1H, J = 15.8, 5.7), 7.13-7.39 (m, 7H), 8.33-8.38 (m, 1H), 8.59 (s, 1H); Anal. $C_{28}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 10

Preparation of Compound 10: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3''-[([1''',3''']dithiolane-2'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester

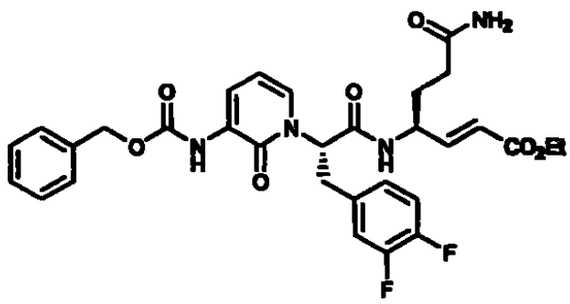


The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate [1,3]dithiolane-2-carbonyl chloride (prepared as described in *Helv. Chim. Acta* 1975, *58*, 2509) where appropriate: IR (cm^{-1}) 3295, 1672 (br), 1590, 1519 (br), 1273; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.66-2.22 (m, 4H), 3.17 (dd, 1H, J = 13.7, 7.8), 3.28-3.45 (m, 4H), 3.52 (dd, 1H, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.43-4.55 (m, 1H), 5.01 (s, 1H), 5.66 (dd, 1H, J = 15.8, 1.5), 5.67 (s, 1H), 5.86 (s, 2H), 6.29 (t, 1H, J = 7.3), 6.67 (dd, 1H, J = 15.8, 5.5), 7.12-7.40 (m, 7H), 8.31 (dd, 1H, J = 7.3, 1.6), 9.57 (s, 1H); Anal. $C_{27}H_{32}N_4O_6S_4 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 11

Preparation of Compound 11: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxy carbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-(3''',4'''-difluorophenyl) propionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2*R*)-3-(3',4'-Difluorophenyl)-2-hydroxypropionic Acid

Boc-D-3,4-Difluorophenylalanine (3.05 g, 11.0 mmol, 1 equiv) was dissolved in 1,4-dioxane (10 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added. The reaction was stirred at 23 °C for 5 h, then the solvent was removed under reduced pressure. The residue was dissolved in 1 M H_2SO_4 (22 mL), cooled to 0 °C and 2 N $NaNO_2$ (22 mL) was added via addition funnel under argon. The reaction mixture was stirred at 0 °C for 3 h and warmed to room temperature overnight. The resulting mixture was extracted with MTBE (3 x 40 mL), dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether/petroleum ether to afford the title intermediate (1.29 g, 58%) as off-white solid. ^1H NMR (DMSO-d_6) δ 0.82-0.86 (m, 2H), 1.10-1.27 (m, 4H), 1.40-1.48 (m, 2H), 1.63-1.78 (m, 5H), 3.95-4.00 (m, 1H).

Preparation of Compound 11

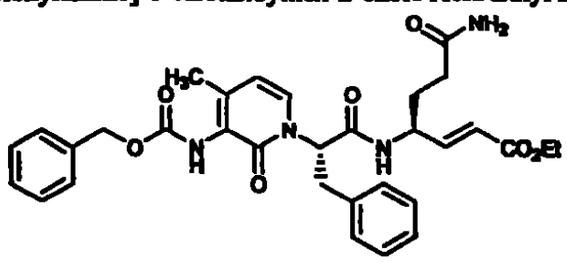
Intermediate C1 (Example 5) was converted to compound 11 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing (2*R*)-3-(3',4'-difluorophenyl)-2-hydroxypropionic acid (Example 11) where appropriate: mp = 175-178 °C; IR (cm^{-1}) 3298, 1661, 1516, 1266; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.2), 1.74-1.95 (m, 2H), 2.12-2.20 (m, 2H), 3.05-3.12 (m, 1H), 3.42-3.50 (m, 1H), 4.21 (q, 2H, J = 7.2), 4.45-4.56 (m, 1H), 5.21 (s, 2H), 5.58-5.71 (m, 3H), 6.07-6.10 (m, 1H), 6.32-6.34 (m, 1H), 6.71 (dd, 1H, J = 15.6, 5.1), 6.88-6.91 (m, 1H), 6.99-7.11 (m, 2H), 7.30-7.33 (m, 1H),

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7.36-7.39 (m, 5H), 7.53 (s, br. 1H), 7.86 (s, br. 1H), 8.04 (s, br. 1H); Anal. $C_{31}H_{32}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 12

Preparation of Compound 12: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxy carbonylamino-4''-methyl-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenyl propionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2-Hydroxy-6-methylphenyl) carbamic Acid Benzyl Ester

A suspension of 10% palladium on carbon (0.045 g) and 2-hydroxy-4-methyl-3-nitropyridine (0.600 g, 3.89 mmol, 1 equiv) in EtOH (20 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-4-methyl-3-aminopyridine which was used without further purification. This crude material was stirred in THF (18 mL) at 23 °C. Benzyl chloroformate (0.611 mL, 4.28 mmol, 1.1 equiv) and Na_2CO_3 (0.907 g, 8.56 mmol, 2.2 equiv) were added and the reaction mixture was stirred for 60 h, but TLC showed the reaction to be only 25% complete. The reaction mixture was heated to reflux for 24 h. More benzyl chloroformate (0.611 mL, 4.28 mmol, 1.1 equiv) and Na_2CO_3 (0.454 g, 4.28 mmol, 1.1 equiv) were added. The reaction mixture was heated to reflux for 24 h more, allowed to cool, diluted with EtOAc (200 mL), washed with half-saturated brine (2 x 40 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography (gradient elution, 3→5% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.363 g, 35%) as a white solid: ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 3.31-3.35 (m, 2H), 5.06 (s, 2H), 6.83 (d, 1H, J = 6.7), 7.17 (d, 1H, J = 6.7), 7.28-7.39 (m, 5H); Anal. $C_{14}H_{14}N_2O_3$: C, H, N.

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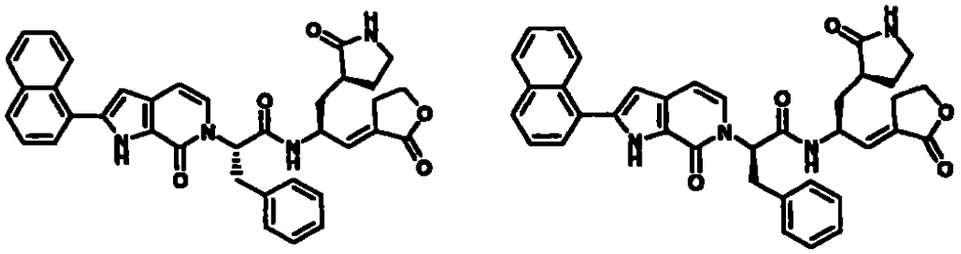
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Preparation of Compound 12

The preceding intermediate was converted to compound 12 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid and C1 (Example 5) where appropriate: IR (cm^{-1}) 3284, 1684 (br), 1596, 1327, (br), 1308, 1267, 1237; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1), 1.55-1.68 (m, 1H), 1.82-2.07 (m, 4H), 2.14 (s, 3H), 3.08 (dd, 1H, J = 13.6, 7.1), 3.47 (dd, J = 13.6, 8.8), 4.17 (q, 2H, J = 7.1), 4.41-4.52 (m, 1H), 5.06 (d, 1H, J = 12.3), 5.12 (d, 1H, J = 12.3), 5.59 (dd, 1H, J = 15.7, 1.6), 5.67-5.74 (m, 1H), 5.90 (s, 1H), 6.02 (s, 1H), 6.17 (d, 1H, J = 7.3), 6.68 (dd, 1H, J = 15.7, 5.1), 7.01 (s, 1H), 7.13-7.38 (m, 10H), 7.48 (d, 1H, J = 7.3); Anal. $C_{32}H_{36}N_4O_7 \cdot 0.75H_2O$: C, H, N.

EXAMPLE 13

Preparation of a 1:1 mixture of Compound 13: *trans*-(2*S*,2''*S*,3*S*)-2-(2'-Naphthalen-1'-yl-7'-oxo-1',7'-dihydropyrrolo[2',3'-*c*]pyridin-6'-yl)-*N*-[2''-(2'''-oxodihydrofuran-3'''-ylidene)-1''-(2''''-oxopyrrolidin-3''''-ylmethyl)ethyl]-3-phenylpropionamide and Compound 14: *trans*-(2*R*,2''*S*,3*S*)-2-(2'-Naphthalen-1'-yl-7'-oxo-1',7'-dihydropyrrolo[2',3'-*c*]pyridin-6'-yl)-*N*-[2''-(2'''-oxodihydrofuran-3'''-ylidene)-1''-(2''''-oxopyrrolidin-3''''-ylmethyl)ethyl]-3-phenylpropionamide



Preparation of Intermediate Pyrrole-2-carboxylic Acid Methyl Ester

Pyrrole-2-carboxylic acid (10.0 g, 90.0 mmol) in diethyl ether (200 mL) was treated with diazomethane (270 mmol, generated from *N*-nitroso-*N*-methyl urea), then back titrated with acetic acid until the yellow color dissipated. The solution was washed with saturated aqueous sodium bicarbonate (3 x 20 mL), followed by brine (3 x 20 mL), then was evaporated to obtain 10 g (88%) of product. ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.26-6.29 (m, 1H), 6.91-6.94 (m, 1H), 6.65-6.98 (m, 1H), 9.14 (s, 1H).

Preparation of Intermediate 5-Bromo-1H-pyrrole-2-carboxylic Acid Methyl Ester

A solution of the preceding intermediate (10.0 g, 79.9 mmol, 1 equiv) in carbon tetrachloride (300 mL) was heated to 70 °C, then treated dropwise with a solution of bromine (126.0 mL, 99.9 mmol, 1.25 equiv) in carbon tetrachloride (200 mL). The reaction was initiated by the addition of iodine (40 mg). After the addition was complete, the reaction was held at 70 °C for 10 min, then cooled to 23 °C using an ice bath. The mixture was washed with 10% aqueous sodium carbonate (100 mL), followed by water (100 mL). The volatiles were evaporated, and the residue was purified by silica gel chromatography to obtain 4.5 g (27%) of product: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.23 (dd, 1H, J = 3.8, 2.6), 6.80 (dd, 1H, J = 3.9, 2.7), 9.29 (s, 1H).

Preparation of Intermediate 5-Naphthalene-1-yl-1H-pyrrole-2-carboxylic Acid Methyl Ester

Argon gas was bubbled for 15 min through a solution of the preceding intermediate (2.04 g, 10.0 mmol, 1 equiv) in 2 M aqueous sodium carbonate (20 mL), and DMF (150 mL). The mixture was then treated with tris(dibenzylidieneacetone)dipalladium (0) (0.46 g, 0.50 mmol, 0.05 equiv), and triphenylarsine (0.61 g, 2.0 mmol, 0.20 equiv), then heated to reflux, under argon, for 12 h. The mixture was taken up in ethyl acetate (500 mL) and water (150 mL), then filtered through celite. The organic layer was washed with brine (3 x 50 mL), then evaporated. Purification of the residue by silica gel chromatography yielded 2.05 g (81%) of product. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.22 (dd, 1H, J = 3.8, 2.6), 7.50-7.59 (m, 4H), 7.88 (dd, 1H, J = 3.9, 2.7), 7.89-8.16 (m, 2H), 8.17-8.22 (m, 1H), 9.37 (s, 1H). This material was taken up in 1:1 1,4-dioxane-water (30 mL), and treated with lithium hydroxide hydrate (1.02 g, 24.4 mmol, 2.4 equiv), then heated to reflux for 15 min. The solution was acidified with 20% aqueous citric acid (30 mL), then extracted with ethyl acetate (75 mL). The organic layer was washed with brine (2 x 20 mL), then evaporated. The residue was taken up in CH_2Cl_2, (30 mL), and treated with oxalyl chloride (2.10 mL, 24.0 mmol, 2.4 equiv), and DMF (one drop), then heated to reflux for 30 min. Evaporation yielded 5-naphthalen-1-yl-1H-pyrrole-2-carboxylic acid chloride which was used in the subsequent procedure without additional purification.

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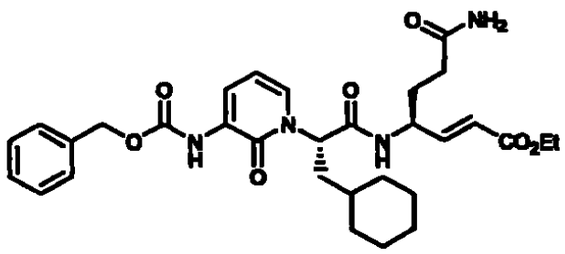
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Preparation of Products 13 and 14

The preceding intermediate was converted to an inseparable 1:1 mixture of the title compounds by a process that was analogous to that described in Example 3 for the conversion of pyrrole-2-carbonyl chloride to compounds 3 and 4 and utilizing intermediate Y1 (Example 22) in lieu of Y2 where appropriate. ^{1}H NMR ($CDCl_3$) δ 1.55-2.00 (m, 6H), 2.50-3.50 (m, 7H), 4.00-4.50 (m, 3H), 4.42-5.60 (m, 1H), 5.90-8.40 (m, 15H), 10.49 (s, 0.5H), 11.54 (s, 0.5H).

EXAMPLE 14

Preparation of Compound 15: *trans*-(2'*S*,4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-cyclohexylpropionylamino]-6-carbamoyl-hex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2*R*)-3-Cyclohexyl-2-hydroxypropionic Acid

Boc-D-Cyclohexylalanine-OH (3.00 g, 11.1 mmol, 1 equiv) was dissolved in 1,4-dioxane (10 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added. The reaction was stirred at 23 °C for 5 h, then the solvent was removed under reduced pressure. The residue was dissolved in 1 M H_2SO_4 (22 mL), cooled to 0 °C and 2 N $NaNO_2$ (22 mL) was added via addition funnel under argon. The reaction mixture was stirred at 0 °C for 3 h and warmed to room temperature overnight. The resulting mixture was extracted with MTBE (3 x 40 mL), dried over Na_2SO_4 and concentrated. The residue was triturated with petroleum ether, filtered and dried in the air to afford the title intermediate (0.6 g, 31%) as off-white solid. ^{1}H NMR (DMSO-d_6) δ 3.09-3.24 (m, 2H), 4.20-4.24 (m, 1H), 7.13-7.18 (m, 1H), 7.38-7.47 (m, 2H), 8.49 (s, br. 1H).

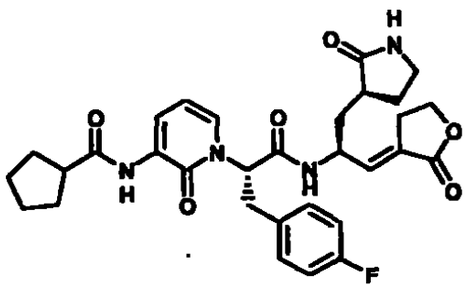
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Preparation of Compound 15

Intermediate C1 (Example 5) was converted to product 15 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing (2*R*)-3-cyclohexyl-2-hydroxypropionic acid (Example 14) where appropriate: mp = 64-66 °C; IR (cm^{-1}) 3302, 2925, 1721, 1651, 1197; ^1H NMR ($CDCl_3$) δ 0.93-1.05 (m, 2H), 1.18-1.22 (m, 4H), 1.32 (t, 3H, *J* = 7.2), 1.66-1.75 (m, 4H), 1.82-1.91 (m, 2H), 1.94-2.06 (m, 2H), 2.10-2.17 (m, 2H), 2.90-2.92 (m, 2H), 4.23 (q, 2H, *J* = 7.2), 4.52-4.60 (m, 1H), 5.23 (s, 2H), 5.65 (t, 1H, *J* = 8.1), 5.82-5.86 (m, 1H), 5.62 (dd, 1H, *J* = 15.9, 1.8), 6.01-6.05 (m, 1H), 6.37 (t, 1H, *J* = 7.2), 6.85 (dd, 1H, *J* = 15.9, 5.7), 7.25-7.29 (m, 1H), 7.36-7.43 (m, 5H), 7.88 (s, br. 1H), 8.09 (d, 1H, *J* = 6.9); Anal. $C_{31}H_{40}N_4O_7 \cdot 1.0H_2O$: C, H, N.

EXAMPLE 15

Preparation of Compound 16: *trans*-(2'*S*,2'''*S*,3''''''*S*)-Cyclopentanecarboxylic acid (1-{2'-(4''-fluorophenyl)-1'-[2'''-(2''''-oxo-dihydrofuran-3''''-ylidene)-1'''-(2''''''-oxopyrrolidin-3''''''-ylmethyl)ethylcarbamoyl]ethyl}-2-oxo-1,2-dihydropyridin-3-yl)amide



Preparation of Intermediate Cyclopentanecarboxylic Acid (2-Hydroxypyridin-3-yl)amide

A sample of 10% Pd on C (0.40 g) was added to a solution of 2-hydroxy-3-nitropyridine (3.52 g, 25.0 mmol, 1 equiv) in EtOH. The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) overnight and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (100 mL), cooled to 0 °C, and cyclopentanecarbonyl chloride (25 mmol, 3.04 mL, 1 equiv) and NMM (2.75 mL, 25 mmol, 1 equiv) were added sequentially. The resulting mixture was stirred at 0 °C for 20 min, then was partitioned between water (400

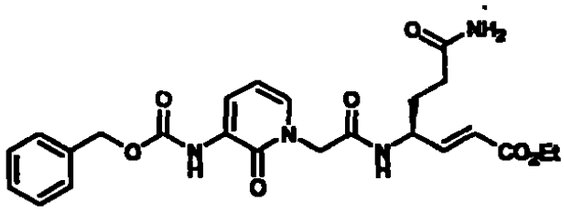
mL) and 10% CH_3OH in CH_2Cl_2 (2 x 400 mL). The organic layers were dried over Na_2SO_4, concentrated, and the resulting residue recrystallized from CH_2Cl_2/hexanes to afford the title intermediate as a off-white solid (3.36 g, 65%); mp = 242-243 °C; IR (cm^{-1}) 3263, 1644, 1605, 1521, 1199; ^1H NMR (DMSO-d_6) δ 1.51-1.57 (m, 2H), 1.60-1.72 (m, 4H), 1.79-1.88 (m, 2H), 2.98-3.08 (m, 1H), 6.20 (t, 1H, J = 6.9), 7.08 (d, 1H, J = 6.6), 8.23 (d, 1H, J = 7.5), 9.02 (s, br. 1H), 11.95 (s, br. 1H); Anal. $C_{11}H_{14}N_2O_2$: C, H, N.

Preparation of Compound 16

The preceding intermediate was converted to compound 16 by a process that was analogous to that described in Example 19 for the conversion of F2 to R1: mp = 135-137 °C; IR (cm^{-1}) 3288, 2954, 1754, 1682, 1511, 1219; ^1H NMR ($CDCl_3$) δ 0.84-0.93 (m, 2H), 1.55-1.66 (m, 4H), 1.82-2.02 (m, 5H), 2.27-3.22 (m, 2H), 2.70-2.89 (m, 3H), 3.09-3.17 (m, 1H), 3.20-3.37 (m, 2H), 3.42-3.39 (m, 1H), 5.63 (t, 1H, J = 7.2), 6.03 (s, br. 1H), 6.25-6.35 (m, 2H), 6.94 (t, 2H, J = 8.7), 7.08-7.12 (m, 2H), 7.25 (d, 1H, J = 9.0), 8.30-8.35 (m, 2H), 8.44 (d, 1H, J = 6.0); Anal. $C_{31}H_{35}FN_4O_6 \cdot 1.0H_2O$: C, H, N.

EXAMPLE 16

Preparation of Compound 17: *trans*-(4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)acetylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



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Preparation of intermediate (3-benzyloxycarbonylamino-2-oxo-2*h*-pyridin-1-yl)acetic acid *tert*-butyl ester

Sodium hydride (0.070 g of a 60% suspension in mineral oil, 1.75 mmol, 1.0 equiv) was added to a solution of (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (prepared as described in Example 1) (0.415 g, 1.70 mmol, 1 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C, then *tert*-butyl bromoacetate (0.275 mL, 1.86 mmol, 1.1 equiv) was added. The reaction mixture was warmed to 23 °C for 45 min, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 100 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided the title compound (0.485 g, 85%) as an off-white solid: mp = 88-90 °C; IR (cm^{-1}) 3380, 1739, 1652, 1604; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 4.57 (s, 2H), 5.20 (s, 2H), 6.25 (t, 1H, J = 7.1), 6.87 (dd, 1H, J = 6.9, 1.7), 7.27-7.41 (m, 5H), 7.86 (s, br, 1H), 8.05 (d, br, 1H J = 6.8); Anal. $C_{19}H_{22}N_2O_5$: C, H, N.

Preparation of Intermediate (3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)acetic Acid

(3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)acetic acid *tert*-butyl ester (0.485 g, 1.35 mmol) was stirred in a 1:1 mixture of trifluoroacetic acid and CH_2Cl_2 at 23 °C for 1 h. The volatiles were then removed under reduced pressure and the residue was triturated with Et_2O (40 mL). The resulting solid was filtered through a medium frit, washed with Et_2O (20 mL) and air-dried to give the title intermediate (0.315 g, 77%): mp = 171-173 °C; ^1H NMR (DMSO-d_6) δ 4.67 (s, 2H), 5.15 (s, 2H), 6.28 (t, 1H, J = 7.1), 7.29-7.43 (m, 7H), 7.85 (dd, 1H, J = 7.4, 1.7), 8.47 (s, 1H).

Preparation of Compound 17

The preceding intermediate was converted to compound 17 by a process analogous to that described in Example 23 for the conversion of W2 to J2: mp = 169-174 °C; IR (cm^{-1}) 3273, 1719, 1649; ^1H NMR (DMSO-d_6) δ 1.19 (t, 3H, J = 7.1), 1.64-1.85 (m, 2H), 2.10 (t, 2H, J = 7.6), 4.11 (q, 2H, J = 7.1), 4.38-4.41 (m, 1H), 4.60 (d, 1H, J = 15.5), 4.67 (d, 1H, J = 15.5), 5.15 (s, 2H), 5.92 (dd, 1H, J = 15.8, 1.3), 6.26 (t, 1H, J = 7.1), 6.76-6.83 (m, 2H),

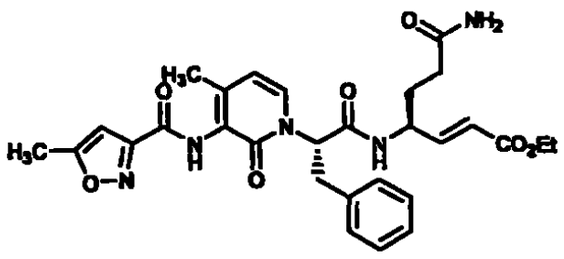
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7.09-7.42 (m, 7H), 7.84 (d, 1H, J = 7.3), 8.41-8.44 (m, 2H); Anal. $C_{24}H_{28}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 17

Preparation of Compound 18: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{4''-methyl-3''-{5'''-methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester



Preparation of Intermediate 5-Methylisoxazole-3-carboxylic Acid (2'-hydroxy-4'-methylpyridin-3'-yl)amide

A sample of 10% Pd on C (0.35g) was added to a solution of 2-hydroxy-3-nitropyridine (2.03 g, 14.5 mmol, 1 equiv) in EtOH. The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) overnight and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (100 mL), cooled to 0 °C, and 5-methylisoxazole-3-carbonyl chloride (2.11g, 14.5 mmol, 1 equiv) and NMM (1.51 mL, 14.5 mmol, 1 equiv) were added sequentially. The resulting mixture was stirred at 0 °C for 20 min, and then was partitioned between water (400 mL) and 10% CH_3OH in CH_2Cl_2 (2 x 400 mL). The organic layers were dried over Na_2SO_4, concentrated and the resulting residue was recrystallized from CH_2Cl_2/hexanes to afford the title intermediate as an off-white solid (2.42 g, 76%): IR (cm^{-1}) 3330, 1650, 1536; ^1H NMR (DMSO-d_6) δ 3.34 (s, 3H), 6.31 (t, 1H, J = 6.6), 6.73 (s, 1H), 7.21 (d, 1H, J = 7.2), 8.29 (s, 1H, J = 7.2), 9.46 (s, br. 1H), 12.23 (s, br. 1H).

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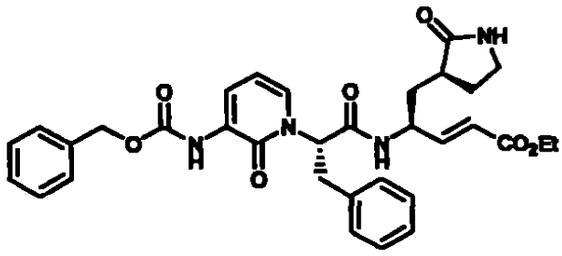
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Preparation of Compound 18

The preceding intermediate was converted to Compound 18 by a process analogous to that described in Example 7 for the conversion of C1 to Compound 7 utilizing (2*R*)-2-hydroxy-3-phenylpropionic acid where appropriate: mp = 138-141 °C; IR (cm^{-1}) 3289, 1663, 1542, 1203; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, *J* = 7.2), 1.62-1.89 (m, 2H), 1.99 (s, 3H), 2.02-2.07 (m, 1H), 2.47 (s, 3H), 3.03-3.39 (m, 5H), 4.12 (q, 2H, *J* = 7.2), 4.32-4.41 (m, 1H), 5.76 (dd, 1H, *J* = 15.6, 1.5), 5.80-5.83 (m, 1H), 6.13 (d, 1H, *J* = 7.5), 6.60 (s, br. 1H), 6.75 (dd, 1H, *J* = 15.6, 5.4), 7.15-7.24 (m, 5H), 7.76 (d, 1H, *J* = 7.2), 8.65 (d, 1H, *J* = 7.8), 9.59 (s, br. 1H); Anal. $C_{29}H_{33}N_5O_7 \cdot 1.5TFA$: C, H, N.

EXAMPLE 18

Preparation of Compound 19: *trans*-(2'*S*,3'''*S*,4*S*)-4-[2'-(3''-Benzyloxy-carbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester

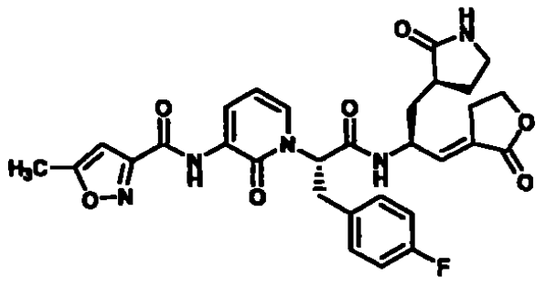


The title compound was prepared from K1 (Example 19) by a process analogous to that described in Example 19 for the conversion of K1 to R1 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid, (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 2), and commercially available (carbethoxymethylene)-triphenylphosphorane where appropriate: IR (cm^{-1}) 3272, 1684 (br), 1590, 1514, 1273, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.1), 1.42-1.55 (m, 1H), 1.59-1.75 (m, 1H), 2.00-2.27 (m, 3H), 3.07-3.28 (m, 3H), 3.43 (dd, 1H, *J* = 13.7, 7.3), 4.19 (q, 2H, *J* = 7.1), 4.36-4.47 (m, 1H), 5.12-5.21 (m, 2H), 5.75 (dd, 1H, *J* = 15.6, 1.2), 5.85-5.94 (m, 1H), 6.26 (t, 1H, *J* = 7.2), 6.58 (s, 1H), 6.70 (dd, 1H, *J* = 15.6, 5.7), 7.10-7.41 (m, 10H), 7.44-7.50 (m, 1H), 7.71 (s, 1H), 7.97 (d, 1H *J* = 6.2), 8.28 (d, 1H, *J* = 6.8); Anal. $C_{33}H_{36}N_4O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 19

Preparation of Compound 20: *trans*-(2''*S*,2''''*S*,3''''''*S*)-5-Methylisoxazole-3-carboxylic Acid (1'-{2''-(4'''-fluorophenyl)-1''-[2''''-(2'''''-oxodihydrofuran-3'''''-ylidene)-1''''-(2''''''-oxopyrrolidin-3''''''-ylmethyl)ethylcarbamoyl]ethyl}-2'-oxo-1',2'-dihydropyridin-3'-yl)amide (R1)



Preparation of Intermediate (1*S*,3'*S*)-{2-(*tert*-Butyldiphenylsilanyloxy)-1-[1'-(2'',4''-dimethoxybenzyl)-2'-oxopyrrolidin-3'-ylmethyl]ethyl}carbamic Acid *tert*-Butyl Ester (L1)

Intermediate K1 (4.41 g, 10.8 mmol, 1 equiv) was stirred in CH_2Cl_2 (50 mL) and the mixture was cooled to 0 °C. Triethylamine (7.52 mL, 54.0 mmol, 5 equiv), *tert*-butylchlorodiphenylsilane (5.53 mL, 21.6 mmol, 2 equiv) and 4-(dimethylamino)pyridine (0.330 g, 2.70 mmol, 0.25 equiv) were added successively. The mixture was allowed to warm to 23 °C and was stirred for 2 h. It was then diluted with MTBE (400 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography to provide the title intermediate (3.51 g, 50%) as a white foam: IR (cm^{-1}) 3319, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.42 (s, 9H), 1.44-1.65 (m, 2H), 2.05-2.17 (m, 1H), 2.23-2.35 (m, 1H), 2.44-2.56 (m, 1H), 3.14-3.21 (m, 2H), 3.55-3.68 (m, 2H), 3.69-3.81 (m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 4.42 (s, 2H), 4.77 (d, 1H, J = 9.3), 6.41-6.46 (m, 2H), 7.09-7.13 (m, 1H), 7.34-7.46 (m, 6H), 7.61-7.67 (m, 4H); Anal. $C_{37}H_{50}N_2O_6Si$: C, H, N.

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Preparation of Intermediate (1'*S*,2*R*,3''*S*)-*N*-{2'-(*tert*-Butyldiphenylsilanyloxy)-1'-[1''-(2''',4'''-dimethoxybenzyl)-2''-oxopyrrolidin-3''-ylmethyl]ethyl}-2-hydroxy-3-(4''''-fluorophenyl)propionamide (M1)

Intermediate L1 from above (3.4 g, 5.26 mmol, 1 equiv) was dissolved in 1,4-dioxane (20 mL) at 23 °C. A solution of HCl in the same solvent (4.0 M, 20 mL) was added. After stirring 75 min, the volatiles were evaporated to provide a residue which was dissolved in CH_3CN (25 mL) and cooled to 0 °C. (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic acid (intermediate S1, see below, 0.968 g, 5.26 mmol, 1 equiv), 4-methylmorpholine (1.91 mL, 17.4 mmol, 3.3 equiv) and HATU (2.20 g, 5.79 mmol, 1.1 equiv) were added successively and the reaction mixture was allowed to warm to 23 °C and stirred 2.5 h. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 100 mL) and a mixture of brine and $NaHCO_3$ (1:1, 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (first in 5% CH_3OH in CH_2Cl_2, then in 3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.90 g, 51%) as a white foam: IR (cm^{-1}) 3389, 3319, 1660, 1508; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.52-1.66 (m, 2H), 2.02-2.13 (m, 2H), 2.20-2.39 (m, 2H), 2.77-2.86 (m, 1H), 3.07-3.23 (m, 3H), 3.47 (dd, 1H, J = 9.9, 5.9), 3.59 (dd, 1H, J = 9.9, 3.6), 3.77 (s, 3H), 3.78 (s, 3H), 3.99-4.11 (m, 1H), 4.22-4.29 (m, 1H), 4.31-4.41 (m, 2H), 6.36-6.45 (m, 2H), 6.81-6.89 (m, 2H), 7.05 (d, 1H, J = 8.0), 7.13-7.22 (m, 3H), 7.34-7.46 (m, 6H), 7.59-7.67 (m, 4H); Anal. $C_{41}H_{49}FN_2O_6Si \cdot 0.25H_2O$: C, H, N.

Preparation of Intermediate (1'*S*,2*R*,3''*S*)-Methanesulfonic Acid 1-{2'-(*tert*-butyldiphenylsilanyloxy)-1'-[1''-(2''',4'''-dimethoxybenzyl)-2''-oxopyrrolidin-3''-ylmethyl]ethylcarbamoyl}-2-(4''''-fluorophenyl)ethyl Ester (N1)

Intermediate M1 from above (2.13 g, 2.99 mmol, 1 equiv) and iPr_2NEt (0.729 mL, 4.19 mmol, 1.4 equiv) were dissolved in CH_2C_2 (35 mL) and cooled to –10 °C. Methanesulfonyl chloride (0.277 mL, 3.58 mmol, 1.2 equiv) was added dropwise, slowly, with vigorous stirring. After 30 min, the reaction mixture was diluted with MTBE (500 mL), washed with a mixture of brine and 10% $KHSO_4$ (2:1, 100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

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Preparation of Intermediate 5-Methylisoxazole-3-carboxylic Acid (2'-hydroxypyridin-3'-yl)amide (F2)

A suspension of 10% palladium on carbon (0.45 g) and 2-hydroxy-3-nitropyridine (7.00 g, 50.0 mmol, 1 equiv) in EtOH (210 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was suspended in CH_3CN (170 mL) and cooled to 0 °C. 5-Methylisoxazole-3-carbonyl chloride (8.00 g, 55.0 mmol, 1 equiv) was added in one portion. After 25 min at 0 °C, the reaction mixture was allowed to warm to 23 °C and stirred for an additional 75 min. The thick mixture was then poured into dilute HCl (0.02 M, 150 mL) and mixed thoroughly. The undissolved solid was collected by filtration and washed with H_2O (2 x 20 mL) then dried under vacuum overnight to provide the title intermediate (7.1 g, 65%): ^1H NMR (DMSO-d_6) δ 2.48 (s, 3H), 6.29 (dd, 1H, J = 7.2, 6.6), 6.69 (s, 1H), 7.19 (dd, 1H, J = 6.6, 1.8), 8.26 (dd, 1H, J = 7.2, 1.8), 9.43 (s, 1H), 12.20 (s, 1H).

Preparation of Intermediate (1'''*S*,2''*S*,3''''*S*)-5-Methylisoxazole-3-carboxylic Acid {1'-[1''-{2'''-(*tert*-butyldiphenylsilanyloxy)-1'''-[1''''-(2''''',4''''')-dimethoxybenzyl)-2''''-oxopyrrolidin-3''''-ylmethyl]ethylcarbamoyl}-2''-(4'''''-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (O1)

Intermediate F2 from above (1.11 g, 5.06 mmol, 1.7 equiv) was stirred in THF (14 mL). Sodium hydride (60% dispersion in mineral oil, 0.173 g, 4.32 mmol, 1.45 equiv) was added. After stirring 30 min, a solution of intermediate N1 from above (1 equiv based on M1) in THF (11 mL) was added. The resulting mixture was heated to reflux overnight, then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 100 mL) and brine and $NaHCO_3$ (3:1, 100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the desired intermediate O1 as a white foam (2.58 g, 95%): IR (cm^{-1}) 3331, 3284, 1666, 1596, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.45-1.71 (m, 2H), 1.94-2.32 (m, 3H), 2.52 (s, 3H), 3.07-3.19 (m, 3H), 3.42-3.52 (m, 2H), 3.67-3.74 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.99-4.10 (m, 1H), 4.30 (d, 1H, J = 14.6), 4.39 (d, 1H, J = 14.6), 5.54-5.63 (m, 1H), 6.25 (t, 1H, J = 7.3), 6.42-6.50 (m, 3H), 6.81-6.88 (m,

2H), 7.04-7.13 (m, 3H), 7.20-7.26 (m, 1H), 7.36-7.48 (m, 7H), 7.60-7.68 (m, 4H), 8.40 (dd, 1H, J = 7.3, 1.6), 9.60 (s, 1H); Anal. $C_{51}H_{56}FN_5O_8Si$: C, H, N.

Preparation of Intermediate (2''*S*,2'''*S*,3''''*S*)-5-Methylisoxazole-3-carboxylic Acid {1'-[1''-{1'''-[1''''-(2''''',4''''')-dimethoxybenzyl)-2''''-oxo pyrrolidin-3''''-ylmethyl]-2'''-hydroxyethylcarbamoyl}-2''-(4''''''-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (P1)

Intermediate O1 from above (2.51 g, 2.75 mmol, 1 equiv) was dissolved in a mixture of CH_3CN (30 mL) and H_2O (1 mL) in a plastic tube. Hydrofluoric acid (48%, 5 mL) was added dropwise. After 1 h and 1.5 h, more hydrofluoric acid (2.5 mL and 2 mL respectively) was added. After 3.5 h total, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (250 mL), extracted with CH_2Cl_2 (3 x 400 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the title intermediate (1.84 g, 99%) as a white foam: IR (cm^{-1}) 3401 (br), 3331, 1655, 1590, 1531, 1508, 1455, 1208; ^1H NMR ($CDCl_3$) δ 1.47-1.63 (m, 2H), 1.87-1.99 (m, 1H), 2.07-2.18 (m, 1H), 2.33-2.44 (m, 1H), 2.49 (s, 3H), 3.10-3.24 (m, 3H), 3.46-3.56 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.84-3.89 (m, 1H), 3.92-4.03 (m, 1H), 4.19 (d, 1H, J = 14.5), 4.39 (d, 1H, J = 14.5), 5.54-5.61 (m, 1H), 6.22 (t, 1H, J = 7.2), 6.38-6.46 (m, 3H), 6.85-6.93 (m, 2H), 6.99-7.04 (m, 1H), 7.06-7.13 (m, 2H), 7.24 (dd, 1H, J = 7.2, 1.7), 8.33 (d, 1H, J = 7.3), 8.38 (dd, 1H, J = 7.2, 1.7), 9.54 (s, 1H); Anal. $C_{35}H_{38}FN_5O_8 \cdot 0.50H_2O$: C, H, N.

Preparation of Intermediate *trans*-(2''*S*,2'''*S*,3''''*S*)-5-Methylisoxazole-3-carboxylic Acid {1'-[1''-[1'''-[1''''-(2''''',4''''')-dimethoxybenzyl)-2''''-oxo pyrrolidin-3''''-ylmethyl]-2'''-(2-oxocyclopentylidene)ethylcarbamoyl]-2''-(4''''''-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (Q1)

Intermediate P1 from above (1.76 g, 2.60 mmol, 1 equiv) and commercially available Dess-Martin periodinane (1.11 g, 2.60 mmol, 1 equiv) were combined in CH_2Cl_2 (20 mL) at 23 °C and stirred 2 h. The volatiles were evaporated. The residue was suspended in toluene and concentrated to dryness (2 x 25 mL). The resulting residue was dissolved in a mixture of ethylene glycol dimethyl ether and DMF (5:1, 24 mL).

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) (0.902 g, 2.60 mmol, 1

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equiv) was added and the reaction mixture was heated to 100 °C for 1.5 h. It was then allowed to cool, diluted with EtOAc (500 mL), washed with brine (200 mL, 100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed (gradient elution, 2→3% CH_3OH in CH_2Cl_2) then rechromatographed (50% EtOAc in CH_2Cl_2) to give the title intermediate (1.46 g) contaminated with triphenylphosphine oxide (approximately 35% by weight): ^1H NMR ($CDCl_3$) δ 1.47-1.62 (m, 2H), 1.87-1.98 (m, 1H), 2.21-2.31 (m, 1H), 2.38-2.52 (m, 1H), 2.50 (s, 3H), 2.81-2.93 (m, 1H), 3.10-3.33 (m, 4H), 3.50 (dd, 1H, J = 14.1, 7.0), 3.76 (s, 3H), 3.77 (s, 3H), 4.19 (d, 1H, J = 14.3), 4.29-4.52 (m, 3H), 4.38 (d, 1H, J = 14.3), 5.42-5.49 (m, 1H), 6.23 (t, 1H, J = 7.2), 6.27-6.33 (m, 1H), 6.40-6.48 (m, 3H), 6.90-6.97 (m, 2H), 7.00-7.12 (m, 3H), 7.15 (dd, 1H, J = 7.2, 1.6), 8.39 (dd, 1H, J = 7.2, 1.6), 8.83 (d, 1H, J = 5.7), 9.56 (s, 1H).

Preparation of Product R1 (Compound 20)

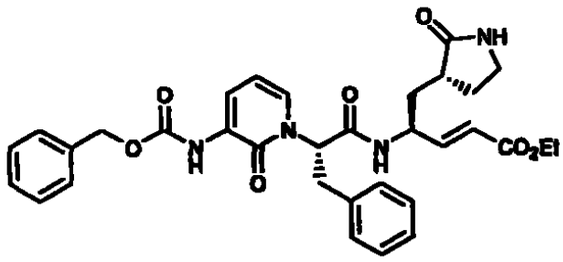
Intermediate Q1, prepared above, was dissolved in a mixture of $CHCl_3$ (30 mL) and H_2O (3 mL). DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was added and the reaction mixture was warmed in a 60 °C oil bath for 1.5 h. More DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was added and the reaction vessel was held in the 60 °C oil bath for 1.5 h more. DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was again added. After stirring 2 h more, the reaction mixture was allowed to cool, diluted with CH_2Cl_2 (250 mL), and washed sequentially with a mixture of brine and 1 N HCl (2:1, 80 mL), a mixture of brine and $NaHCO_3$ (2:1, 80 mL) and brine (80 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (2.5% CH_3OH in CH_2Cl_2) to provide the desired product (0.530 g, 73%) as an off-white amorphous solid: IR (cm^{-1}) 3336, 1750, 1682, 1530; ^1H NMR ($CDCl_3$) δ 1.39-1.49 (m, 1H), 1.63-1.80 (m, 1H), 2.09-2.37 (m, 3H), 2.49 (s, 3H), 2.74-2.86 (m, 1H), 3.11 (dd, 1H, J = 13.8, 8.5), 3.14-3.38 (m, 3H), 3.39 (dd, 1H, J = 13.8, 7.5), 4.30-4.46 (m, 3H), 5.72-5.79 (m, 1H), 6.29 (t, 1H, J = 7.2), 6.30-6.36 (m, 1H), 6.44-6.47 (m, 1H), 6.77 (s, 1H), 6.88-6.97 (m, 2H), 7.04-7.11 (m, 2H), 7.44-7.50 (m, 1H), 8.37 (dd, 1H, J = 7.2, 1.6), 8.66 (d, 1H, J = 6.2), 9.47 (s, 1H); Anal. $C_{30}H_{30}FN_5O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 20

Preparation of Compound 21: *trans*-(2'*S*,3'''*R*,4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenyl propionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester

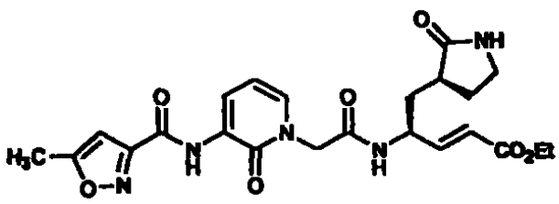


The title compound was prepared from (2*S*,3'*R*)-{1-[1'-(2'',4''-dimethoxybenzyl)-2'-oxopyrrolidin-3'-ylmethyl]-2-hydroxyethyl}carbamic acid *tert*-butyl ester (prepared as described in Dragovich, et al. *J. Med. Chem.* 1999, *42*, 1213) by a process analogous to that described in Example 19 for the conversion of K1 to R1 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid, (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 2), and commercially available (triphenyl-λ^5-phosphanylidene)acetic acid ethyl ester where appropriate: IR (cm^{-1}) 3483, 3272, 1684 (br), 1514, 1267, 1196; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 1.48-1.79 (m, 2H), 2.02-2.24 (m, 2H), 2.27-2.39 (m, 1H), 3.12 (dd, 1H, J = 13.7, 8.2), 3.19-3.34 (m, 2H), 3.48 (dd, 1H, J = 13.7, 7.8), 4.19 (q, 2H, J = 7.1), 4.43-4.53 (m, 1H), 5.17 (s, 2H), 5.73 (dd, 1H, J = 15.6, 1.3), 5.90-5.98 (m, 1H), 6.27 (t, 1H, J = 7.1), 6.63 (dd, 1H, J = 15.6, 6.0), 6.65-6.71 (m, 1H), 7.13-7.27 (m, 6H), 7.31-7.40 (m, 4H), 7.50 (dd, 1H, J = 7.1, 1.6), 7.75 (s, 1H), 7.97 (d, 1H, J = 6.6), 8.69 (d, 1H, J = 7.0); Anal. $C_{33}H_{36}N_4O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 21

Preparation of Compound 22: *trans*-(4*S*,3''''*S*)-4-(2'-{3''-[(5'''-Methyl isoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl} acetylamino)-5-(2''''-oxopyrrilidin-3''''-yl)pent-2-enoic Acid Ethyl Ester



Preparation of Intermediate {3-[(5'-Methylisoxazole-3'-carbonyl)amino]-2-oxo-2*H*-pyridin-1-yl}acetic Acid *tert*-Butyl Ester

To a solution of 5-methylisoxazole-3-carboxylic acid (2'-hydroxy-4'-methylpyridin-3'-yl)amide (F2, Example 19) (0.520 g, 2.37 mmol, 1 equiv) in THF (20 mL) at 0 °C was added NaH (0.095 g, 2.37 mmol, 1.0 equiv). The resulting mixture was stirred at 0 °C for 20 min, and then *t*-butyl bromoacetate (0.385 mL, 2.61 mmol, 1.1 equiv) was added. The reaction mixture was stirred and warmed to room temperature for 30 min, then was partitioned between 0.5 N HCl (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided the title intermediate (0.628 g, 79%) as a white solid: IR (cm^{-1}) 3343, 1743, 1651, 1581, 1156; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.53 (s, 3H), 4.65 (s, 2H), 6.32 (t, 1H, J = 7.2), 6.51 (s, 1H), 7.01 (dd, 1H, J = 6.9, 1.8), 8.50 (dd, 1H, J = 7.5, 1.8), 9.63 (s, br. 1H); Anal. $C_{16}H_{19}N_3O_5$: C, H, N.

Preparation of Compound 22

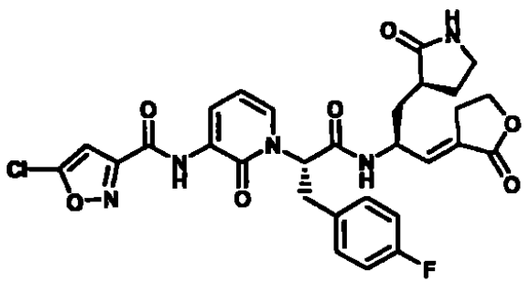
The preceding intermediate was transformed into Compound 22 by a process that was analogous to that described in Example 25 for the transformation of V3 to product R3: mp = 102-106 °C; IR (cm^{-1}) 3336, 1684, 1534, 1457; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2), 1.67-1.75 (m, 1H), 1.98-2.09 (m, 1H), 2.37-2.49 (m, 1H), 2.53 (s, 3H), 2.55-2.61 (m, 1H), 3.34-3.46 (m, 2H), 3.51-3.52 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.61-4.78 (m, 3H), 5.98 (dd, 1H, J = 15.6, 1.5), 6.20 (s, br. 1H), 6.35 (t, 1H, J = 7.8), 6.51 (s, 1H), 6.85 (dd, 1H, J = 15.6, 5.1),

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7.17 (d, 1H, J = 7.2), 8.33 (d, 1H, J = 7.2), 8.49 (d, 1H, J = 7.5), 9.57 (s, br. 1H); Anal. $C_{23}H_{27}N_5O_7$: C, H, N.

EXAMPLE 22

Preparation of Compound 23: *trans*-(2''*S*,2''''*S*,3''''''*S*)-5-Chloroisoxazole-3-carboxylic Acid (1'-{2''-(4'''-fluorophenyl)-1''-[2''''-(2'''''-oxodihydro furan-3'''''-ylidene)-1''''-(2''''''-oxopyrrolidin-3''''''-ylmethyl)ethyl carbamoyl]ethyl}-2'-oxo-1',2'-dihydropyridin-3'-yl)amide (R2)



Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid (S1)

This intermediate was prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,365, filed August 24, 1999.

Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid Methyl Ester (T1)

This intermediate was prepared as described in co-pending U.S. Provisional Patent Application No. 60/150,365, filed August 24, 1999.

Preparation of Intermediate (2*R*)-3-(4-Fluorophenyl)-2-trifluoromethanesulfonyloxypropionic Acid Methyl Ester (U1)

Intermediate T1 from above (0.198 g, 1.00 mmol, 1 equiv) was dissolved in CH_2Cl_2 (6 mL) and cooled in an ice bath. 2,6-Lutidine (0.198 mL, 1.70 mmol, 1.7 equiv) and trifluoromethanesulfonic anhydride (0.269 mL, 1.60 mmol, 1.6 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (200 mL), washed with a mixture of brine and 1 N HCl (2:1, 75 mL) and brine (75 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

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Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid Ethyl Ester

To a solution of ethyl chlorooximidoacetate (11.0 g, 72.6 mmol, 1 equiv) in 1,1-dichloroethylene (350 mL) was added Et_3N (25.3 mL, 181 mmol, 2.5 equiv) in 1,1-dichloroethylene (100 mL) via addition funnel over 30 min. The reaction mixture was stirred at room temperature for 23 h, 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. The residue was purified by flash column chromatography (10% EtOAc in hexanes) to give the title intermediate (4.49 g, 35%) as a pale yellow oil: IR (cm^{-1}) 1735, 1436, 1253; ^1H NMR ($CDCl_3$) δ 1.45 (t, 3H, J = 7.2), 4.49 (q, 2H, J = 7.2), 7.29 (s, 1H).

Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid

An aqueous solution of LiOH (2.0 M, 22.5 mL, 45.0 mmol, 2.0 equiv) was added to a solution of the preceding intermediate (3.95 g, 22.5 mmol, 1 equiv) in EtOH (80 mL) at 23 °C. The resulting mixture was stirred at room temperature for 45 min, then the volatiles were removed under reduced pressure. The residue thus obtained was partitioned between 1.0 N HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated to give the title intermediate (crude) (2.84 g, 86%) as a off-white solid which was used without further purification: ^1H NMR (DMSO-d_6) δ 7.15 (s, 1H).

Preparation of Intermediate 5-Chloroisoxazole-3-carbonyl Chloride

A solution of 5-chloroisoxazole-3-carboxylic acid (0.750 g, 4.32 mmol, 1 equiv) and thionyl chloride (9.0 mL, 120 mmol, 28 equiv) in $CHCl_3$ (21 mL) was heated to reflux for 28 h. The volatiles were evaporated to provide a residue which was dissolved in benzene (40 mL), which was subsequently evaporated to give the title intermediate as a yellow oil which was used without further purification.

Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid (2'-hydroxypyridin-3'-yl)amide (F3)

A suspension of 10% palladium on carbon (0.15 g) and 2-hydroxy-3-nitropyridine (1.70 g, 12.1 mmol, 2.8 equiv) in EtOH (60 mL) was subjected to one atmosphere of

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hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine (1.33 g, 99%) which was used without further purification. A portion of this material (0.524 g, 4.76 mmol, 1.1 equiv) was combined with the 5-chloroisoxazole-3-carbonyl chloride prepared above (4.32 mmol, 1 equiv based on theoretical yield) in THF (50 mL) and stirred 60 min. The volatiles were evaporated and the residue was stirred in half saturated $NaHCO_3$ (20 mL) for 30 min. The undissolved solid was collected by filtration, washed with H_2O (3 x 5 mL) and dried under vacuum overnight to provide the title intermediate (0.900 g, 87%) as a tan solid which was used without further purification. ^1H NMR (DMSO-d_6) δ 6.30 (t, 1H, J = 6.9), 7.22 (dd, 1H, J = 6.9, 1.7), 7.25 (s, 1H), 8.24 (dd, 1H, J = 6.9, 1.7), 9.47 (s, 1H), 12.22 (s, 1H).

Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}-3-(4'''-fluorophenyl)propionic Acid Methyl Ester (V1)

Intermediate F3 from above (0.280 g, 1.17 mmol, 1.17 equiv) was suspended in THF (7 mL). Sodium hydride (60% dispersion in mineral oil, 0.044 g, 1.1 mmol, 1.1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U1 from above (1.00 mmol, 1 equiv, based on T1) in THF (10 mL) was added dropwise. The resulting mixture was stirred 16 hours, then diluted with MTBE (250 mL) and washed with brine (2 x 80 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (33% EtOAc in hexanes) to provide the title intermediate (0.316 g, 75%) as a white foam: IR (cm^{-1}) 3331, 1743, 1690, 1643, 1602, 1531, 1437; ^1H NMR ($CDCl_3$) δ 3.33 (dd, 1H, J = 14.5, 10.3), 3.53 (dd, 1H, J = 14.5, 5.5), 3.78 (s, 3H), 5.36 (dd, 1H, J = 10.3, 5.5), 6.18 (t, 1H, J = 7.2), 6.67 (s, 1H), 6.82 (dd, 1H, J = 7.2, 1.7), 6.89-6.97 (m, 2H), 7.01-7.07 (m, 2H), 8.38 (dd, 1H, J = 7.2, 1.7), 9.52 (s, 1H); Anal. $C_{19}H_{15}ClFN_3O_5$: C, H, N.

Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}-3-(4'''-fluorophenyl)propionic Acid (W1)

Intermediate V1 from above (0.445 g, 1.06 mmol, 1 equiv) was dissolved in CH_3OH (10 mL). An aqueous solution of NaOH (1.0 M, 4.2 mL, 4.2 mmol, 4 equiv) was added

dropwise. The reaction mixture was stirred 2 h, then poured into a mixture of brine and 10% $KHSO_4$ (1:1, 50 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to provide the title intermediate as a yellow foam which was used without further purification.

Preparation of Intermediate *trans*-(2'*S*,3''*S*)-3-[2'-Amino-3'-(2''-oxodihydrofuran-3''-ylidene)propyl]pyrrolidin-2-one (Y1)

Intermediate X1 (prepared in a manner analogous to that described in Baldwin et al., *J. Org. Chem.* 1971, *36*, 1441) (0.413 g, 1.27 mmol, 1.2 equiv) was stirred for 45 min in a mixture of TFA (5 mL) in CH_2Cl_2 (10 mL). Then the volatiles were evaporated to provide the title intermediate which was used without purification.

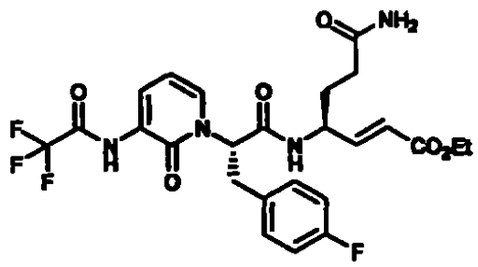
Preparation of Product R2 (Compound 23)

Intermediates W1 (1.06 mmol, 1 equiv based on V1) and Y1 (1.27 mmol, 1.2 equiv based on X1) were combined in CH_3CN (14 mL) and cooled in an ice bath. 4-Methylmorpholine (0.583 mL, 5.30 mmol, 5 equiv) and HATU (0.403 g, 1.06 mmol, 1 equiv) were added and the reaction mixture was allowed to warm to 23 °C and stirred 1.5 h. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 80 mL), a mixture of brine and $NaHCO_3$ (3:1, 80 mL) and brine (80 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was chromatographed (5% CH_3OH in CH_2Cl_2) then rechromatographed (2.5% CH_3OH in CH_2Cl_2) to provide the desired product R2 (0.418 g, 64%) contaminated with a diastereomer (approximately 30%, presumably the 2''R epimer): ^1H NMR ($CDCl_3$) (mixture of isomers) δ 1.33-1.51 (m), 1.62-1.88 (m), 2.06-2.39 (m), 2.73-2.88 (m), 2.98-3.45 (m), 4.27-4.44 (m), 5.71-5.88 (m), 6.27-6.43 (m), 6.66 (s), 6.68 (s), 6.81 (s), 6.88-6.98 (m), 7.03-7.24 (m), 7.48 (d, J = 7.3), 7.55-7.62 (m), 8.34-8.42 (m), 8.65 (d, J = 6.2), 8.77 (d, J = 7.0), 9.41-9.48 (m).

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EXAMPLE 23

Preparation of Compound 24: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{3'-(4''-fluorophenyl)-2'-[2'''-oxo-3'''-(2'''',2'''',2''''-trifluoroacetylamino)-2'''*H*-pyridin-1'''-yl]propionylamino}hex-2-enoic Acid Ethyl Ester (J2)



Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid Benzyl Ester (T2)

Intermediate S1 (1.00 g, 5.43 mmol, 1 equiv) was dissolved in CH_3CN (8 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.812 mL, 5.43 mmol, 1 equiv) and benzyl bromide (0.646 mL, 5.43 mmol, 1 equiv) were added successively. The resulting solution was stirred 40 h, then diluted with MTBE (250 mL) and washed with 5% $KHSO_4$ and brine (75 mL each). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (1.25 g, 84%) as a colorless oil which solidified over several days: IR (cm^{-1}) 3450, 1954, 1890, 1725, 1602; ^1H NMR ($CDCl_3$) δ 2.76-2.81 (m, 1H), 2.94 (dd, 1H, J = 14.1, 6.2), 3.08 (dd, 1H, J = 14.1, 4.6), 4.42-4.49 (m, 1H), 5.14 (d, 1H, J = 12.1), 5.21 (d, 1H, J = 12.1), 6.86-6.94 (m, 2H), 7.03-7.11 (m, 2H), 7.29-7.42 (m, 5H); Anal. $C_{16}H_{15}FO_3$: C, H.

Preparation of Intermediate (2*R*)-3-(4-Fluorophenyl)-2-trifluoromethanesulfonyloxypropionic Acid Benzyl Ester (U2)

Intermediate T2 from above (0.134 g, 0.489 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice bath. 2,6-Lutidine (0.114 mL, 0.979 mmol, 2 equiv) and trifluoromethanesulfonic anhydride (0.156 mL, 0.927 mmol, 1.9 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (150 mL), washed with a mixture of brine and 1 N HCl (2:1, 75 mL) and brine (50 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate 2,2,2-Trifluoro-*N*-(2'-hydroxypyridin-3'-yl)acetamide (F4)

TFA (4 mL) was added to a solution of intermediate F1 (0.700 g, 3.33 mmol, 1 equiv) in CH_2Cl_2 (6 mL). After stirring 30 min, the volatiles were evaporated. The residue was suspended in toluene and concentrated to dryness to provide crude 2-hydroxy-3-aminopyridine which was (without further purification) suspended in CH_2Cl_2 (14 mL) and cooled in an ice bath. 4-Methylmorpholine (1.10 mL, 10.0 mmol, 3 equiv) and trifluoroacetic anhydride (0.471 mL, 3.33 mmol, 1 equiv) were added successively. After 30 min, more 4-methylmorpholine (0.550 mL, 5 mmol, 1.5 equiv) was added. The reaction mixture was stirred an additional 1.5 h, then diluted with EtOAc (250 mL) and washed with brine, H_2O and brine (25 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.173 g, 25%) as a white amorphous solid: ^1H NMR (DMSO-d_6) δ 6.27 (t, 1H, J = 6.9), 7.32 (dd, 1H, J = 6.9, 1.8), 7.94 (dd, 1H, J = 6.9, 1.8), 10.16 (s, 1H), 12.20 (s, 1H); Anal. $C_7H_5F_3N_2O_2$: C, H, N.

Preparation of Intermediate (2*S*)-3-(4'-Fluorophenyl)-2-[2''-oxo-3''-(2''',2''',2'''-trifluoroacetylamino)-2''*H*-pyridin-1''-yl]propionic Acid Benzyl Ester (V2)

Intermediate F4 from above (0.111 g, 0.539 mmol, 1.1 equiv) was suspended in THF (3 mL). Sodium hydride (60% dispersion in mineral oil, 0.020 g, 0.50 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U2 (0.489 mmol, 1 equiv, based on T2) in THF (5 mL) was added dropwise. The resulting mixture was stirred 2 hours, then diluted with MTBE (150 mL) and washed with brine (2 x 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (0.190 g, 84%) as a thick oil: IR (cm^{-1}) 3343, 1743, 1727, 1655, 1602, 1296, 1214, 1161; ^1H NMR ($CDCl_3$) δ 3.31 (dd, 1H, J = 14.4, 10.0), 3.52 (dd, 1H, J = 14.4, 5.4), 5.21 (s, 2H), 5.39 (dd, 1H, J = 10.0, 5.4), 6.18 (t, 1H, J = 7.3), 6.85 (dd, 1H, J = 7.3, 1.7), 6.87-7.04 (m, 4H), 7.25-7.38 (m, 5H), 8.31 (dd, 1H, J = 7.3, 1.7), 9.03 (s, 1H); Anal. $C_{23}H_{18}F_4N_2O_4$: C, H, N.

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Preparation of Intermediate (2*S*)-3-(4'-Fluorophenyl)-2-[2''-oxo-3''-(2''',2''',2'''-trifluoroacetylamino)-2''*H*-pyridin-1''-yl]propionic Acid (W2)

A suspension of 10% palladium on carbon (0.030 g) and intermediate V2 from above (0.151 g, 0.327 mmol, 1 equiv) in EtOH (5 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(4*S*)-4-Amino-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (AA1)

Intermediate Z1 (prepared according to Dragovich, et al., *J. Med. Chem.* 1998, *41*, 2806) (0.177 g, 0.326 mmol, 1 equiv) was stirred for 2 h in a solution of HCl in 1,4-dioxane (2.0 M, 8 mL). Then the volatiles were evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-{3'-(4''-Fluorophenyl)-2'-[2'''-oxo-3'''-(2'''',2'''',2''''-trifluoroacetylamino)-2'''*H*-pyridin-1'''-yl]propionylamino}-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (I3)

Intermediates W2 and AA1 (as prepared above) were combined in CH_2Cl_2 (5 mL) and cooled in an ice bath. HOBt (0.049 g, 0.36 mmol, 1.1 equiv), iPr_2NEt (0.171 mL, 0.982 mmol, 3 equiv) and EDC (0.063 g, 0.33 mmol, 1 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C overnight, then diluted with EtOAc (200 mL) and washed with 5% $KHSO_4$ and brine (50 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (44% EtOAc in hexanes) to provide the title intermediate (0.138 g, 53%) as a white amorphous solid: ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.26-2.34 (m, 2H), 3.01-3.10 (m, 1H), 3.31-3.40 (m, 1H), 4.19 (q, 2H, J = 7.1), 4.46-4.56 (m, 1H), 5.42-5.49 (m, 1H), 5.63 (dd, 1H, J = 15.7, 1.6), 6.18 (t, 1H, J = 7.3), 6.62-6.71 (m, 2H), 6.88-6.96 (m, 2H), 7.00-7.06 (m, 2H), 7.10-7.34 (m, 17H), 8.25 (dd, 1H, J = 7.3, 1.6), 9.02 (s, 1H); Anal. $C_{44}H_{40}F_4N_4O_6$: C, H, N.

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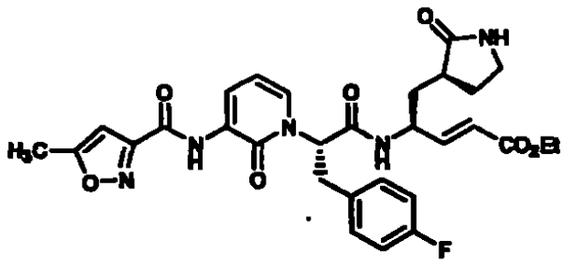
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Preparation of Product J2 (Compound 24)

Intermediate I3 from above (0.112 g, 0.141 mmol, 1 equiv) and triisopropylsilane (0.086 mL, 0.420 mmol, 3 equiv) were combined in CH_2Cl_2 (4 mL). TFA (2 mL) was added. After stirring 30 min, CCl_4 (4 mL) was added and the volatiles were evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the desired product (0.078 g, 100%) as a tan amorphous powder: ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 1.75-1.96 (m, 2H), 2.13-2.30 (m, 2H), 3.12 (dd, 1H, J = 13.7, 7.5), 3.46 (dd, 1H, J = 13.7, 8.5), 4.20 (d, 2H, J = 7.1), 4.45-4.55 (m, 1H), 5.63 (dd, 1H, J = 15.7, 1.6), 5.66-5.74 (m, 1H), 5.92 (s, 1H), 6.28 (s, 1H), 6.37 (t, 1H, J = 7.3), 6.67 (dd, 1H, J = 15.7, 5.7), 6.92-7.00 (m, 2H), 7.09-7.17 (m, 2H), 7.54 (dd, 1H, J = 7.3, 1.6), 7.60 (d, 1H, J = 7.5), 8.34 (dd, 1H, J = 7.3, 1.6), 9.04 (s, 1H); Anal. $C_{25}H_{26}F_4N_4O_6 \cdot 1.25H_2O$: C, H, N.

EXAMPLE 24

Preparation of Compound 25: trans-(2'*S*,3''''*S*,4*S*)-4-(3'-(4''-Fluorophenyl)-2'-{3'''-[(5''''-methylisoxazole-3''''-carbonyl)amino]-2'''-oxo-2'''*H*-pyridin-1'''-yl}propionylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester



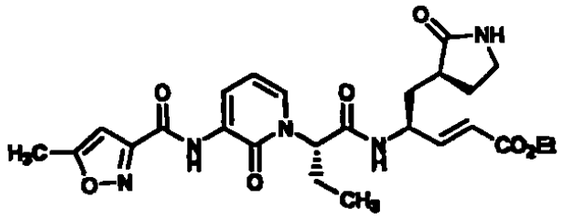
The title compound was prepared from F2 (Example 19) in a manner analogous to that described for the conversion of U2 to I3 in Example 23 utilizing intermediate Y2 (Example 25) where appropriate: IR (cm^{-1}) 3331, 1690, 1590, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0), 1.45-1.55 (m, 1H), 1.64-1.75 (m, 1H), 2.03-2.31 (m, 3H), 2.49 (s, 3H), 3.10 (dd, 1H, J = 13.7, 7.9), 3.20-3.46 (m, 3H), 4.20 (q, 2H, J = 7.0), 4.36-4.47 (m, 1H), 5.67 (dd, 1H, J = 15.7, 1.4), 5.85-5.92 (m, 1H), 6.29 (t, 1H, J = 7.2), 6.45 (s, 1H), 6.70 (dd, 1H, J = 15.7, 5.7), 6.86 (s, 1H), 6.90-6.97 (m, 2H), 7.10-7.16 (m, 2H), 7.60 (dd, 1H, J = 7.2, 1.6), 8.37 (dd, 1H, J = 7.2, 1.6), 8.51 (d, 1H, J = 6.6), 9.47 (s, 1H).

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EXAMPLE 25

Preparation of Compound 26: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5'''-Methyl-isoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester (R3)



Preparation of Intermediate (2*R*)-2-Trifluoromethanesulfonyl-oxybutyric acid *tert*-butyl ester (U3)

Commercially available T3 (0.575 g, 3.59 mmol, 1 equiv) was dissolved in CH_2Cl_2 (25 mL) and cooled in an ice bath. 2,6-Lutidine (0.836 mL, 7.18 mmol, 2 equiv) and trifluoromethanesulfonic anhydride (1.15 mL, 6.84 mmol, 1.9 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (400 mL), washed with a mixture of brine and 1 N HCl (2:1, 100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (2*S*)-2-{3'-[(5''-Methylisoxazole-3''-carbonyl) amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid *tert*-Butyl Ester (V3)

Intermediate F2 from above (0.200 g, 0.912 mmol, 1.1 equiv) was suspended in THF (6 mL). Sodium hydride (60% dispersion in mineral oil, 0.0332 g, 0.830 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U3 (0.830 mmol, 1 equiv, based on T3) in THF (7 mL) was added dropwise. The resulting mixture was stirred 2 hours, then diluted with EtOAc (200 mL) and washed with brine (2 x 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (0.178 g, 59%) as an oil: R_f = 0.30 (25% EtOAc in hexanes); IR (cm^{-1}) 3331, 1731, 1690, 1649, 1602, 1531; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.3), 1.45 (s, 9H), 1.83-2.01 (m, 1H), 2.17-2.31 (m, 1H), 2.50 (s, 3H), 5.44-5.51 (m, 1H), 6.32 (t, 1H, J = 7.2), 6.48 (s, 1H), 7.10 (dd, 1H, J = 7.2, 1.8), 8.45 (dd, 1H, J = 7.2, 1.8), 9.64 (s, 1H); Anal. $C_{18}H_{23}N_3O_5$: C, H, N.

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Preparation of Intermediate (2*S*)-2-{3'-[(5''-Methylisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid (W3)

Intermediate V3 from above (0.143 g, 0.397 mmol, 1 equiv) was stirred for 1 h in a solution of TFA (2 mL) in CH_2Cl_2 (3 mL). The volatiles were evaporated. The residue was suspended in toluene (10 mL) and concentrated to dryness, providing the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-Amino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic Acid Ethyl Ester (Y2)

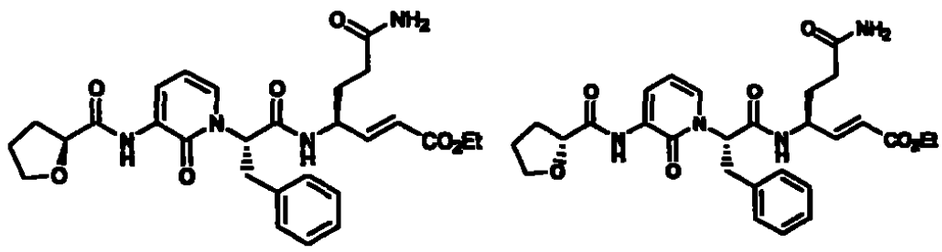
Intermediate X2, prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999(0.130 g, 0.398 mmol, 1 equiv), was stirred for 30 min in a solution of TFA (2 mL) in CH_2Cl_2 (3 mL). The volatiles were evaporated. The residue was suspended in toluene (10 mL) and concentrated to dryness, providing the title intermediate which was used without further purification.

Preparation of Product R3 (Compound 26)

Intermediates W3 and Y2 (as prepared above) were combined in CH_2Cl_2 (7 mL) and cooled in an ice bath. HOBt (0.064 g, 0.47 mmol, 1.2 equiv), iPr_2NEt (0.484 mL, 2.78 mmol, 7 equiv) and EDC (0.084 g, 0.44 mmol, 1.1 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C overnight, then diluted with EtOAc (500 mL) and washed with 5% $KHSO_4$, half saturated $NaHCO_3$, and brine (100 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.119 g, 58%) as a white foam: IR (cm^{-1}) 3331, 1684, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.3), 1.29 (t, 3H, J = 7.1), 1.47-1.58 (m, 1H), 1.62-1.77 (m, 1H), 1.85-2.00 (m, 1H), 2.08-2.33 (m, 4H), 2.49 (s, 3H), 3.25-3.42 (m, 2H), 4.19 (q, 2H, J = 7.1), 4.39-4.50 (m, 1H), 5.73 (dd, 1H, J = 8.8, 6.8), 5.97 (dd, 1H, J = 15.7, 1.4), 6.34 (t, 1H, J = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, J = 15.7, 5.9), 7.18 (s, 1H), 7.59 (dd, 1H, J = 7.2, 1.8), 8.42 (dd, 1H, J = 7.2, 1.8), 8.58-8.62 (m, 1H), 9.56 (s, 1); Anal. $C_{25}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 26

Preparation of a 1:1 Mixture of Compound 27: *trans*-(2'*S*,2'''*S*,4*S*)-6-Carbamoyl-4-(2'-{2''-oxo-3''-[(tetrahydrofuran-2'''-carbonyl)amino]-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester and Compound 28: *trans*-(2'*S*,2'''*R*,4*S*)-6-Carbamoyl-4-(2'-{2''-oxo-3''-[(tetrahydrofuran-2'''-carbonyl)amino]-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester

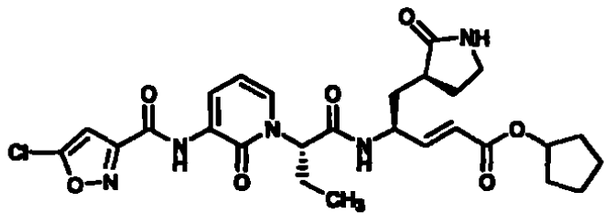


The title compounds were prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate tetrahydrofuran-2-carbonyl chloride (racemic, Aldrich) where appropriate: IR (cm^{-1}) 3344, 1646, 1519, 1178; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 7.2), 1.72-1.82 (m, 1H), 1.95-2.04 (m, 2H), 2.16-2.23 (m, 2H), 2.32-2.43 (m, 1H), 3.18-3.27 (m, 1H), 3.51-3.60 (m, 5H), 3.93-4.00 (m, 1H), 4.05-4.12 (m, 1H), 4.22 (q, 2H, J = 7.20, 4.46-4.55 (m, 2H), 5.54-5.69 (m, 2H), 6.34-6.41 (m, 2H), 6.68 (dd, 1H, J = 15.6, 5.4), 6.86-6.93 (m, 1H), 7.17-7.41 (m, 5H), 8.42-8.45 (m, 1H), 9.37 (d, 1H, J = 10.2); Anal. $C_{28}H_{34}N_4O_7 \cdot 1.5TFA$: C, H, N.

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EXAMPLE 27

Preparation of Compound 29:
trans-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Chloroisoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrroldin-3''''-yl)pent-2-enoic Acid Cyclopentyl Ester (R4)



Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid *tert*-Butyl Ester (V4)

Intermediate F3 from above (0.781 g, 3.26 mmol, 1.1 equiv) was suspended in THF (10 mL). Sodium hydride (60% dispersion in mineral oil, 0.119 g, 2.98 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U3 (2.96 mmol, 1 equiv, based on T3) in THF (15 mL) was by syringe. The resulting mixture was stirred 2 hours, then diluted with EtOAc (500 mL) and washed with brine (2 x 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the title intermediate (0.834 g, 74%): R_f = 0.33 (20% EtOAc in hexanes); IR (cm^{-1}) 3334, 1732, 1694, 1650, 1603, 1537; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.4), 1.46 (s, 9H), 1.85-2.00 (m, 1H), 2.17-2.32 (m, 1H), 5.44-5.50 (m, 1H), 6.33 (t, 1H, J = 7.3), 6.68 (s, 1H), 7.12 (dd, 1H, J = 7.3, 1.7), 8.43 (dd, 1H, J = 7.3, 1.7), 9.61 (s, 1H); Anal. $C_{17}H_{20}ClN_3O_5$: C, H, N.

Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid (W4)

Intermediate V4 from above (0.544 g, 1.42 mmol, 1 equiv) was stirred for 1 h in a mixture of TFA (9 mL) and CH_2Cl_2 (9 mL). The volatiles were evaporated. The residue was suspended in CCl_4 and concentrated to dryness (2 x 10 mL), providing the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-*tert*-Butoxycarbonylamino-5-[1'-(2'',4''-dimethoxybenzyl)-2'-oxopyrrolidin-3'-yl]pent-2-enoic Acid Cyclopentyl Ester (X3)

Intermediate K1 (prepared according to Dragovich, et al., *J. Med. Chem.* 1999, *42*, 1213) (2.00 g, 4.90 mmol, 1 equiv) and commercially available Dess-Martin periodinane (2.30 g, 5.38 mmol, 1.1 equiv) were combined in CH_2Cl_2 (50 mL) and stirred 2 h. The solvent was evaporated and the residue was suspended in and then evaporated from toluene (2 x 25 mL). The resulting residue was dissolved in THF (100 mL). (Triphenyl-λ^5-phosphanylidene)acetic acid cyclopentyl ester (prepared in a manner analogous to that described in Baldwin, et al. *J. Org. Chem.* 1971, *36*, 1441) (2.28 g, 5.87 mmol, 1.2 equiv) was added. The reaction mixture was heated to reflux for 100 min, allowed to cool, diluted with EtOAc (300 mL) and washed with a mixture of brine and $NaHCO_3$ (1:1, 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 44→50% EtOAc in hexanes) to provide the title intermediate (1.58 g, 62%) as a foam: IR (cm^{-1}) 3307, 1708, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.50-1.93 (m, 10H), 1.97-2.08 (m, 1H), 2.21-2.33 (m, 1H), 2.48-2.60 (m, 1H), 3.17-3.23 (m, 2H), 3.80 (s, 6H), 4.26-4.40 (m, 1H), 4.41 (s, 2H), 5.18-5.24 (m, 1H), 5.26-5.33 (m, 1H), 5.92 (dd, 1H, J = 15.6, 1.6), 6.41-6.47 (m, 2H), 6.82 (dd, 1H, J = 15.6, 5.2), 7.08-7.13 (m, 1H); Anal. $C_{28}H_{40}N_2O_7 \cdot 0.75H_2O$: C, H, N.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-*tert*-Butoxycarbonylamino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic Acid Cyclopentyl Ester (X4)

Intermediate X3 from above (1.54 g, 2.98 mmol, 1 equiv) was dissolved in a mixture of H_2O (5 mL) and $CHCl_3$ (50 mL). DDQ (0.947 g, 4.17 mmol, 1.4 equiv) was added and the reaction mixture was heated in a 60 °C oil bath for 1.5 h. More DDQ (0.90 g, 3.96 mmol, 1.3 equiv) was added and heating at 60 °C was continued for 2 h more. After cooling to 23 °C, the reaction mixture was diluted with CH_2Cl_2 (600 mL) and washed with a mixture of brine and 10% $KHSO_4$ (1:1, 150 mL) and a mixture of brine and $NaHCO_3$ (2 x 200 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.850 g, 78%) as a tan foam: IR (cm^{-1}) 3305, 1698, 1522, 1279, 1165; ^1H NMR

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(CDCl$_3$) δ 1.44 (s, 9H), 1.52-2.05 (m, 1H), 2.38-2.54 (m, 2H), 3.29-3.40 (m, 2H), 4.29-4.41 (m, 1H), 5.17-5.27 (m, 2H), 5.93 (dd, 1H, *J* = 15.7, 1.6), 5.96-6.40 (m, 1H), 6.82 (dd, 1H, *J* = 15.7, 5.3); Anal. $C_{19}H_{30}N_2O_5 \cdot 0.30H_2O$: C, H, N.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-Amino-5-(2'-oxo-pyrrolidin-3'-yl)pent-2-enoic acid Cyclopentyl Ester (Y3)

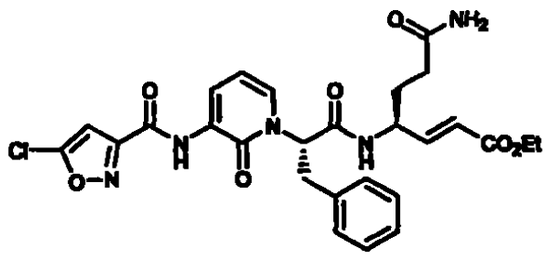
Intermediate X4 (0.522 g, 1.42 mmol, 1 equiv) was stirred for 40 min in a solution of TFA (7 mL) in CH_2Cl_2 (10 mL). The volatiles were evaporated. The residue was suspended in CCl_4 and concentrated to dryness (2 x 20 mL), providing the title intermediate which was used without further purification.

Preparation of Product R4 (Compound 29)

Intermediates W4 and Y3 (as prepared above) were combined in CH_2Cl_2 (25 mL) and cooled in an ice bath. HOBt (0.269 g, 1.99 mmol, 1.4 equiv), iPr_2NEt (1.74 mL, 9.99 mmol, 7 equiv) and EDC (0.341 g, 0.1.78 mmol, 1.25 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C over the weekend. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (1:1, 100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.590 g, 72%) as a white foam: IR (cm^{-1}) 3295, 1690, 1649, 1590, 1531; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.3), 1.50-2.02 (m, 10H), 2.11-2.37 (m, 4H), 3.25-3.44 (m, 2H), 3.64-3.74 (m, 1H), 4.41-4.52 (m, 1H), 5.18-5.24 (m, 1H), 5.69 (dd, 1H, J = 9.0, 6.6), 5.94 (dd, 1H, J = 15.6, 1.4), 6.36 (t, 1H, J = 7.3), 6.67 (s, 1H), 6.82 (dd, 1H, J = 15.6, 5.9), 7.15 (s, 1H), 7.58 (dd, 1H, J = 7.3, 1.7), 8.42 (dd, 1H, J = 7.3, 1.7), 8.49 (m, 1H), 9.52 (s, 1H); Anal. $C_{27}H_{32}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 28

Preparation of Compound 30: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3''-[(5'''-chloroisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (1'*S*,4''*S*)-5-Chloroisoxazole-3-carboxylic Acid {1'-[1''-Benzyl-4''-(*tert*-butyldimethylsilanyloxymethyl)-2''-oxo-6''-(tritylcarbamoyl)hexyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide

To solution of 5-chloroisoxazole-3-carboxylic acid (Example 22, 0.253 g, 1.71 mmol, 2.0 equiv) in $CHCl_3$ (21 mL) was added $SOCl_2$ (9 mL). The reaction mixture was heated to reflux for 26 h. The volatiles were removed under reduced pressure to give crude 5-chloroisoxazole-3-carbonyl chloride.

A sample of 10% Pd on C (0.070 g) was added to a solution of (1'*S*,4''*S*)-5-chloroisoxazole-3-carboxylic acid {1'-[1''-Benzyl-4''-(*tert*-butyldimethylsilanyloxy-methyl)-2''-oxo-6''-(tritylcarbamoyl)hexyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (Example 1, 0.74 g, 0.855 mmol, 1 equiv) in EtOAc (15 mL). The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) for 4 h, and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in THF (15 mL), cooled to 0 °C, and 5-chloroisoxazole-3-carbonyl chloride (1.71 mmol, 2.0 equiv) and NMM (0.188 mL, 1.71 mmol, 2.0 equiv) were added sequentially. The resulting mixture was stirred at 0 °C for 1 h, then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (35% EtOAc in hexanes) to afford the title intermediate (0.666 g, 90%): IR (cm^{-1}) 3332, 1684, 1531; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.60-1.71 (m, 1H),

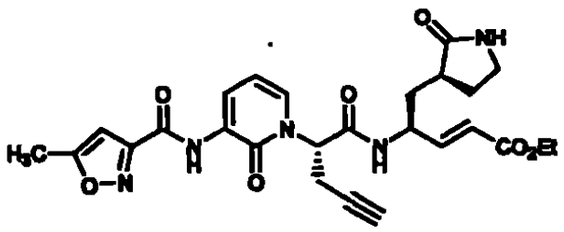
1.80-1.83 (m, 1H), 2.12-2.16 (m, 2H), 3.16-3.23 (m, 1H), 3.36-3.41 (m, 1H), 3.47-3.55 (m, 2H), 3.81-3.90 (m, 1H), 5.64-5.70 (m, 1H), 6.26 (t, 1H, J = 7.2), 6.47 (d, 1H, J = 8.7), 6.70 (s, 1H), 7.02 (s, br. 1H), 7.17-7.33 (m, 20H), 7.37 (d, 1H, J = 7.2), 8.40 (d, J = 7.8), 9.56 (s, br. 1H).

Preparation of Compound 30

The preceding intermediate was converted into compound 30 by a process that was analogous to that described in Example 7 for the conversion of intermediate C1 to compound 7: mp = 163-165 °C; IR (cm^{-1}) 3335, 1648, 1533, 1179; ^1H NMR ($CDCl_3$) δ 0.34 (t, 3H, J = 7.2), 1.76-1.86 (m, 1H), 1.94-2.00 (m, 1H), 2.23 (t, 2H, J = 6.9), 3.20-3.27 (m, 1H), 3.35-3.42 (m, 2H), 3.51-3.58 (m, 1H), 4.22 (q, 2H, J = 7.2), 4.52-4.57 (m, 1H), 5.69 (dd, 1H, J = 15.6, 1.5), 6.70 (s, br. 1H), 6.14 (s, br. 1H), 6.32 (s, br. 1H), 6.39 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.6, 5.4), 7.21-7.33 (m, 4H), 7.47 (d, 1H, J = 7.2), 8.44 (d, 1H, J = 7.5), 9.47 (s, br. 1H); Anal. $C_{27}H_{28}ClN_5O_7 \cdot 0.6H_2O$: C, H, N.

EXAMPLE 29

Preparation of Compound 31: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Methyl-isoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}pent-4'-ynoyl-amino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester

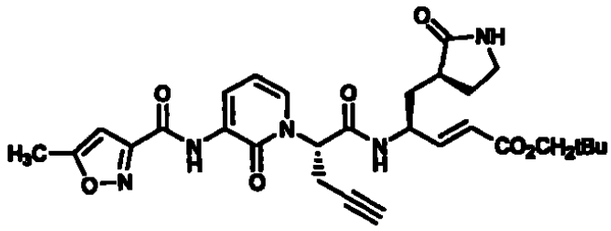


The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and Y2 and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3295, 1684, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.1), 1.52-1.62 (m, 1H), 1.64-1.80 (m, 1H), 2.04 (t, 1H, J = 2.6), 2.08-2.38 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, J = 17.0, 8.4, 2.6), 3.01 (ddd,

1H, *J* = 17.0, 6.8, 2.6), 3.22-3.39 (m, 2H), 4.18 (q, 2H, *J* = 7.1), 4.44-4.55 (m, 1H), 5.71-5.78 (m, 1H), 6.03 (dd, 1H, *J* = 15.6, 1.5), 6.32 (t, 1H, *J* = 7.2), 6.46 (s, 1H), 6.85 (dd, 1H, *J* = 15.6, 5.4), 6.89 (s, 1H), 7.49 (dd, 1H, *J* = 7.2, 1.7), 8.41 (dd, 1H, *J* = 7.2, 1.7), 8.68 (d, 1H, *J* = 6.8), 9.52 (s, 1H); Anal. $C_{26}H_{29}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EXAMPLE 30

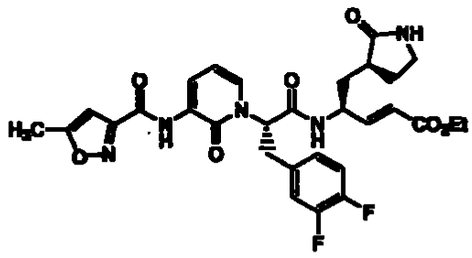
Preparation of Compound 32: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Methylisoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-pent-4'-ynoylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic acid 2,2-Dimethylpropyl Ester



The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and trans-(3'*S*,4*S*)4-*tert*-butoxycarbonylamino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic acid 2,2-dimethylpropyl ester (prepared from K1 in a manner similar to that described for the preparation of X4 in Example 27) and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3295, 1690, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.54-1.80 (m, 2H), 2.05 (t, 1H, *J* = 2.6), 2.10-2.39 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, *J* = 17.0, 8.2, 2.6), 3.01 (ddd, 1H, *J* = 17.0, 6.8, 2.6), 3.22-3.38 (m, 2H), 3.82 (s, 2H), 4.45-4.56 (m, 1H), 5.72-5.79 (m, 1H), 6.06 (dd, 1H, *J* = 15.7, 1.5), 6.33 (t, 1H, *J* = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J* = 15.7, 5.4), 6.93 (s, 1H), 7.51 (dd, 1H, *J* = 7.2, 1.7), 8.41 (dd, 1H, *J* = 7.2, 1.7), 8.69 (d, 1H, *J* = 6.6), 9.52 (s, 1H); Anal. $C_{29}H_{35}N_5O_7 \cdot 0.25H_2O$: C, H, N.

EXAMPLE 31

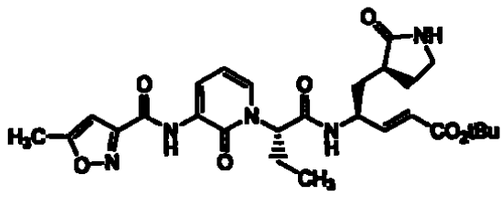
Preparation of Compound 33:
trans-(2'*S*,3''''*S*,4*S*)-4-(3'-(3'',4''-Difluorophenyl)-2'-{3'''-[(5''''-methylisoxazole-3''''-carbonyl)amino]-2'''-oxo-2'''*H*-pyridin-1'''-yl}propionylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester



The title compound was prepared by a method analogous to that described in Example 19 for the preparation of specific intermediate R1 utilizing (2*R*)-3-(3',4'-difluorophenyl)-2-hydroxypropionic acid (synthesized from (2*R*)-2-*tert*-butoxycarbonylamino-3-(3',4'-difluorophenyl)propionic acid in analogy to the preparation of intermediate S1 described in Example 22) and triethylphosphonoacetate where appropriate: IR (cm^{-1}) 3331, 1690, 1649, 1596, 1531, 1455, 1278; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.1), 1.44-1.54 (m, 1H), 1.63-1.78 (m, 1H), 2.08-2.29 (m, 3H), 2.49 (d, 3H, *J* = 0.9), 3.05 (dd, 1H, *J* = 13.6, 7.5), 3.20-3.42 (m, 3H), 4.19 (dq, 2H, *J* = 7.1, 1.7), 4.34-4.45 (m, 1H), 5.64 (dd, 1H, *J* = 15.7, 1.4), 6.00 (t, 1H, *J* = 7.8), 6.32 (t, 1H, *J* = 7.3), 6.45 (s, 1H), 6.71 (dd, 1H, *J* = 15.7, 5.6), 6.86-6.91 (m, 1H), 6.98-7.08 (m, 2H), 7.15 (s, 1H), 7.68 (dd, 1H, *J* = 7.3, 1.7), 8.39 (dd, 1H, *J* = 7.3, 1.7), 8.65 (d, 1H, *J* = 6.8), 9.46 (s, 1H); Anal. $C_{30}H_{31}F_2N_5O_7$: C, H, N.

EXAMPLE 32

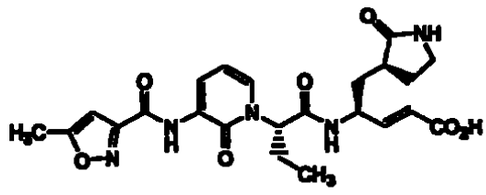
Preparation of Compound 34: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Methylisoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid *tert*-Butyl Ester



The title compound was prepared by a method analogous to that described for the synthesis of compound R3 in Example 25: IR (cm^{-1}) 3331, 3295, 1690, 1649, 1590, 1531, 1455, 1155; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.3), 1.40-1.60 (m, 1H), 1.49 (s, 9H), 1.62-1.78 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.36 (m, 4H), 2.50 (s, 3H), 3.26-3.43 (m, 2H), 4.39-4.50 (m, 1H), 5.78 (dd, 1H, J = 8.9, 6.7), 5.89 (dd, 1H, J = 15.7, 1.3), 6.35 (t, 1H, J = 7.3), 6.47 (s, 1H), 6.76 (dd, 1H, J = 15.7, 5.9), 7.33 (s, 1H), 7.64 (dd, 1H, J = 7.3, 1.8), 8.43 (dd, 1H, J = 7.3, 1.8), 8.59 (d, 1H, J = 6.8), 9.57 (s, 1H); Anal. $C_{27}H_{35}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EXAMPLE 33

Preparation of Compound 35: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Methylisoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid

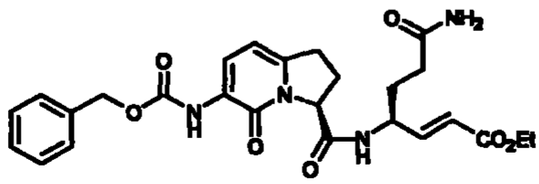


The title compound was prepared from compound 34 by acidic deprotection of the *tert*-butyl ester moiety present in that compound (following standard literature procedures): IR (cm^{-1}) 3319, 1678, 1643, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.2), 1.61-1.99

(m, 3H), 2.08-2.32 (m, 3H), 2.40-2.54 (m, 1H), 2.49 (s, 3H), 3.25-3.41 (m, 2H), 4.58-4.69 (m, 1H), 5.56-5.64 (m, 1H), 5.98 (d, 1H, J = 15.6), 6.21 (br, 1H), 6.37 (t, 1H, J = 7.3), 6.47 (s, 1H), 6.96 (dd, 1H, J = 15.6, 6.6), 7.50 (dd, 1H, J = 7.3, 1.6), 7.52 (s, 1H), 8.26 (d, 1H, J = 7.7), 8.44 (dd, 1H, J = 7.3, 1.6), 8.62 (s, 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EXAMPLE 34

Preparation of Compound 36: *trans*-(3'*S*,4*S*)-4-[(6'-Benzyloxycarbonylamino-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl)amino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinonitrile (a1)

n-Butyllithium (100 mL of a 1.6 M solution in hexanes, 160 mmol, 2.5 equiv) was added via cannula over 10 min to a solution of diisopropylamine (22.4 mL, 160 mmol, 2.5 equiv) in THF (600 mL) at -78 °C. The resulting pale yellow solution was stirred at -78 °C for 5 min, then was warmed to 0 °C for an additional 5 min. 2-Hydroxy-6-methylnicotinonitrile (8) (8.58 g, 64.0 mmol, 1 equiv) was added as a solid in small portions over 15 min and the deep orange *solution* thus obtained was stirred for 1 h at 0 °C. Allyl bromide (8.31 mL, 96.0 mmol, 1.5 equiv) was then added and the reaction mixture was warmed to 23 °C, maintained at that temperature for 30 min, and was partitioned between 1.0 M HCl (300 mL) and EtOAc (2 x 250 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The resulting orange solid was triturated with boiling Et_2O (100 mL) and subsequently cooled to 23 °C, then was filtered through a medium frit, washed with Et_2O (2 x 50 mL) and air-dried to give a1 (6.42 g, 58%) as a tan solid: mp = 122-125 °C; IR (KBr pellet, cm^{-1}) 2223, 1654; ^1H NMR (DMSO-d_6) δ 2.32-2.37 (m, 2H), 2.62 (t, 2H, J = 7.6), 4.96-5.06 (m, 2H), 5.69-5.83 (m, 1H), 6.23 (d, 1H, J = 7.3), 8.03 (d, 1H, J = 7.3), 12.55 (s, br, 1H); Anal. $C_{10}H_{10}N_2O \cdot 0.10H_2O$: C, H, N.

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Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinamide (b1)

Hydrogen peroxide (30 wt. % solution in water, 45 mL) was added to a solution of a1 (12.13 g, 70.2 mmol) in a mixture of EtOH (150 mL) and 10% aqueous NaOH (280 mL) at 23 °C. The reaction mixture was heated to 50 °C for 18 h, then was cooled to 23 °C and the volatiles were removed under reduced pressure. The residue was acidified with 12 M HCl to pH 2-3, and the resulting precipitate was filtered, washed with water (2 x 50 mL), and air-dried to afford b1 as a yellow solid (13.48 g, 100%): mp = 195-198 °C; IR (cm^{-1}) 3329, 3134, 1688, 1642; ^1H NMR (DMSO-d_6) δ 2.31-2.38 (m, 2H), 2.64 (t, 2H, J = 7.6), 4.96-5.05 (m, 2H), 5.71-5.84 (m, 1H), 6.29 (d, 1H, J = 7.3), 7.45 (s, br, 1H), 8.21 (d, 1H, J = 7.3), 9.00 (s, br, 1H), 12.37 (s, br, 1H); Anal. $C_{10}H_{12}N_2O_2 \cdot 0.15H_2O$: C, H, N.

Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinic Acid (c1)

A solution of b1 (12.38 g, 70.1 mmol) in 10% aqueous KOH (350 mL) was heated to reflux for 20 h and subsequently cooled to room temperature. The reaction mixture was acidified with 12 M HCl to pH 2-3, and the resulting precipitate was filtered, washed with water (2 x 50 mL), and dried under vacuum to afford c1 as a yellow solid (12.46 g, 92%): mp = 151-155 °C; IR (cm^{-1}) 2905 (br), 1736, 1652; ^1H NMR (DMSO-d_6) δ 2.34-2.29 (m, 2H), 2.73 (t, 2H, J = 7.6), 4.96-5.07 (m, 2H), 5.72-5.85 (m, 1H), 6.56 (d, 1H, J = 7.5), 8.28 (d, 1H, J = 7.5), 13.26 (s, br, 1H), 14.64 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparation of Intermediate (6-But-3-enyl-2-hydroxypyridin-3-yl) carbamic Acid Benzyl Ester (d1)

Triethylamine (13.9 mL, 99.7 mmol, 2.0 equiv) and diphenylphosphoryl azide (16.1 mL, 74.7 mmol, 1.5 equiv) were added sequentially to a suspension of c1 (9.63 g, 49.8 mmol, 1 equiv) in 1,4-dioxane (450 mL) at 23 °C. The resulting solution was heated to reflux for 7.5 h, then benzyl alcohol (10.3 mL, 99.5 mmol, 2.0 equiv) was added and reflux was continued for an additional 16 h. The dark brown reaction mixture was cooled to 23 °C and the volatiles were removed under reduced pressure. The resulting dark brown oil was

partitioned between water (300 mL) and EtOAc (2 x 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The solid thus obtained was triturated with Et_2O (150 mL) and was filtered through a medium frit, washed with Et_2O (2 x 50 mL) and air-dried to give d1 (7.34 g, 49%) as an off-white powder: mp = 179-180 °C; IR (cm^{-1}) 3386, 1727, 1645; ^1H NMR ($CDCl_3$) δ 2.39-2.46 (m, 2H), 2.65 (t, 2H, J = 7.5), 4.97-5.07 (m, 2H), 5.21 (s, 2H), 5.73-5.87 (m, 1H), 6.10 (d, 1H, J = 7.5), 7.32-7.44 (m, 5H), 7.68 (s, br, 1H), 8.06 (s, br, 1H), 12.74 (s, br, 1H); Anal. $C_{17}H_{18}N_2O_3$: C, H, N.

Preparation of Intermediate (6-But-3-enyl-2-methoxypyridin-3-yl) carbamic Acid Benzyl Ester (e1)

Trimethyloxonium tetrafluoroborate (2.0 g, 13.5 mmol, 1.2 equiv) and 2,6-di-*tert*-butylpyridine (1.52 mL, 6.76 mmol, 0.6 equiv) were added to a solution of d1 (3.36 g, 11.26 mmol, 1 equiv) in CH_2Cl_2 (80 mL) at 23 °C. The reaction mixture was stirred at that temperature for 65 h, then was partitioned between water (2 x 50 mL) and CH_2Cl_2 (2 x 200 mL) and combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (5% EtOAc in hexanes) to afford e1 (3.19 g, 91%) as colorless oil: IR (cm^{-1}) 3432, 1733; ^1H NMR ($CDCl_3$) δ 2.42-2.49 (m, 2H), 2.73 (t, 2H, J = 7.6), 3.96 (s, 3H), 4.94-5.07 (m, 2H), 5.20 (s, 2H), 5.80-5.94 (m, 1H), 6.71 (d, 1H, J = 7.9), 7.11 (s, br, 1H), 7.32-7.43 (m, 5H), 8.16 (s, br, 1H); Anal. $C_{18}H_{20}N_2O_3$: C, H, N.

Preparation of Intermediate (3'*R*)-[6-(3',4'-Dihydroxybutyl)-2-methoxypyridin-3-yl]carbamic Acid Benzyl Ester (f1)

To a mixture of 1:1 *t*-BuOH and water (300 mL) at 0 °C was added $(DHQD)_2AQN$ (0.148 g, 0.164 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (16.2 g, 49.2 mmol, 3 equiv), K_2CO_3 (6.8 g, 49.2 mmol, 3 equiv), potassium osmate dihydrate (0.024 g, 0.066 mmol, 0.004 equiv), and then e1 in t-BuOH (25 mL), sequentially. The resulting mixture was stirred at 0 ° C for 20 h, then warmed to room temperature and Na_2SO_3 (30 g) was added carefully. The mixture was stirred at room temperature for 2 h, then the volatiles were removed under reduced pressure. The residue was partitioned between water (200 mL) and EtOAc (3 x 200 mL) and the

combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to afford f1 (5.57 g, 98%) as pale yellow oil: IR (cm^{-1}) 3427 (br), 1731; ^1H NMR ($CDCl_3$) δ 1.76-1.87 (m, 2H), 2.07-2.11 (m, 1H), 2.80-2.89 (m, 2H), 3.46-3.53 (m, 1H), 3.60-3.67 (m, 1H), 3.71-3.77 (m, 1H), 3.96 (s, 3H), 4.64 (d, 1H, J = 3.2), 5.21 (s, 2H), 6.76 (d, 1H, J = 7.8), 7.12 (s, br, 1H), 7.34-7.43 (m, 5H), 8.22 (s, br, 1H); Anal. $C_{18}H_{22}N_2O_5$: C, H, N.

Preparation of Intermediate (3'*R*)-{6-[4'-(*tert*-Butyl-dimethyl-silanyloxy)-3'-hydroxybutyl]-2-methoxypyridin-3-yl}carbamic Acid Benzyl Ester (g1)

Triethylamine (1.55 mL, 11.1 mmol, 2.5 equiv), *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol, 1.6 equiv), and 4-dimethylaminopyridine (0.025 g, 0.20 mmol, 0.045 equiv) were added sequentially to a solution of f1 (1.54 g, 4.45 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 23 °C. The reaction mixture was stirred for 19 h at 23 °C, then was 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 (20% EtOAc in hexanes) provided g1 (1.69 g, 82%) as a colorless oil: IR (cm^{-1}) 3436, 1734; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.72-1.94 (m, 2H), 2.72-2.88 m, 2H), 3.26 (d, 1H, J = 3.1), 3.50 (dd, 1H, J = 9.8, 6.9), 3.58-3.63 (m, 1H), 3.65-3.70 (m, 1H), 3.95 (s, 3H), 5.20 (s, 2H), 6.75 (d, 1H, J = 8.1), 7.11 (s, br, 1H), 7.33-7.43 (m, 5H), 8.20 (s, br, 1H); Anal. $C_{24}H_{36}N_2O_5Si$: C, H, N.

Preparation of Intermediate (3*S*)-(3-Hydroxymethyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)-Carbamic Acid Benzyl Ester (h1)

2,6-Lutidine (2.43 mL, 20.84 mmol, 4.0 equiv) and trifluoromethanesulfonic anhydride (1.31 mL, 7.82 mmol, 1.5 equiv) were added sequentially to a solution of g1 (2.4 g, 5.21 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at –78 °C. The colorless reaction mixture was stirred at –78 °C for 45 min, warmed to 23 °C for an additional 15 min, then was partitioned between 0.5 M HCl (150 mL) and CH_2Cl_2 (2 x 150 mL). The organic layer was dried over Na_2SO_4 and was concentrated. The residue thus obtained was dissolved in THF (120 mL) at 23 °C and tetrabutylammonium fluoride (15.63 mL of a 1.0 M solution in THF, 15.63 mmol,

3.0 equiv) was added. The reaction mixture was stirred at that temperature for 1 h, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The residue thus obtained was purified by flash column chromatography (80% EtOAc in hexanes) to give h1 (0.953 g, 58%) as a colorless oil: IR (cm^{-1}) 3379 (br), 1727, 1649; ^1H NMR ($CDCl_3$) δ 1.86-1.97 (m, 1H), 2.29-2.41 (m, 1H), 2.90-3.15 (m, 2H), 3.80-3.93 (m, 2H), 4.78-4.86 (m, 1H), 5.11-5.15 (m, 1H), 5.20 (s, 2H), 6.20 (d, 1H, J = 7.5), 7.30-7.41 (m, 5H), 7.75 (s, br, 1H), 8.07 (d, 1H, J = 7.5); Anal. $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

Preparation of Intermediate
(3*S*)-6-Benzyloxycarbonylamino-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i1)

Dimethylsulfoxide (0.522 mL, 7.36 mmol, 2.6 equiv) was added dropwise to a solution of oxalyl chloride (0.321 mL, 3.68 mmol, 1.3 equiv) in CH_2Cl_2 (80 mL) at –78 °C. The reaction mixture was stirred for 20 min at that temperature, then a solution of h1 (0.890 g, 2.83 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added via cannula. After stirring an additional 20 min at –78 °C, triethylamine (1.97 mL, 14.15 mmol, 5.0 equiv) was added dropwise. The reaction mixture was maintained at –78 °C for 1.5 h, then acetic acid (15.57 mmol, 0.891 mL, 5.5 equiv) was added. The reaction mixture was warmed to 0 °C for 5 min, then was washed with water (50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford the crude aldehyde product as off-white foam. This material was utilized without further purification.

A solution of $NaClO_2$ (2.88 g, 25.47 mmol, 9.0 equiv) and NaH_2PO_4 (2.73 g, 19.81 mmol, 7.0 equiv) in water (60 mL) was added dropwise to a solution of the proceeding crude aldehyde (2.83 mmol, 1 equiv) in a mixture of *t*BuOH (60 mL) and 2-methyl-2-butene (10 mL) over 15 min at 23 °C. The resulting mixture was stirred at room temperature for 1 h, then, the volatiles were removed under reduced pressure. The residue thus obtained was partitioned between 0.5 M HCl (150 mL) and 10% CH_3OH in CH_2Cl_2 (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The resulting residue was purified by flash column chromatography (10% CH_3OH in CH_2Cl_2) to give i1 (0.346 g,

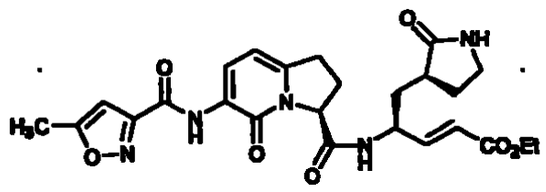
37%) as off-white solid: mp = 204-206 °C; IR (cm^{-1}) 3298, 1722, 1564, 1208; ^1H NMR (DMSO-d_6) δ 2.17-2.55 (m, 2H), 2.45-2.59 (m, 2H), 4.98 (dd, 1H, J = 9.6, 2.7), 5.16 (s, 2H), 6.23 (d, 1H, J = 7.5), 7.34-7.45 (m, 5H), 7.83 (d, 1H, J = 7.5), 8.34 (s, 1H); Anal. $C_{17}H_{16}N_2O_5$: C, H, N.

Preparation of Product k1 (Compound 36)

Intermediate i1 was transformed into compound 36 (via coupling with intermediate AA1) by a process that was analogous to that described in Example 23 for the transformation of W2 to product J2: ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.1), 1.64-1.84 (m, 2H), 2.01-2.16 (m, 2H), 2.41-2.50 (m, 1H), 3.01-3.06 (m, 2H), 4.11 (q, 2H, J = 7.1), 4.41 (m, br, 1H), 5.01 (dd, 1H, J = 9.2, 2.7), 5.14 (s, 2H), 5.87 (dd, 1H, J = 15.8, 1.4), 6.20 (d, 1H, J = 7.6), 6.75 (s, br, 1H), 6.82 (dd, 1H, J = 15.8, 5.0), 7.09-7.42 (m, 7H), 7.81 (d, 1H, J = 7.6), 8.38 (s, 1H), 8.55 (d, 1H, J = 8.4).

EXAMPLE 35

Preparation of Compound 37: *trans*-(3'*S*,3'''*S*,4*S*)-4-({6'-[(5''-Methylisoxazole-3''-carbonyl)amino]-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl} amino)-5-(2'''-oxopyrrolidin-3'''-yl)-pent-2-enoic Acid Ethyl Ester



Preparation of Intermediate (3''*R*)-(5-Methylisoxazole-3-carboxylic Acid {6'-[4''-(*tert*-butyldimethylsilanyloxy)-3''-hydroxybutyl]-2'-methoxy pyridin-3'-yl}amide (g2)

A suspension of intermediate g1 (prepared as described in Example 34) (4.21 g, 9.14 mmol, 1 equiv) and Pd on C (10%, 0.375 g) in EtOAc (120 mL) was stirred under an H_2 atmosphere (balloon) at 23 °C for 1 h. The reaction mixture was filtered through Celite and

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the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (120 mL), cooled to 0 °C, and NMM (1.00 mL, 9.10 mmol, 1.0 equiv) and 5-methylisoxazole-3-carbonyl chloride (1.33 g, 9.14 mmol, 1.0 equiv) were added sequentially. The reaction mixture was stirred at 0 °C for 1 h, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Trituration of the residue with a 1:3 mixture of Et_2O and hexanes (130 mL) provided a white solid which was collected by filtration, washed with hexanes (25 mL), and air-dried (2.61 g, 66%): mp = 100-102 °C; IR (cm^{-1}) 3390, 1696, 1593, 1536; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.78-1.95 (m, 2H), 2.52 (s, 3H), 2.78-2.90 (m, 2H), 3.45-3.53 (m, 2H), 3.60-3.74 (m, 2H), 4.03 (s, 3H), 6.51 (s, 1H), 6.79 (d, 1H, J = 7.9), 8.55 (d, 1H, J = 7.9), 8.95 (s, 1H); Anal. $C_{21}H_{33}N_3O_5Si$: C, H, N.

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Preparation of Intermediates (3*S*)-6-[(5'-Methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i2) and (3*S*)-8-Chloro-6-[(5'-methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i3)

The preceding intermediate (g2) was transformed into a 1:4 mixture of intermediates i2 and i3 by a process that was analogous to that described in Example 34 for the transformation of g1 to i1: (i2) IR (cm^{-1}) 3343, 2977 (br), 1741, 1688, 1648; ^1H NMR ($CDCl_3$) δ 2.28-2.74 (m, 2H), 2.50 (s, 3H), 3.04-3.32 (m, 2H), 5.31 (d, 1H, J = 7.9), 6.36 (d, 1H, J = 7.7), 6.48 (s, 1H), 8.58 (d, 1H, J = 7.7), 9.40 (s, 1H); (i3) IR (cm^{-1}) 2240, 1652, 1532, 1260; ^1H NMR (DMSO-d_6) δ 1.53-1.63 (m, 2H), 3.11-3.20 (m, 2H), 5.14 (dd, 1H, J = 6.9, 2.7), 6.75 (s, 1H), 8.32 (s, 1H), 9.41 (s, br. 1H).

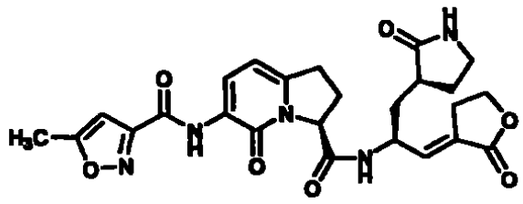
Preparation of Product I1 (Compound 37)

Intermediate i2 was transformed into compound 37 (via coupling with intermediate Y2) by a process that was analogous to that described in Example 25 for the transformation of W3 to product R3: IR (cm^{-1}) 3336, 1684, 1651, 1596, 1536; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.63-1.89 (m, 2H), 2.04-2.15 (m, 1H), 2.38-2.64 (m, 3H), 2.50 (s, 3H), 2.98-3.06 (m, 1H), 3.26-3.42 (m, 4H), 4.19 (q, 2H, J = 7.1), 4.63-4.65 (m, 1H), 5.15 (dd, 1H, J = 8.3, 2.7),

5.97-6.05 (m, 2H), 6.21 (d, 1H, J = 7.3), 6.48 (s, 1H), 6.89 (dd, 1H, J = 15.6, 5.5), 8.44-8.52 (m, 2H), 9.40 (s, 1H); Anal. $C_{25}H_{29}N_5O_7 \cdot 0.6TFA$: C, H, N.

EXAMPLE 36

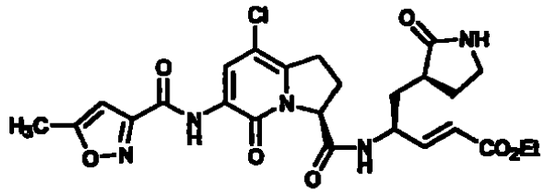
Preparation of Compound 38:
trans-(2''*S*,3*S*,3''''*S*)-6-[(5'-Methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid [2''-(2''''-oxodihydrofuran-3''''-ylidene)-1''-(2''''-oxopyrrolidin-3''''-ylmethyl)ethyl]amide



The title compound was prepared from intermediate i2 (via coupling with intermediate Y1) by a process that was analogous to that described in Example 22 for the transformation of W1 to product R2: IR (cm^{-1}) 3336, 1752, 1686, 1651, 1594, 1535; ^1H NMR ($CDCl_3$) δ 1.59-1.68 (m, 1H), 1.77-1.81 (m, 1H), 2.09-1.81 (m, 1H), 2.37-2.45 (m, 2H), 2.50 (s, 3H), 2.58-2.66 (m, 1H), 2.91-3.05 (m, 2H), 3.23-3.44 (m, 4H), 4.39 (t, 2H, J = 7.2), 4.60-4.67 (m, 1H), 5.10-5.13 (m, 1H), 6.09 (s, 1H), 6.21 (d, 1H, J = 7.9), 6.41-6.48 (m, 2H), 8.45-8.50 (m, 2H), 8.77 (d, 1H, J = 6.2), 9.39 (s, 1H).

EXAMPLE 37

Preparation of Compound 39: *trans*-(3'*S*,3'''*S*,4*S*)-4-({8'-Chloro-6'-[(5''-methyl isoxazole-3''-carbonyl)amino]-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl} amino)-5-(2'''-oxopyrrolidin-3'''-yl)-pent-2-enoic Acid Ethyl Ester



The title compound was prepared from intermediate i3 (via coupling with intermediate Y2) by a process that was analogous to that described in Example 25 for the transformation of W3 to product R3: IR (cm^{-1}) 3334, 1683, 1532; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.2), 1.66-1.89 (m, 4H), 2.33-2.50 (m, 1H), 2.53 (s, 3H), 2.67-2.72 (m, 1H), 3.04-3.20 (m, 2H), 3.27-3.48 (m, 2H), 4.21 (q, 2H, J = 7.2), 4.62-4.64 (m, 1H), 5.16-5.20 (m, 1H), 5.94 (s, br. 1H), 5.99 (dd, 1H, J = 15.6, 1.5), 6.51 (s, 1H), 6.89 (dd, 1H, J = 15.6, 5.7), 8.52 (s, 1H), 8.56 (s, br. 1H), 9.41 (s, br. 1H); Anal. $C_{25}H_{28}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

Results of tests conducted using exemplary 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), vol. 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 1 μM 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 the table below. The tabulated 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). Test results for the HRV assay are shown in the table below.

Anticoxsackieviral Cell Culture Assay:

Coxsackievirus types A-21 (CAV-21) and B3 (CVB3) 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 the compounds of this invention to protect cells against either CAV-21 or CVB3 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 CVB3 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 (CVB3) 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}.

Anti-Echoviral and Anti-Enteroviral Cell Culture Assays

Echovirus type 11 (ECHO 11) was 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 the compounds of this invention to protect cells against ECHO 11 infection was measured by the XTT dye reduction method (Weislow et al., *J. Natl.*

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Cancer Inst. (1989), vol. 81, 577-586). MRC-5 cells were infected with ECHO 11 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 1×10^4 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}. Activity of the compounds against enterovirus type 70 (EV 70) may be measured by the same assay as described above in this section. Enterovirus type 70 (EV 70) may be obtained from the American Type Culture Collection ATCC (Rockville, MD).

Results obtained for the compounds of the invention may be compared to results obtained in the same manner for 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 the table below. The designation "ND" indicates that a value was not determined for that compound, and the designation "NA" means not applicable.

WO 96/26203 PCT/US96/02359

TABLE

Compd. #	Virus Serotype	$k_{obs}/[I]$ $(M^{-1}s^{-1})^b$	EC_{50} (μM)	CC_{50} (μM)	TI
1+2 (1:1)	HRV-14[a]	36,900	0.179	50.1	280
	HRV-1A	ND	0.825	74.1	90
	HRV-10	ND	0.145	60.3	416
1	HRV-14	114,000	0.033	50.1	1518
	CAV-21[c]	ND	1.48	>10	>7
	ECHO-11[d]	ND	0.16	>10	>63
	CVB3[e]	ND	0.539	>10	>19
	ENT-70[f]	ND	0.012	>10	>833
3	HRV-14	2,900	1.27	>10	>8
4	HRV-14	574	ND	ND	ND
5	HRV-14	329,000	0.016	>10	>625
	CAV-21	ND	1.39	>10	>7
	ECHO-11	ND	0.054	>10	>185
	CVB3	ND	0.577	>10	>17
	ENT-70	ND	0.018	>10	>556
6	HRV-14	37,400	0.034	>10	>294
	CAV-21	ND	4.68	>10	>2
	ECHO-11	ND	0.346	>10	>29
	CVB3	ND	2.50	>10	>4
	ENT-70	ND	0.061	>10	>164
7	HRV-14	81,000	0.014	>10	>714
8	HRV-14	7,660	0.888	>10	>11
9	HRV-14	5,040	0.518	>10	>19
10	HRV-14	113,600	0.104	>10	>96
	HRV-1A	ND	1.182	>10	>9
	HRV-10	ND	1.406	>10	>7
11	HRV-14	193,000	<0.0032	>10	>3125
12	HRV-14	25,800	0.075	>10	>133
13+14 (1:1)	HRV-14	31,000	ND	ND	ND
15	HRV-14	6,500	0.178	>10	>56
16	HRV-14	74,000	0.325	>10	>31
17	HRV-14	348	>10	>10	ND
18	HRV-14	116,000	0.125	>10	>80
19	HRV-14	380,000	0.003	>1	>333
20	HRV-14	600,000	0.015	>10	>667
21	HRV-14	6,340	0.469	>10	>21
22	HRV-14	18,500	1.0	>10	>10
23	HRV-14	385,000	0.064	>10	>156

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Compd. #	Virus Serotype	$k_{obs}/[I]$ $(M^{-1}s^{-1})^b$	EC_{50} (μM)	CC_{50} (μM)	TI
24	HRV-14	8,800	ND	ND	ND
25	HRV-14	1,250,000	0.002	>10	>5000
	HRV-1A	ND	0.015	>10	>667
	HRV-10	ND	0.004	>10	>2500
	HRV-2	ND	0.004	>10	>2500
	HRV-16	ND	0.005	>10	>2000
	HRV-3	ND	0.004	>10	>2500
	HRV-25	ND	0.022	>10	>454
	HRV-9	ND	0.01	>10	>1000
	HRV-39	ND	0.009	>10	>1111
	HRV-87	ND	0.008	>10	>1250
26	HRV-14	170,000	0.055	>10	>182
	HRV-1A	ND	0.014	>10	>714
	HRV-10	ND	0.027	>10	>370
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.050	>10	>200
	HRV-3	ND	0.029	>10	>344
	HRV-25	ND	0.102	>10	>98
	HRV-9	ND	0.045	>10	>222
	HRV-39	ND	0.047	>10	>212
	HRV-87	ND	0.021	>10	>476
27+28 (1:1)	HRV-14	3,750	1.78	>10	>7
29	HRV-14	148,000	0.079	>10	>126
	HRV-1A	ND	0.046	>10	>217
	HRV-10	ND	0.046	>10	>217
30	HRV-14	133,500	0.024	>10	>416
31	HRV-14	223,400	0.022	>10	>454
	HRV-1A	ND	0.036	>10	>277
	HRV-10	ND	0.048	>10	>208
	HRV-2	ND	0.013	>10	>769
	HRV-16	ND	0.038	>10	>263
	HRV-3	ND	0.021	>10	>476
	HRV-25	ND	0.087	>10	>114
	HRV-9	ND	0.044	>10	>227
	HRV-39	ND	0.043	>10	>232
	HRV-87	ND	0.021	>10	>476
32	HRV-14	127,500	0.126	>10	>79
	HRV-1A	ND	0.179	>10	>55
	HRV-10	ND	0.156	>10	>64
33	HRV-14	1,800,000	0.001	>10	>10000
34	HRV-14	45,100	ND	ND	ND

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Compd. #	Virus Serotype	$k_{obs}/[I]$ $(M^{-1}s^{-1})^b$	EC_{50} (μM)	CC_{50} (μM)	TI
35	HRV-14	220	ND	ND	ND
36	HRV-14	4,540	9.0	>100	>11
37	HRV-14	177,000	0.162	>10	>62
	HRV-1A	ND	0.108	>10	>93
	HRV-10	ND	0.041	>10	>244
	HRV-2	ND	0.037	>10	>270
	HRV-16	ND	0.072	>10	>138
	HRV-3	ND	0.043	>10	>232
	HRV-25	ND	0.162	>10	>61
	HRV-9	ND	0.121	>10	>82
	HRV-39	ND	0.016	>10	>625
	HRV-87	ND	0.058	>10	>172
38	HRV-14	0.08g	16.8	>100	>6
39	HRV-14	200,000	0.040	>10	>250
	HRV-1A	ND	0.042	>10	>238
	HRV-10	ND	0.088	>10	>113
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.057	>10	>175
	HRV-3	ND	0.039	>10	>256
	HRV-25	ND	0.107	>10	>93
	HRV-9	ND	0.048	>10	>208
	HRV-39	ND	0.048	>10	>208
	HRV-87	ND	0.017	>10	>588
WIN 51711	HRV-14	ND	0.78	>60	>77
WIN 52084	HRV-14	ND	0.07	>10	>143
WIN 54954	HRV-14	ND	2.13	>63	>30
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
Pirodavir	HRV-14	ND	0.03	>10	>300
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
	EV-11	ND	3.7	>10	>3
	ENT-70	ND	0.06	>10	>167
Pleconaril	HRV-14	ND	0.01	>10	>1000
	CAV-21	ND	0.09	>10	>107
	CVB3	ND	>10	>10	NA
	EV-11	ND	0.16	>10	>62

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[a]HRV = human rhinovirus of designated serotype.
[b]3C protease inhibition activity.
[c]CAV-21 = coxsackievirus A21.
[d]ECHO-11 = echovirus 11.
[e]CVB3 = coxsackievirus B3.
[f]ENT-70 = enterovirus 70.
[g]K_i value, μM.

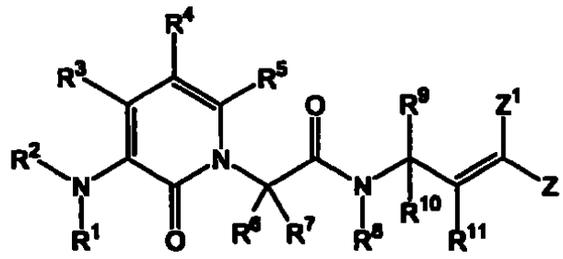
While the invention has been described in terms of preferred embodiments and specific examples, those skilled in the art will recognize that various changes and modifications can be made without departing from the spirit and scope of the invention. Thus, the invention should be understood as not being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

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WE CLAIM:

1. A compound having the formula:



wherein:

R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group;

R^3 is a suitable substituent; or

R^1 together with R^2 form a suitable nitrogen protecting group; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is a suitable substituent;

R^5 is a suitable substituent; and

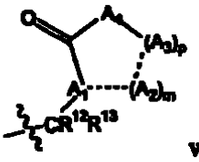
R^6 is a substituted or unsubstituted alkyl group; or

R^5 together with R^6 form a heterocycloalkyl group, which may be optionally substituted;

R^7 and R^{10} are independently H, halogen or a substituted or unsubstituted lower alkyl group;

R^8 is H or a substituted or unsubstituted lower alkyl group;

R^{11} is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

R^9 is a substituent having the formula:  wherein,

R^{12} and R^{13} are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, and $O(R^{18})$, where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, each R^{17} is H, alkyl, aryl, or acyl, and each R^{18} is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0); and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_2R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group,

wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

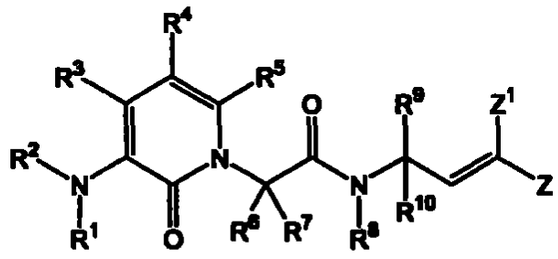
or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof.

2. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1, wherein R^1, R^7, R^8 and R^{19} are each H.

3. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1 wherein when R^4, R^5 and R^6 are suitable substituents, said suitable substituents are independently selected from H, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio and heteroarylthio, wherein any of the alkyl, aryl, cycloalkyl,

heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted.

4. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1 having the formula:



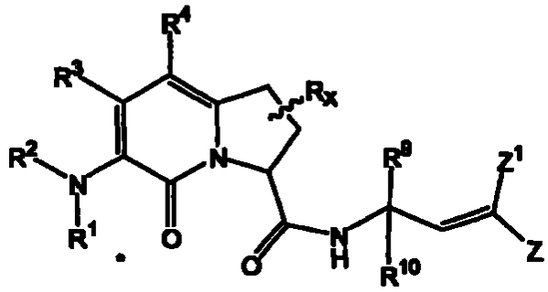
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl moieties of the above groups is substituted or unsubstituted;

R^6 is a substituted or unsubstituted alkyl group;

and R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, Z and Z^1 are as defined in claim 1.

5. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1 having the formula:



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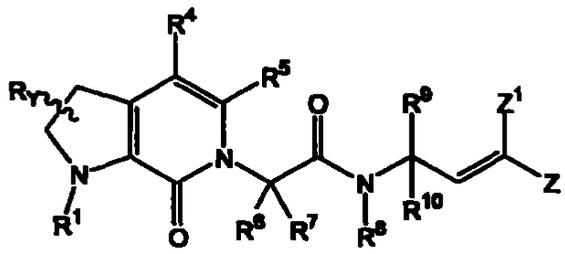
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl moieties of the above groups is substituted or unsubstituted;

R_X represents one or more suitable substituents;

and R^1, R^3, R^4, R^9, R^{10}, Z and Z^1 are as defined in claim 1.

6. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1 having the formula:



wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R^6 is a substituted or unsubstituted alkyl group;

R_Y represents one or more suitable substituents;

and R^1, R^4, R^5, R^9, Z and Z^1 are as defined in claim 1.

7. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 4 or 5, wherein R^2 is an unsubstituted or substituted benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl group.

8. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 7, wherein R^2 is a

heteroarylcarbonyl group, wherein the heteroaryl moiety is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S.

9. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 8, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is a five-membered heterocycle having at least one nitrogen heteroatom and at least one oxygen heteroatom.

10. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 9, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is unsubstituted or substituted 1,2-oxazolyl, 1,3-oxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, or 1,2,5-oxadiazolyl.

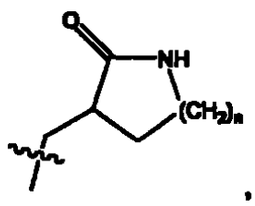
11. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 10, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is selected from unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl.

12. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 11, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is selected from 3-isoxazolyl and 5-isoxazolyl, each unsubstituted or substituted with one or two substituents selected from methyl groups and halogens.

13. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 4 or 6, wherein R^6 is a substituted or unsubstituted lower alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl group, a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety.

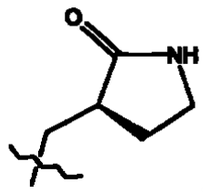
14. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 13, wherein R^6 is ethyl, 2-propyn-1-yl, methylcyclohexyl, or substituted or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy and halogen.

15. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 4, 5 or 6, wherein R^9 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alkyl; $-CH_2NHC(O)CH_3$; and

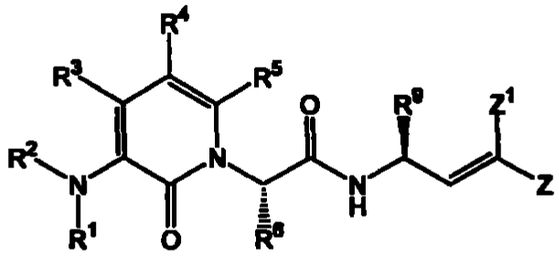


, where n is 1 or 2.

16. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 15, wherein R^9 is

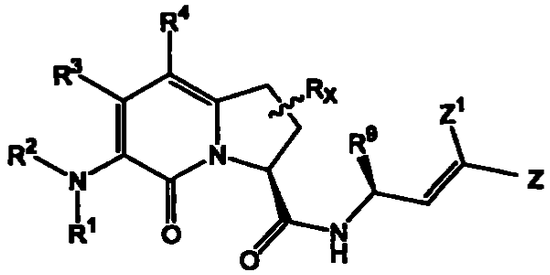


17. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



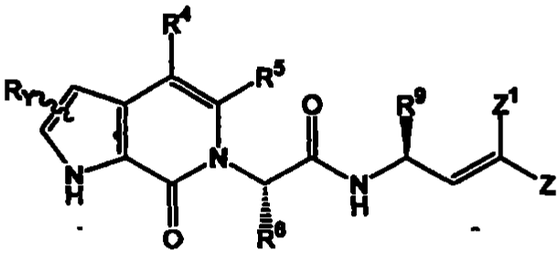
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z and Z^1 are as defined previously.

18. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 5 having the formula:



wherein R^1, R^2, R^3, R^4, R^9, R_x, Z and Z^1 are as previously defined.

19. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 6 having the formula:



wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are previously defined.

20. A compound according to claim 1 having antipicornaviral activity corresponding to an EC_{50} less than or equal to 100 μM in an H1-HeLa cell culture assay.

21. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of at least one antipicornaviral agent selected from compounds, prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable solvates defined in claim 1; and

a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

22. 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 acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in claim 1.

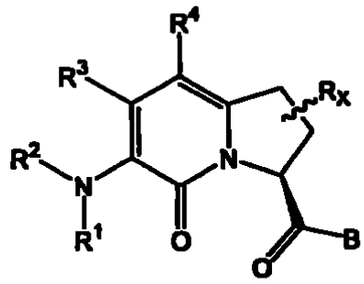
23. A method of inhibiting the activity of a picornaviral 3C protease, comprising contacting the picornaviral 3C protease with an effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in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

24. A method as defined in claim 23, wherein the picornaviral 3C protease is a rhinoviral protease.

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25. A compound having the formula:



wherein:

R^3 and R^4 are independently suitable substituents.;

R_X represents one or more suitable substituents.;

B is H, $-OR^{24}$, where R^{24} is a suitable protecting group for a carboxyl moiety; and

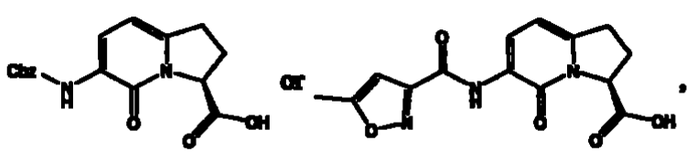
R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstitued, or a suitable nitrogen protecting group; or

R^1 together with R^2 form a suitable nitrogen protecting group;

or a pharmaceutically acceptable salt thereof.

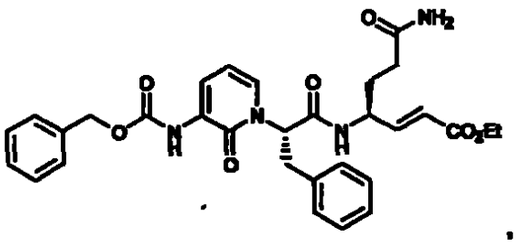
26. A compound according to claim 25 having the formula:

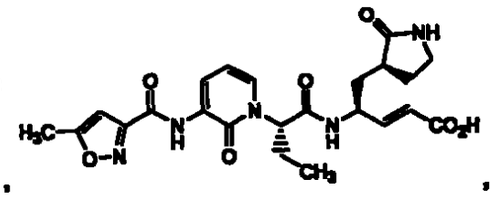


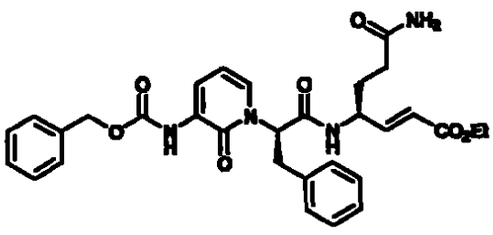
or a pharmaceutically acceptable salt thereof.

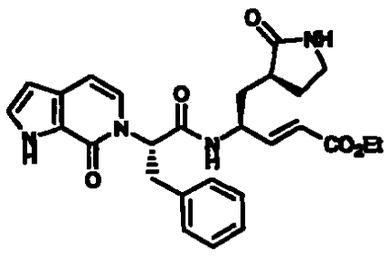
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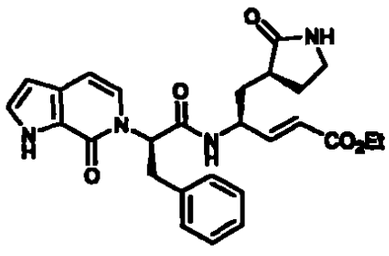
27. A compound selected from:

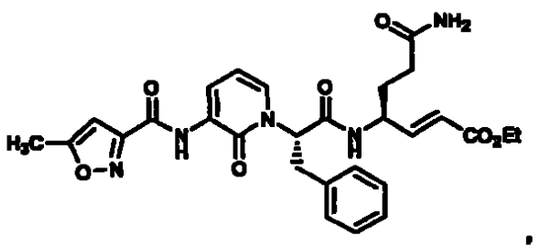


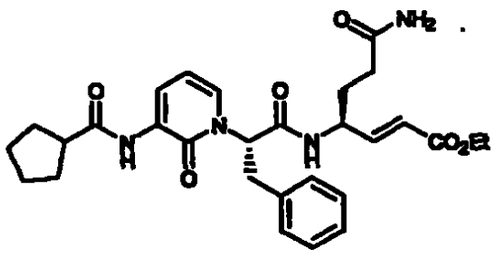


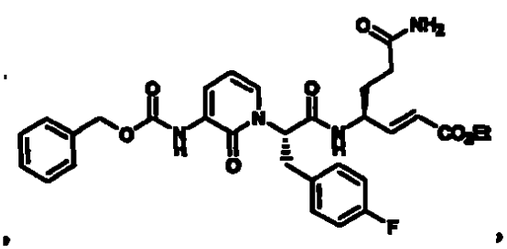


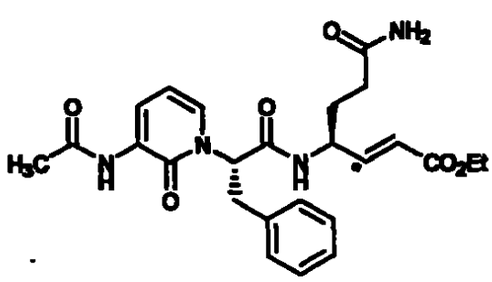


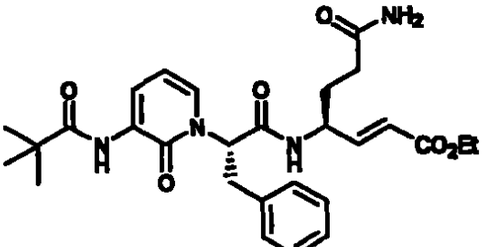




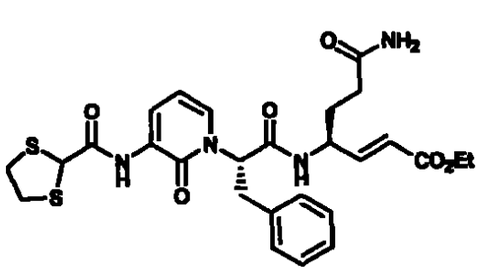


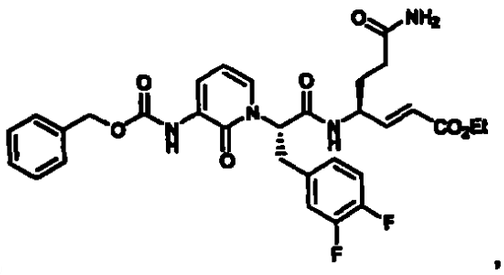


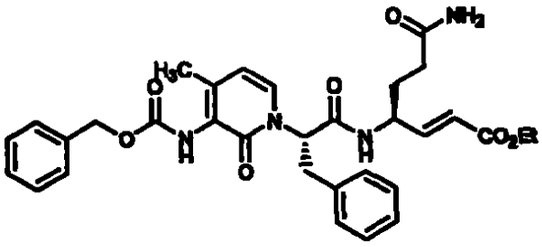


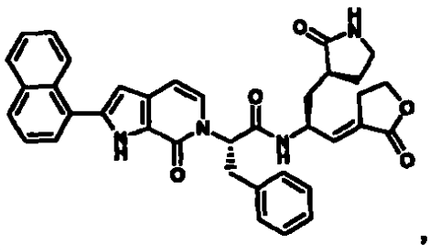


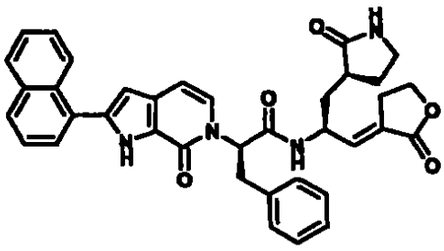
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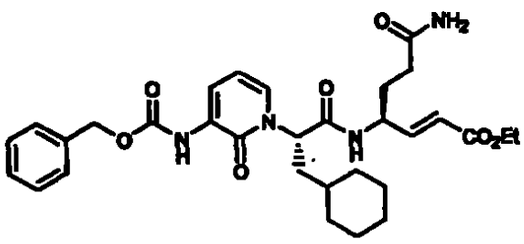


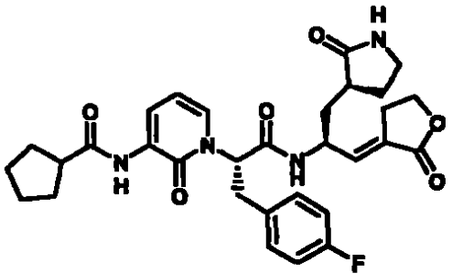


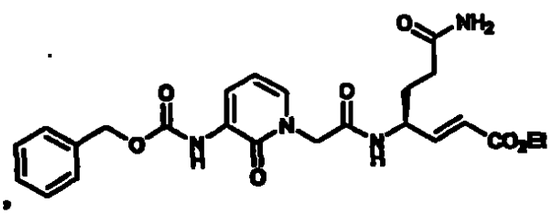


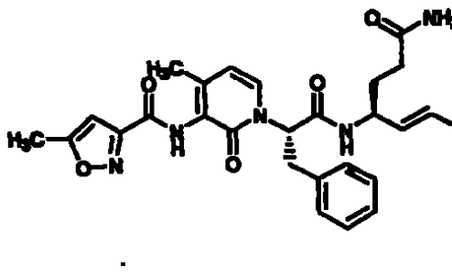


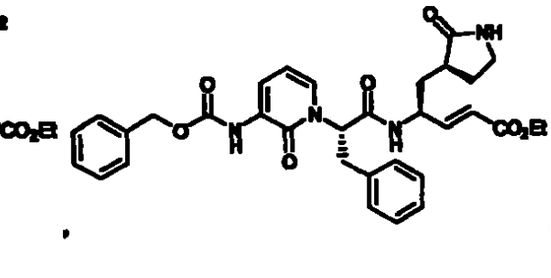


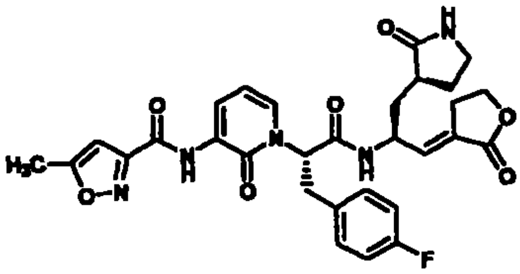




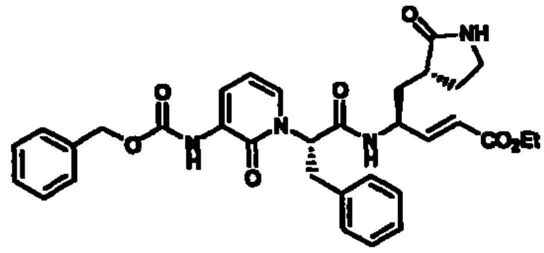




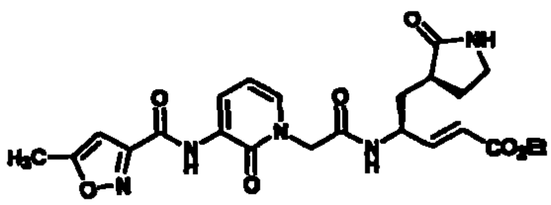




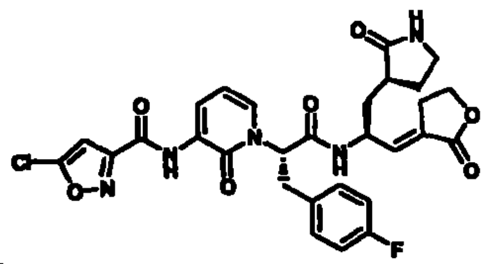
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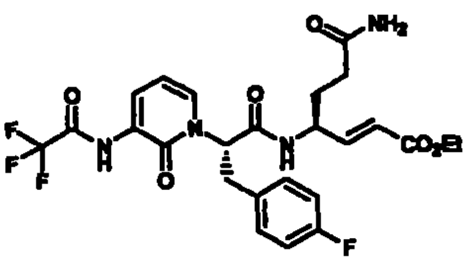
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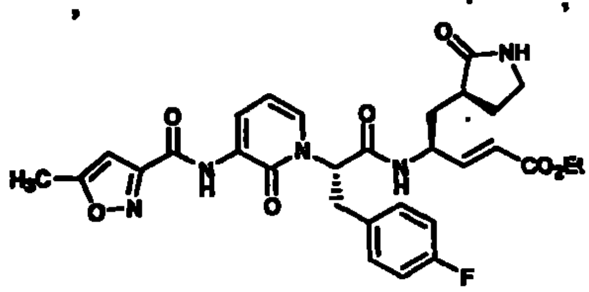
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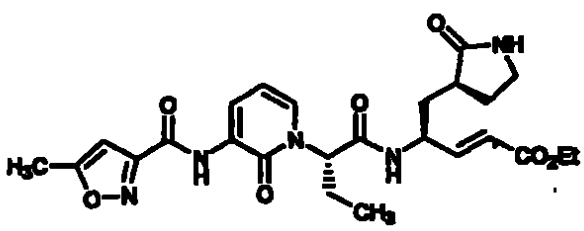
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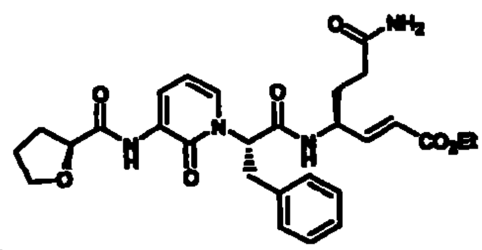
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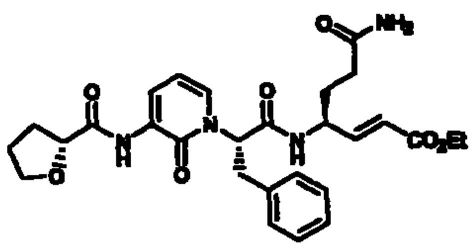
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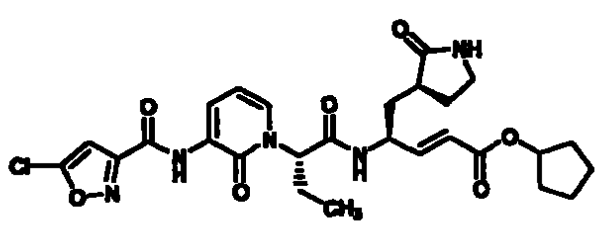
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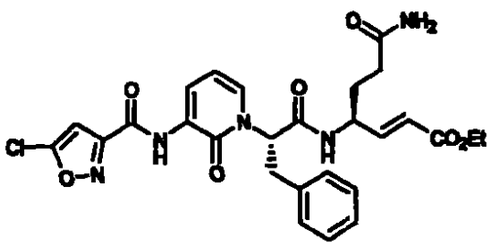


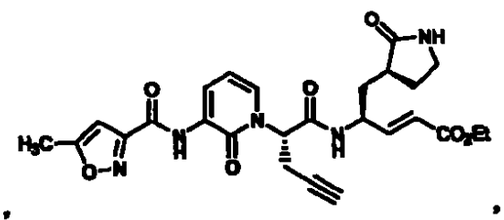
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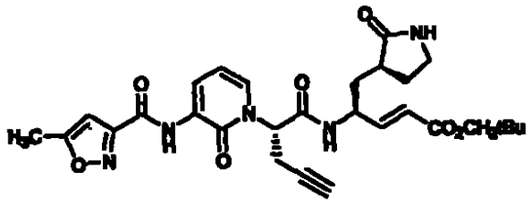


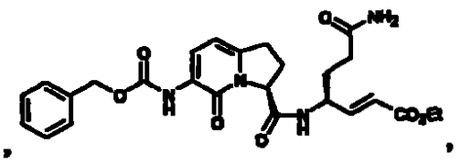
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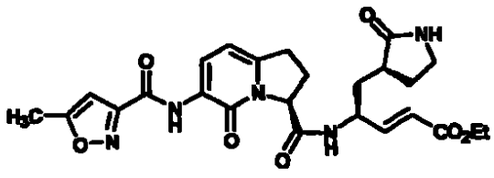
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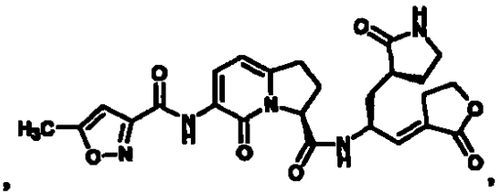


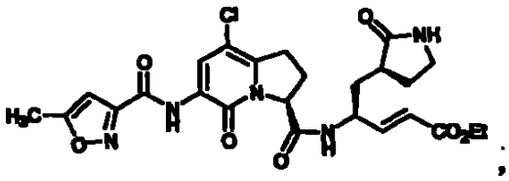


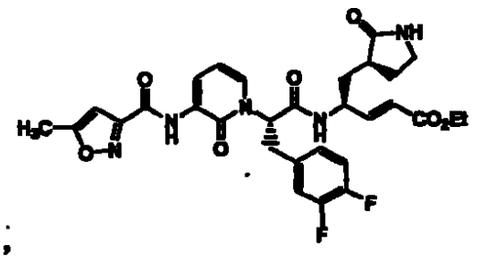


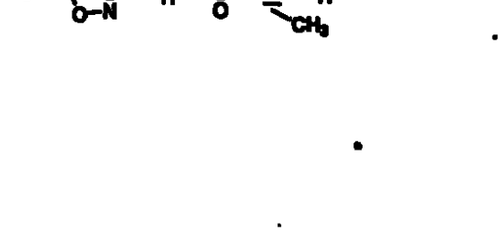








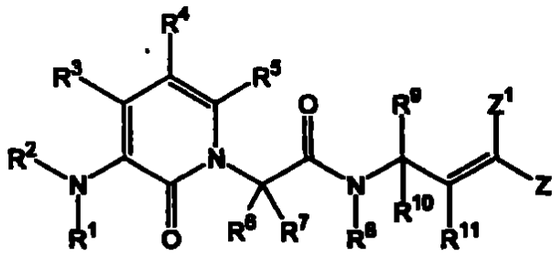




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ABSTRACT OF THE DISCLOSURE

Compounds of the formula:



where the formula variables are as defined in the disclosure, advantageously inhibit or block the biological activity of the picornaviral 3C protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with one or more picornaviruses, such as RVP. Intermediates and synthetic methods for preparing such compounds are also described.

(TRADUCCIÓN DEL INGLES AL ESPAÑOL)

LOS ESTADOS UNIDOS DE AMERICA

A TODOS A QUIENES ESTAS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas Comerciales de los Estados Unidos

Octubre 19 del año 2000

ESTE ES PARA CERTIFICAR QUE ANEXA A LA PRESENTE ESTÁ UNA FIEL COPIA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS COMERCIALES DE LOS ESTADOS UNIDOS DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE LOGRA LOS REQUERIMIENTOS PARA QUE LE SEA OTORGADA UNA FECHA DE PRESENTACIÓN BAJO 35 USC 111.

SOLICITUD NUMERO: 60/168,986

FECHA DE PRESENTACIÓN: Diciembre 03 de 1999

Por Autorización del
COMISIONADO DE PATENTES Y MARCAS COMERCIALES

Firma Ilegible (Firmado)
N. WILLIAMS
Funcionario de Certificaciones

SELLO EN RELIEVE.

++

12 - 06 - 99

HOJA DE CUBIERTA DE SOLICITUD PROVISIONAL

Esta es una solicitud para presentación de una SOLICITUD PROVISIONAL bajo 37 CFR 1.53(c).

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EXPEDIENTE NUMERO	2621.184PVL	Escriba a máquina un signo más (+) dentro de esta casilla	+

INVENTOR(s)/SOLICITANTE(s)

APELLIDO	PRIMER NOMBRE	SEGUNDO NOMBRE	RESIDENCIA (CIUDAD Y YA SEA ESTADO O PAIS EXTRANJERO)
DRAGOVICH	Peter	S.	Encinitas, California
PRINS	Thomas	J.	Cardiff, California
ZHOU	Ru		Carlsbad, California
J NSON, JR	Theodore	O.	San Diego, California

TITULO DE LA INVENCION (280 caracteres máximo)

C MPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

DIRECCION DE LA CORRESPONDENCIA

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Teléfono No. (212) 218-2100

PARTES DE LA SOLICITUD INCLUIDA (Cheque todo lo pertinente)

☐ Especificación Número de Páginas 180 ☐ Cesión únteramente pequeña

☐ Dibujo(s) Número de Cubierta _____ ☐ Otros (Especifique) _____

METODO DE PAGO (chequee uno)

☐ Un cheque o giro está incluido para cubrir los honorarios de presentación provisional	CANTIDAD DE HONORARIO DE PRESENTACIÓN PROVISIONAL ($)	$150.00
☐ El comisionado está por medio del presente autorizado para cargar cualesquiera deficiencias en el pago de los honorarios de presentación y cualesquiera créditos de sobrepago a la Cuenta de Depósito Número: 06-1206		

La invención fue hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos.

☐ No.

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☐ Si, el nombre de la agencia del Gobierno de los E.U. y el número del contrato del Gobierno son: _____

_____

Respetuosamente sometido — FECHA

FIRMA Kathryn L. Sieburth (Firmado) — Diciembre 3 de 1999

NOMBRE IMPRESO o ESCRITO A MAQUINA Kathryn L. Sieburth — REGISTRO NO. 40,072 (si es apropiado)

☐ Inventores adicionales están siendo nombrados en hojas numeradas separadamente adjuntas con ésta.

UNICA PRESENTACIÓN DE SOLICITUD PROVISIONAL

"Correo Expreso" número de etiqueta de envío por correo EL324696952US

Fecha de Depósito Diciembre 3 de 1999

Por medio del presente certifico que este papel de honorario está siendo depositado con el Servicio Postal de los Estados Unidos "Oficina Postal de Correo Expreso para el Destinatario" servicio bajo 37 CFR 1.10 en la fecha arriba indicada y está dirigido al Comisionado Asistente para Marcas Comerciales 2900 Crystal Drive, Arlington, Virginia 22202-3513.

Jose Adames

(Nombre impreso o escrito a máquina de la Persona que envía por correo el papel u honorario)

Firma Ilegible (Firmado)

(Firma de la persona que envía el papel u honorario por correo)

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2621.194PVL

SOLICITUD DE PATENTE PROVISIONAL DE LOS ESTADOS UNIDOS

TITULO

COMPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

Inventores: Peter Scott Dragovich
Thomas Prins
Ru Zhou
Ted Johnson

Agouron Pharmaceuticals, Inc.
Una Compañía de Warner-Lambert
10350 North Torrey Pines Road
La Jolla, California 92037

"Correo Expreso" número de etiqueta de envío por correo EL320469S2US

Fecha de Depósito Diciembre 3 de 1999

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Jose Adames
(Nombre impreso o escrito a máquina de la Persona que envía por correo el papel u honorario)
Firma Ilegible (Firmado)

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(Firma de la persona que envía el papel u honorario por correo)

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EL32046952US

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Firma Ilegible (Firmado)

(Firma de la persona que envía el papel u honorario por correo)

TITULO

COMPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

ANTECEDENTES DE LA INVENCIÓN

Campo de la invención

La invención se refiere a compuestos peptidomiméticos que contienen piridona que ventajosamente inhiben la actividad enzimática de las proteasas picornavirales 3C, especialmente proteasas de rinovirus 3C (RVPs), y aquel crecimiento viral retardado en el cultivo de célula. La invención también se refiere al uso de esos compuestos en composiciones farmacéuticas, métodos de tratamiento de infecciones rinovirales que usan esos

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compuestos y composiciones, y procesos para la síntesis de esos compuestos y compuestos útiles en la síntesis de éstos.

Antecedentes Relacionados del Arte

Los picornavirusos son una familia de virusos que contienen RNA acordonados positivos no envueltos menudos que infectan a humanos y otros animales. Esos virusos incluyen los rinovirusos humanos, polivirusos humanos, coxsackievirusos humanos, ecovirusos humanos; enterovirusos humano y bovino, virusos encefalomiocarditis, virus de meningitis, virusos del pié y la boca, virus de hepatitis A, y otros. Los rinovirusos humanos son una causa mayor del resfriado común. Hasta la fecha, no hay terapias efectivas en el mercado que curen el resfriado común, solamente tratamientos que alivian los síntomas.

Las infecciones picornavirales pueden ser tratadas inhibiendo las enzimas picornavirales proteolíticas 3C. Esas enzimas son requeridas para la nutrición natural de los picornavirusos. Ellos son responsables por la segmentación autocatalítica de poliproteína grande, genómica en las proteínas virales esenciales. Los miembros de la familia de proteasa 3C son proteasas de cisteína, donde el grupo sulfidrilo más a menudo segmenta la unión de amida de glicina-glutamina. La inhibición de proteasas 3C se cree que bloquea la segmentació proteolítica de la poliproteína virtal, la cual a su turno puede retardar la maduración e inhibición del procesamiento de esta proteasa de cisteína con moléculas selectivas pequeñas que son específicamente reconocidas representarían un acercamiento importante y útil para tratar y curar infecciones virales de esta naturaleza y, en particular, el resfriado común.

Algunos inhibidores de moléculas pequeñas de la actividad enzimática de las proteasas picornavirales 3C (es decir, compuestos antipicornavirales) han sido recientemente descubiertos. Ver por ejemplo: Patente de los E.U. No. 5,856,530;

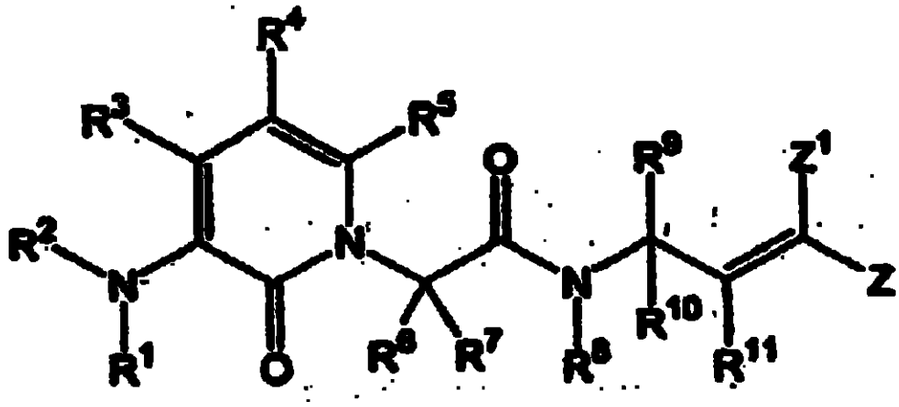
Patente de l s E.U. No. 5,962,487; Solicitud de Patente de los E.U. No. 08/991,282, presentada en Diciembre 16 de 1997, por Dragovich y otros; y Solicitud de Patente de los E.U. No. 09/301,977, presentada en Abril 29 de 1999, por Dragovich y otros. Ver también: Dragovich y otros, "Diseño Estructura Basado, Síntesis, y Evaluación Biológica de Inhibidores de Proteasa de 3C de Rinovirus Humano Irreversible...., "J. Med. Chem. (1999), Vol. 42, No. 7, 1203-1212, 1213-1224; y Dragovich y otros, "Síntesis de Fase Sólida de Inhibidores de Proteasa 3C de Rinovirus Humano Irreversible..., "Bioorg. & Med. Chem. (1999), Vol 7, 589-598. Existe un deseo, sin embargo, para descubrir compuestos de molécula pequeña que son especialmente agentes antipicornavirales potentes.

Los inhibidores de otras proteasas de cisteína relacionados tales como catepsinos han sido descritos en, por ejemplo, la Patente de los E.U. No. 5,374,623; Patente de los E.U. No. 5,498,618; y Publicación Internacional WIPO Nos. WO 94/04172, WO 95/15749, WO 97/19231, y WO 97/49668. Todavía permanece una necesidad para inhibidores objetivos de proteasa de cisteína picornaviral 3C con propiedades farmacéuticas deseables, tales como de alta especificidad.

RESUMEN DE LA INVENCIÓN

Esta invención se refiere a compuestos útiles para inhibir la actividad de proteasa picornaviral 3C que tienen la Fórmula general I:

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(I)

en la cual:

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuado;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, o un grupo alcoxicarbonilo, en los cuales cada una de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo en los grupos de arriba puede ser sustituida o no sustituida, o un grupo adecuado de protección de nitrógeno;

R^3 es un sustituyente adecuable; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o grupo heteroarilo, el cual puede ser opcionalmente sustituido;

R^4 es un sustituyente adecuable;

R^5 es un sustituyente adecuable;

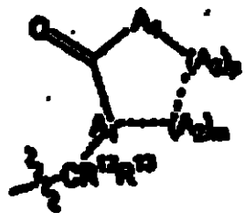
R^6 es un grupo alquilo sustituido o no sustituido; o

R^5 junto con R^6 forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido;

R^7 y R^{10} son independientemente H, halógeno o un grupo de alquilo más bajo sustituido o no sustituido;

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R^8 es H o un grupo alquilo inferior sustituido o no sustituido;
R^{11} es H, halógeno, hidróxilo, un grupo alquiltio o alcox, de alquilo sustituido o no sustituido;

R^9 es un sustituyente que tiene la fórmula: 

En la cual,
R^{12} y R^{13} son independientemente H o alquilo inferior;
m es 0 o 1;
p es un entero de desde 0 hasta 5;
A_1 es CH o N;
A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;
cada A_3 presente esta independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;
cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, y $O(R^{18})$, donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, cada R^{17} es H, alquilo, arilo, o acilo, y cada R^{18} es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada línea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2 está ausente (es decir, m=0); y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, -

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$C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-S_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterociclilloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

En adición a los compuestos de la Fórmula I, los agente antipicornavirales de la invención incluyen prodrogas, metabolitos farmacéuticamente activos, y sales y solventes farmacéuticamente aceptables de tales compuestos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN Y MODALIDADES PREFERIDAS

Preferiblemente, en los compuestos de la Fórmula I:

R^1, R^7, R^8, R^{10} y R^{11} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en el cual cada uno de los alquilo, arilo, cicloalquilo, mitades heteroarilo o heterocicloalquilo de los grupos de arriba pueden ser sustituido o no sustituido;

R^3 es un sustituyente apropiado; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o un grupo heteroalilo, el cual puede ser opcionalmente sustituido;

R^4 es un sustituyente apropiado;

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R^5 es un sustituyente apropiado;

R^6 es un grupo alquilo no sustituido o un grupo alquilo inferior opcionalmente sustituido con un grupo cicloalquilo, un grupo heterocicloalquilo, un grupo arilo, un grupo heteroarilo, un grupo alcoxilo, un grupo arriloxi, un grupo alquiltio, un grupo ariltio, en el cual cada alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo o mitades de estos pueden ser opcionalmente sustituidos; o

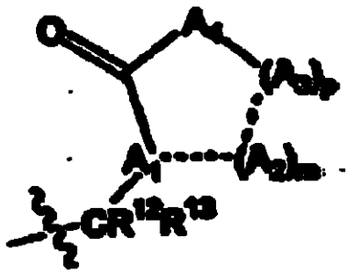
R^5 junto con R^6 forman un grupo hetrocicloalquilo membrado de cinco o seis sustituidos o no sustituidos;

En el cual cuando R^4, R^5 y R^6 son sustituyentes apropiados, dichos sustituyentes apropiados pueden ser independientemente seleccionados de H, alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, hidróxilo, alcoxi, arriloxi, cicloalcoxi, heterocicloalcoxi, heteroarriloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, arriloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroarriloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquiloxicarbonilo, carboxilo, carbamoilo, formilo, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilamincarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilo,

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alquiltiocarboniliamino, cicloalquiltiocarboniliamino, ariltiocarboniliamino, heterocicloalquiltiocarboniliamino, heteroariltiocarboniliamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfoniliamino, arilsulfoniliamino, mercapto, alquiltio, ariltio, y heteroariltio, en el cual cualesquiera de los alquilo, arilo, cicloalquilo, heterocicloalquilo, mitades de heteroarilo presentes en los sustituyentes de arriba pueden ser además sustituido;

R^9 es un grupo aminocarbonilalquilo, un grupo alquilcarboniliaminoalquilo, un grupo alquilaminocarbonilalquilo o un sustituyente que tiene la fórmula:



En el cual:

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 1;

p es 1 o 2;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O;

Cada A_3 presente es independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$ o O;

A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O;

En el cual R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, y en cada R^{17} es H, alquilo, arilo, o acilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4 y C=O, donde cada línea punteada en el anillo describe una unión simple; y

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Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo; grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, $-CN$, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados junto con los átomos los cuales ellos están unidos, forman un grupo heterocicliloalquilo, el cual puede ser opcionalmente sustituido.

Preferiblemente, R^4, R^5 y R^8 pueden ser independientemente seleccionados de H, alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, amino, halógeno, hidroxilo, alcoxi, ariloxi, arilcxi, cicloalcoxi, heterocicloalcoxi, alquiloxicarbonilo, ariloxicarbonilo, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroariloxicarbonilo, heteroarilcarboniloxi, heterocicloalquiloxicarbonilo, carboxilo, alquilamino, arilamino, dialquilamino, alquilaminocarbonilo, alquilsulfonilo, o arilsulfonilo.

De acuerdo con una convención usada en la del arte, es usada en fórmulas estructurales aquí en el presente para describir la unión que es el punto de unión de la mitad o sustituyente para el alma o columna estructural.

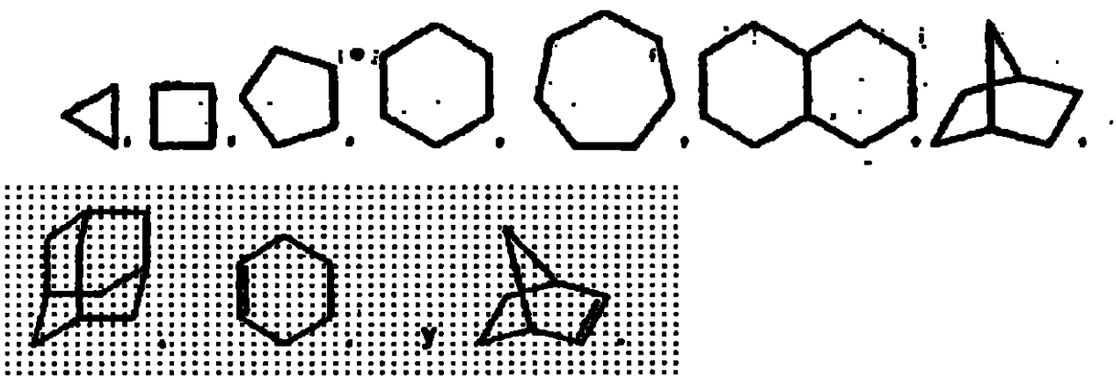
Tal como es usado aquí, el termino "alquilo" representa una cadena saturada o no saturada ramificada o recta de hidrocarburo, que contiene 1 hasta 10 átomos de carbono. Ejemplarmente sustituyentes de alquilo incluyen, pero no están limitados a, metilo

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(Me), etilo, (Et), propilo, isopropilo, butilo, isobutilo, t-butilo, etenilo, propenilo, butenilo, pentenilo, etinilo, butinilo, propinilo, pentinilo, hexinilo, y el deseado. El termino "alquilo inferior" se refiere a un grupo alquilo que contiene desde 1 hasta 4 átomos de carbono.

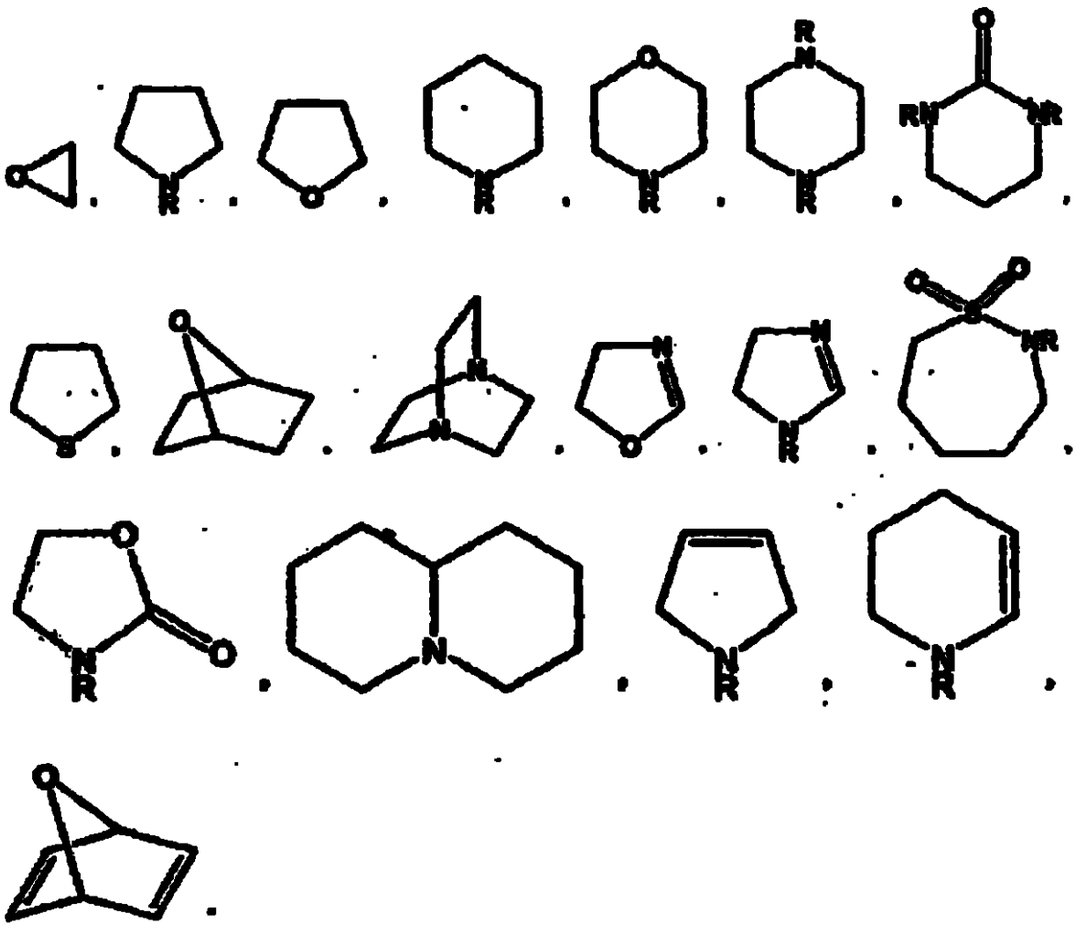
"Cicloalquilo" representa un grupo que comprende un hidrocarburo o tricicio o, biciclo, monociclo no aromático que contiene desde 3 hasta 14 átomos de carbono tal que puede ser saturado o parcialmente no saturado, anillo mono-opolicarboxílico, preferiblemente que tiene 5-14 átomos de anillo de carbono. Los cicloalquilos ejemplares incluyen anillo monocíclicos que tienen desde 3-7, preferiblemente 3-6, átomos de carbono tal como ciclopropilo, ciclobutilo, ciclopentino, ciclohexilo, cicloheptilo y similares, que pueden ser completamente saturados o parcialmente no saturados. Los ejemplos ilustrativos de grupos cicloalquilo incluyen lo siguiente:



"Heterocicloalquilo" representa un grupo que comprende un radical tricíclico o, biciclo, monocíclico monovalente, no aromático, el cual es saturado o parcialmente no saturado, que contiene 3 hasta 18 átomos de anillo y el cual incluye 1 hasta 5 heteroátomos seleccionados de nitrógeno, oxigeno y azufre, y el cual pueden ser fusionados uno o más grupos cicloalquilo, grupos arilo, o grupos heteroarilos los cuales pueden ser no sustituidos o sustituidos por uno o más de los sustituyentes descritos abajo. Los

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ejemplos ilustrativos de grupos heterocicloalquilos incluyen, pero no están limitados a, azetidinilo, pirrolidino, piperidilo, piperazinilo, morfolinilo, tetrahidro-2H-1, 4-tiazinilo, tetrahidrofurilo, dihidrofurilo, tetrahidropiranilo, 1,3-oxatianilo, 1,3-ditianilo, azabicilo[4.3.0]nonilo, oxabicilo[2.2.1]heptilo, , 1,5,9-triazaciclododecilo, y el deseado. Los ejemplos ilustrativos de grupos heterocicloalquilo incluyen las siguientes mitades:

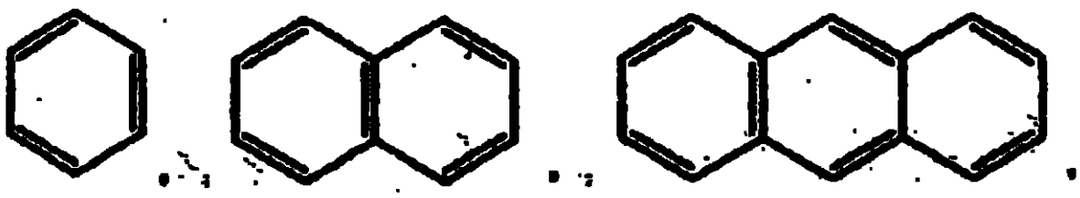


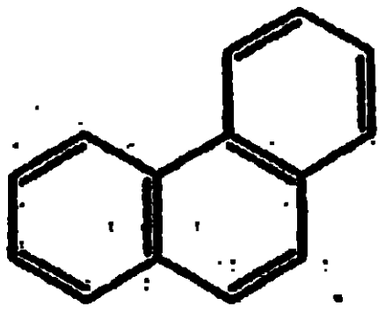
y

"Arilo" representa un grupo que comprende un radical tricicio o, bicíclico, monocíclico monovalente, aromático, que contiene de 6 hasta 18 átomos de anillo de carbono, los cuales pueden ser saturados o no saturados por uno o más de los sustituyentes

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descritos abajo. Los ejemplos ilustrativos de grupos arilo incluyen las siguientes mitades:

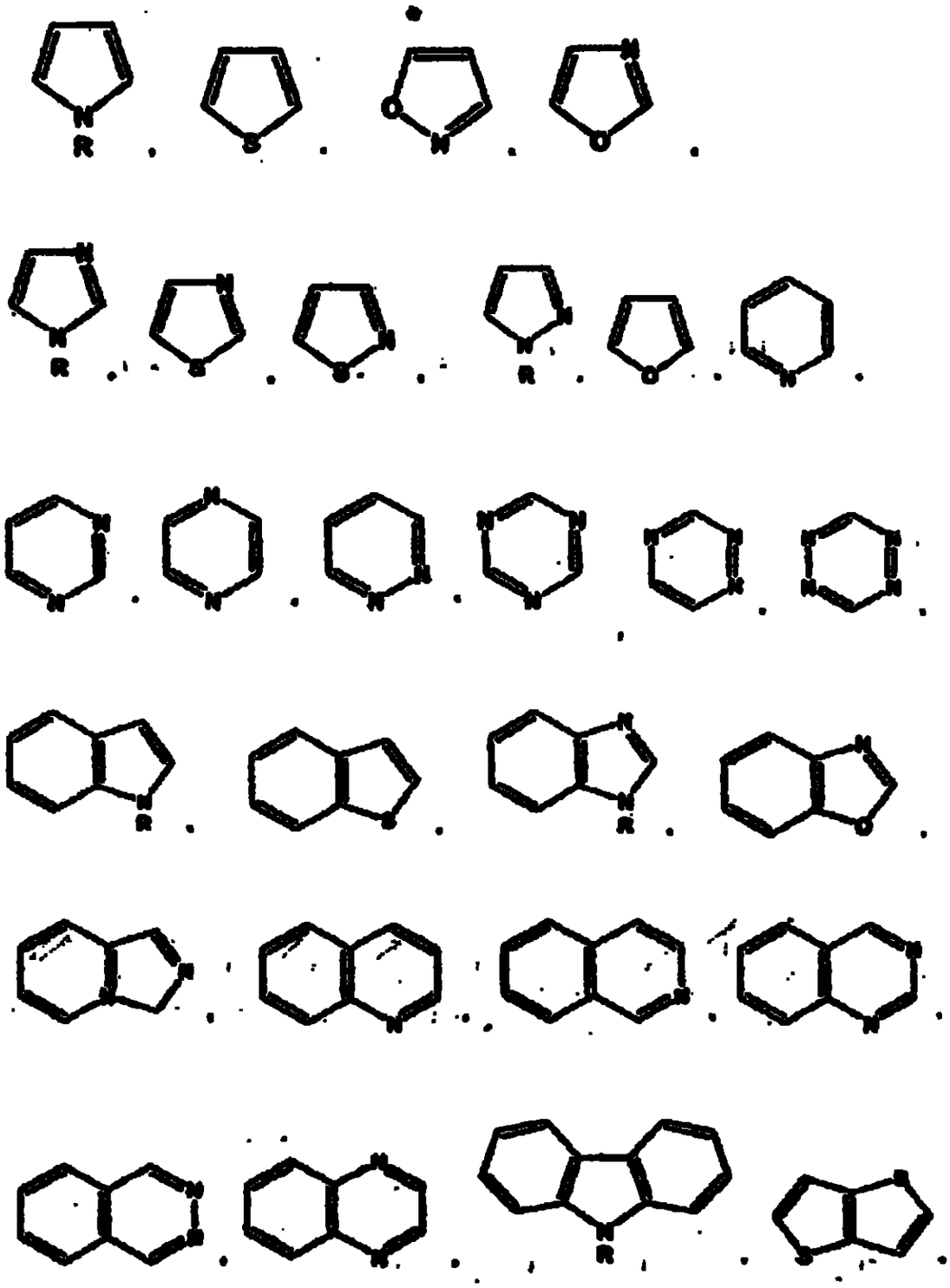




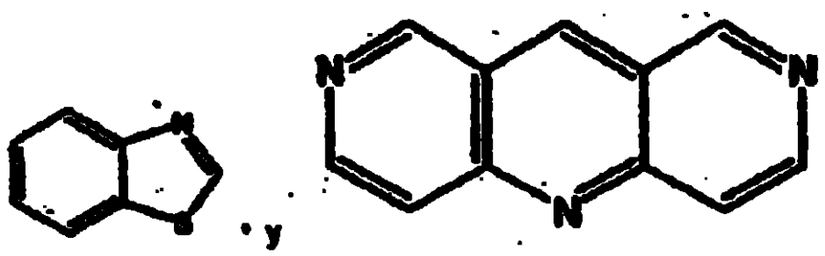
y

"Heteroarilo" representa un grupo que comprende un radical tricíclico o, bicíclico, monocíclico monovalente aromático, que contiene 5 hasta 18 átomos de anillos, que incluyen 1 hasta 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, el cual puede ser sustituido o no sustituido por uno o más de los sustituyentes descritos abajo. Los ejemplos ilustrativos de grupos heteroarilo incluyen, pero no están limitados a, tienilo, pirrolilo, imidazolilo, pirazolilo, furilo, isotiazolilo, furazanilo, isoxazolilo, tiazolilo, piridilo, pirazinilo, pirimidinilo, piridizinilo, triazinilo, benzo[b]tienilo, nafto[2,3-b]tiantrenilo, isobenzofuranilo, cloromenilo, xantenilo, fenoxatienilo, indolizinilo, isoindolilo, indolilo, indazolilo, purinilo, isoquinolilo, quinolilo, ftalazinilo, naftiridinilo, quinoxalinilo, quinzolinilo, benzotiazolilo, benzimidazolilo, tetrahidroquinolinilo, cinnolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fentatridinilo, acridinilo, perimidinilo, fenantrolinilo, fenazinilo, isotiazolilo, fenotiazinilo, y fenoxazipilo. Además ejemplos de grupos heteroarilo incluyen las siguientes mitades:

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Tal como está indicado aquí, el alquilo, cicloalquilo, arilo, heterocicloalquilo, y grupos heteroarilo pueden ser opcionalmente sustituidos por uno o más sustituyentes. El término "opcionalmente sustituidos" es entendido para expresamente indicar que el grupo especificado es sustituido o no sustituido por uno o más sustituyentes apropiados. Varios grupos pueden ser sustituidos o no sustituidos (por *ejemplo, ellos son opcionalmente sustituidos*) tal como se ha indicado. El término "sustituyente" o "sustituyente adecuado" es entendido para significar cualquier sustituyente adecuable o puede ser reconocido o seleccionado, tal como a través de prueba de rutina, por aquellos versados en el arte.

Los "sustituyentes adecuables" Ejemplares que pueden estar presentes en cualquier de los grupos de arriba alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo están descritos en la presente e incluyen alquilo (excepto para alquilo), arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, hidróxilo, alcoxi, arilioxi, cicloalcoxi, heterocicloalcoxi, heteroarilioxi, laquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, arilioxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalcoxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroarilioxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquioxicarbonilo, carboxilo, carbamoilo, formilo, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo,

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cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, ariltio, heteroariltio, heteroariltio, en los cuales cualquiera de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los sustituyentes de arriba pueden ser además sustituidos. Los "sustituyentes adecuables" preferidos incluyen alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halógeno, hidroxilo, alcoxi, arilóxi, cicloalcoxi, heteroariloxi, y carboxilo. Las mitades de alquilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de cualquiera de los sustituyentes de arriba pueden ser opcionalmente sustituidas por uno o más de grupos alquilo (excepto para alquilo), haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidróxilo, alcoxi, arilóxi, mercapto, alquiltio.

Si los sustituyentes por sí mismo no son compatibles con los métodos sintéticos de esta invención, el sustituyente puede ser protegido con un grupo de protección adecuable que es estable para las condiciones de reacción usadas en esos métodos. El grupo de protector pueden ser removido a un punto adecuable en la secuencia de reacción del método para proporcionar un compuesto intermedio deseado u objetivo. Los grupos de protección adecubles y los métodos para proteger y desproteger diferentes sustituyentes usando tales grupos de protección adecuados son bien conocidos por aquellos versados en el arte; los ejemplos de los cuales pueden ser encontrados en T. Greene y P. Wuts, Síntesis Químicas en Grupos de Protección (3^{era} ed.),

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John Wiley & Sons, NY (1999), los cuales están incorporados aquí en adelante por referencia en su totalidad. En algunos casos, un sustituyente puede ser específicamente seleccionado para ser reactivo bajo las condiciones de reacción usadas en los métodos de esta invención. Bajo esas circunstancias, las condiciones de reacción convierten al seleccionado sustituyente en otro sustituyente que es ya sea útil como un compuesto intermediario en los métodos de ésta invención o es un sustituyente deseado en un compuesto objetivo.

En los compuestos de esta invención, R^1 y R^2, independientemente o tomados juntos, pueden ser un grupo protector de nitrógeno adecuable. Tal como está indicado arriba, los grupos protectores de nitrógeno son bien conocidos en el arte y cualquier grupo de protección de nitrógeno que es útil en los métodos de preparación de los compuestos de esta invención o puede ser útil en los compuestos antipicornavirales de esta invención pueden ser usados. Los grupos protectores de nitrógeno ejemplares incluyen alquilo, alquilo sustituido, carbamato, urea, amida, imida, enamina, sulfenilo, sulfonilo, nitro, nitroso, óxido, fosfinilo, fosforilo, cililo, organometálico, ácido borínico y grupos de ácido borínico. Los ejemplos de cada uno de esos grupos, métodos para proteger mitades de nitrógeno usando esos grupos y métodos para remover esos grupos de mitades de nitrógeno están revelados en T. Greene y P. Wuts, Supra. Preferiblemente, cuando R^1 y/o R^2 son independientemente grupos protectores de nitrógeno adecuados tales como alquiloxicarbonilo (por ejemplo, Boc:t-butiloxicarbonilo) y ariloxicarbonilo (por ejemplo, Cbz: benziloxicarbonilo, o FMOC: fluoreno-9-metiloxicarbonilo), alcoxicarbonilos (por ejemplo, metoxicarbonilo), alquilo o arilcarbonilo, alquilo sustituido, especialmente arilalquilo (por ejemplo, tritilo (trifenilmetilo), benzilo y benzilo sustituido), y similares. Cuando R^1 y R^2 tomados juntos son un grupo de protección de nitrógeno adecuado, los sustituyentes adecuados R^1/R^2 incluyen ftalimido y una estabase (1,2-bis (dialquil))etileno).

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Los términos "halógeno" y "halo" representan sustituyentes cloro, fluoro, bromo o yodo. "Heterociclo" está destinado para significar un grupo heteroarilo o heterocicloalquilo. "Acilo" está destinado para significar un radical $-C(O)-R$, donde R es un alquilo sustituido o no sustituido, cicloalquilo, arilo, heterocicloalquilo o grupo heteroarilo. "Aciloxi" está destinado para significar un radical $-OC(O)-R$, donde R es un grupo sustituido o no sustituido de alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo. "Tioacilo" está destinado para significar un radical $-C(S)-R$, donde R es un grupo heteroarilo o heterocicloalquilo, arilo, cicloalquilo, alquilo sustituido o no sustituido. "Sulfonilo" está destinado para significar un birradical $-SO_2-$. "Sulfenilo" está destinado para significar un birradical $-SO-$. "Sulfo" está destinado para significar un radical $-SO_2H$. "Hidroxi" está destinado para significar el radical $-OH$. "Amina" o "amino" está destinado para significar el radical $-NH_2$. "Alquilamino" está destinado para significar el radical $-NHR_a$, donde R_a es un grupo alquilo. "Dialquilamino" está destinado para significar el radical $-NR_aR_b$, donde R_a y R_b son cada una independientemente un grupo alquilo, y está destinado para incluir grupos heterocicloalquilo, en los cuales R_a y R_b, tomados juntos, forman un radical $-OR_a$, donde R_a es un grupo alquilo. Los grupos alcoxi ejemplares incluyen metoxi, etoxi, propoxi, y similares. Los grupos "alcoxi inferior" tienen mitades de alquilo que tienen desde 1 hasta 4 carbonos. "Alcoxicarbonilo" está destinado para significar el radical $-C(O)OR_a$, donde R_a es un grupo alquilo. "Alquilsulfonilo" está destinado para significar el radical $-SO_2R_a$, donde R_a es un grupo alquilo. "Alquilaminocarbonilo" está destinado para significar el radical $-C(O)NHR_a$, donde R_a es un grupo alquilo. "Dialquilocarbonilo" está destinado para significar el radical $-C(O)NHR_aR_b$, donde R_a y R_b son cada uno independientemente un grupo alquilo. "Mercapto" está destinado para significar el radical $-SH$. "Alquiltio" esta destinado para significar el radical $-SR_a$, donde R_a es un grupo alquilo. "Carboxi" está destinado para significar el radical $-C(O)OH$. "Carbamoilo"

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está destinado para significar $-C(O)NH_2$. "Cicloalquilalquilo" está destinado para significar el radical -alquil-cicloalquilo, donde alquilo y cicloalquilo están definidos arriba, y está representado por el orden de unión presente en los grupos $-CH_2$-ciclohexano o $-CH_2$-ciclohexeno. "Arilalquilo" está destinado para significar el radical -alquilarilo, donde alquilo y arilo están definidos arriba, y está representado por el orden de unión presente en un grupo benzilo. "Aminocarbonilalquilo" está destinado para significar el radical -alquilC(O) NH_2 y está representado por el orden de unión presente en el grupo $-CH_2CH_2C(O)NH_2$. "Alquilaminocarbonilalquilo" está destinado para significar el radical -alquilC(O)NHR_a, donde R_a es un grupo alquilo y está representado por el orden de unión presente en el grupo $-CH_2CH_2C(O)NHCH$. "Alquilcarbonilaminoalquilo" está destinado para significar el radical -alquilNHC(O)-alquilo y está representado por el orden de unión presente en el grupo $-CH_2NHC(O)CH_3$. "Dialquilaminocarbonilalquilo" está destinado para significar el radical -alquilC(O)NR_aR_b, donde R_a y R_b son cada uno independientemente un grupo alquilo. "Ariloxi" está destinado para significar el radical $-OR_c$, donde R_c es un grupo arilo. "Heteroariloxi" esta destinado para significar el radical $-OR_d$, donde R_d es un grupo heteroarilo. "Ariltio" esta destinado para significar el radical $-SR_c$, donde R_c es un grupo arilo. "Heteroariltio" está destinado para significar el radical $-SR_d$, donde R_d es un grupo heteroarilo.

Si un compuesto inventivo es una base, una sal deseada puede ser preparada por cualquier método adecuado conocido en el arte, que incluye el tratamiento de la base libre con un ácido inorgánico, tal como ácido de hidrocloruro, ácido hidrobrómico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y el deseado. O con un ácido orgánico, tal como ácido acético, ácido maléico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, ácido piranosidilo, tal como ácido glucurónico o ácido galacturónico,

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ácido alfa hidroxi, tal como ácido cítrico o ácido tartárico, ácido de amonio, tal como ácido aspártico o ácido glutámico, ácido aromático, tal como ácido benzóico, ácido cinnámico, ácido sulfónico, tal como ácido p-toluenosulfónico o ácido etanosulfónico, o similares.

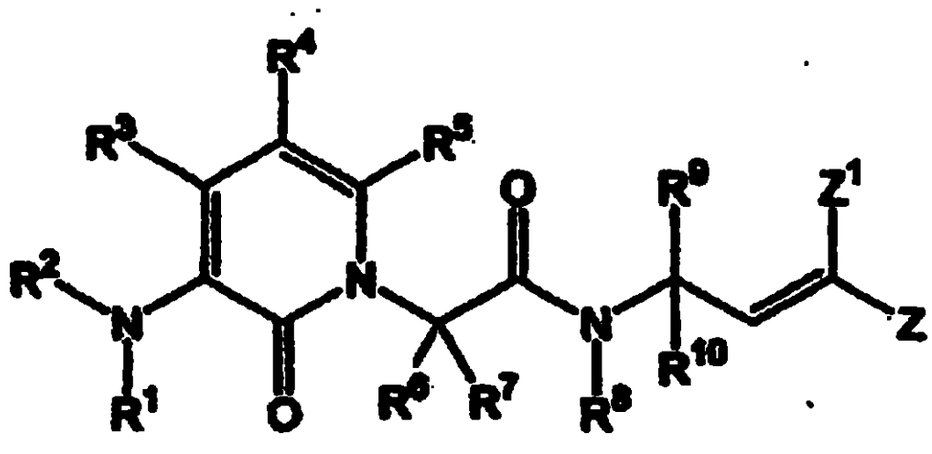
Si un compuesto de la invención es un ácido, una sal deseada puede ser preparada por cualquier método adecuable conocido en el arte, incluyendo tratamiento del ácido libre con una base inorgánico u orgánica, tal como una amina (primaria, secundaria, o terciaria); un metal alcali o un hidróxido de metal de tierra alcalina; o similares. Los ejemplos ilustrativos de sales adecuables incluyen sales orgánicas derivadas de aminoácidos tales como glicina y arginina; amoniaco; primario, secundario y aminas terciaria; y aminas cíclicas, tales como piperidina, morfolina, y piperacina; así como también sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, zinc, aluminio, y litio.

Los compuestos de la invención pueden existir como estereoisómeros simples y/o diastereómeros, racematos, y/o mezclas de enanciómeros y/o diastereómeros. Todos tales estereoisómeros simples, diastereómeros, racematos, y mezclas de éstos están destinados para estar comprendidos dentro del amplio alcance de la presente invención. Donde la estereoquímica de los carbonos quirales presentes en las estructuras químicas ilustradas aquí no está especificada, la estructura química está destinada para abarcar compuestos que contienen ya sea estereoisómero de cada carbono quiral. Preferiblemente, sin embargo, Los compuestos de la invención son usados en forma ópticamente pura. Cuando son usados describen un compuesto particular, el término "ópticamente puro" es usado aquí para que el compuesto sea sustancialmente enanciomérica o diastereoméricamente puro. Los compuestos que son sustancialmente enanciomércos puros contienen por lo menos

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90% de un isómero simple y preferiblemente contienen por lo menos 95% de un isómero simple. Los compuestos que son sustancialmente diastereoméricos puros contienen por lo menos 90% de un isómero simple de cada centro de carbono quiral presente en el diastereómero, y preferiblemente contiene por lo menos 95% de un isómero simple de cada carbono quiral. Más preferiblemente, los compuestos ópticamente activos en esta invención contienen por lo menos 97.5% de un isómero simple y más preferiblemente contienen por lo menos 99% de un isómero simple. Los compuestos identificados aquí como estereoisómeros simples están destinados para describir compuestos que están presentes en una forma que contiene por lo menos 90% de un isómero simple; el término "racémico" o "mezcla racémica" se refiere a una mezcla de iguales cantidades de compuestos enantioméricos, los cuales abarcan mezclas de enantiómeros y mezclas de diastereómeros enantioméricos.

Una modalidad preferida de esta invención comprende los compuestos descritos por la Fórmula I-a:



I-a

en el cual

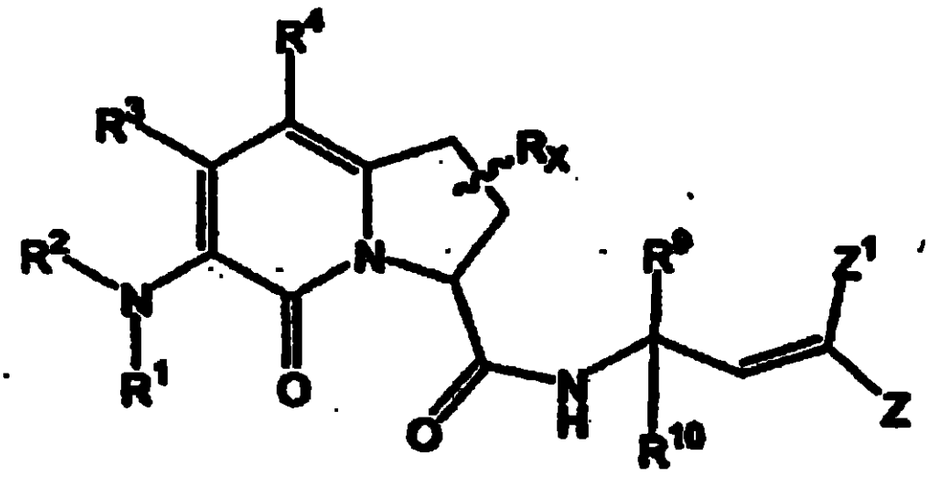
R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo,

un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo aliquiloxicarbonilo, en los cuales cada una de la mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo de los grupos de arriba pueden ser sustituidos o no sustituidos.

R^3, R^4, R^5 son sustituyentes adecuables descritos arriba, y

R^1, R^6, R^7, R^8, R^9, R^{10}, Z y Z^1, y las variables contenidas en estos, son como sean definido arriba.

Otra modalidad preferida de esta invención comprende los compuestos descritos por la Fórmula I-b:



I-b

en el cual:

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo aliquiloxicarbonilo, en los cuales cada una de la mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo de los grupos de arriba pueden ser sustituidos o no sustituidos.

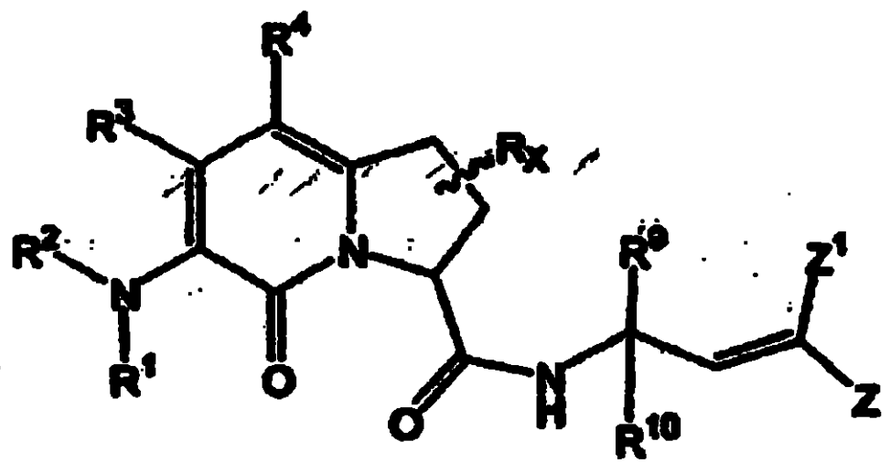
R_X representa uno o más sustituyentes adecuables;

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R^3 y R^4 son sustituyentes adecuables descritos arriba; y

R^1, R^9, R^{10}, Z y Z^1, y las variables contenidos en éstos, son como sean definido

Todavía otra modalidad preferida de esta invención comprende los compuestos descritos por la Fórmula I-c:



I-b

en la cual:

R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R_y representa uno o más sustituyentes adecuables;

R^4 y R^5 son los sustituyentes adecuables descritos arriba; y

R^1, R^8, R^9, Z y Z^1, y las variables contenidas en éstos, son como se han definido arriba.

En modalidades preferidas de las Fórmulas I-a y I-b, R^2 es un grupo alquiloxicarbonilo sustituido o un grupo heteroaricarbonilo o

arilcarbonilo sustituido o no sustituido. Preferiblemente, R^2 es un grupo heteroarilcarbonilo o arilcarbonilo sustituido o no sustituido o un grupo heteroarilcarbonilo. Más preferiblemente, R^2 es un grupo heteroarilcarbonilo o, arilcarbonilo, benziloxicarbonilo sustituido o no sustituido. Aún más preferiblemente, R^2 es un grupo heteroarilcarbonilo o benziloxicarbonilo sustituido o no sustituido, en el cual la mitad heteroarilo es un heterociclo de cinco-miembros de uno hasta tres heteroátomos seleccionados de O, N, y S, más preferiblemente un heterociclo de cinco-miembros que tienen por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxigeno (por ejemplo, 1,2-oxazolilo sustituido o no sustituido (es decir, isoxazolilo), 1,3-oxazolilo (es decir, oxazolilo), u oxadiazolilo (1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo). Cuando la mitad heteroarilo es oxadiazolilo, 1,2,4-oxadiazolilo sustituido-monometilo y no sustituido son preferidos. En modalidades especialmente preferidas, la mitad heteroarilo es 3-isoxazolilo o 5-isoxazolilo, ya sea sustituido o no sustituido con uno o dos grupos metilo y/o halógenos (C, Cl, Br o I), con cloro o fluoro siendo preferidos.

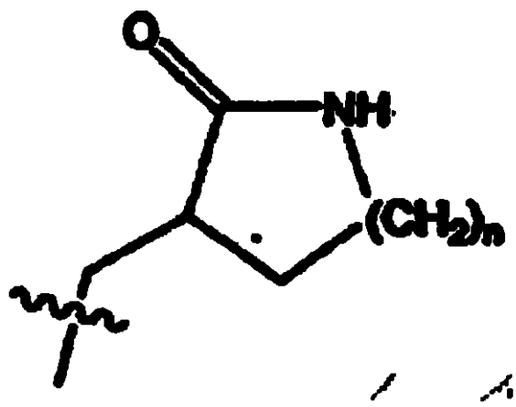
En especialmente modalidades preferidas de las Fórmulas I-a y I-c, R^6 es un grupo alquilo no sustituido o un grupo alquilo inferior opcionalmente sustituido, en los cuales esos grupos están comprendidos de un grupo de hidrocarburo saturado de cadena-ramificada o recta-, un grupo de hidrocarburo saturado sustituido de cadena-ramificada o recta-, o grupo comprendido de una mitad de hidrocarburo saturada de cadena-ramificada o recta- y una mitad de hidrocarburo no saturado. En cada caso, el punto de unión de R^6 es por vía de una mitad de hidrocarburo saturado. Cuando R^6 es un grupo de hidrocarburo saturado sustituido, el grupo de hidrocarburo saturado puede ser opcionalmente sustituido con un grupo cicloalquilo, un grupo heterocicloalquilo, un grupo arilo, un grupo heteroarilo, un grupo alcoxi, un grupo ariloxi, un grupo alquiltio, un grupo ariltio, en los cuales cada alquilo, cicloalquilo, arilo, heterocicloalquilo o mitad heteroarilo de

éstos pueden ser opcionalmente sustituida. Cuando R^6 está comprendida de una mitad de hidrocarburo saturado y una mitad de hidrocarburo no saturado, la mitad de hidrocarburo saturado puede ser unida a una mitad de hidrocarburo no saturado que contiene uno o más uniones dobles o uniones triples, las posiciones terminales de las cuales pueden ser sustituidas por los sustituyentes descritos arriba, o pueden contener mitades de hidrocarburo saturado de cadena-ramificada o recta- adicionales. Preferiblemente la mitad de hidrocarburo no saturado contiene una unión doble o una unión triple, o posición(es) terminal de la cual puede opcionalmente contener una mitad de hidrocarburo saturado de cadena-ramificada o recta-. Preferiblemente, si la mitad de hidrocarburo no saturada contiene una doble unión, ambas posiciones terminales de la unión doble contienen una mitad de hidrocarburo saturado de cadena-ramificada o recta-. En modalidades especialmente preferidas R^6 es un alquilo inferior sustituido o no sustituido, arilalquilo, heteroarilalquilo, grupo cicloalquilo, o un grupo comprendido de una mitad de hidrocarburo saturada de cadena-recta y una mitad de hidrocarburo no saturado. Preferiblemente, R^6 es metilo, metilo sustituido, etilo, propilo, butilo, sec-butilo, 2-propin-1-ilo, 3-metil-3-buten-1-ilo, metilciclohexilo, metiltienilo sustituido o no sustituido o benzilo sustituido o no sustituido, en los cuales la mitad fenilodel benzilo sustituido comprende uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino o halógeno y la mitad tienilo del--metiltienilo sustituido comprende uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino o halógeno. Cuando R^6 es metilo sustituido, la mitad de metilo (metileno) puede ser sustituida con un grupo alcoxi, un grupo arilioxi, un grupo alquililo o un grupo arililo. Más preferiblemente, R^6 es etilo, 2-propin-1-ilo, . -metilciclohexilo, ó bencilo sustituido o no sustituido, en los cuales la mitad de fenilo del bencilo sustituido

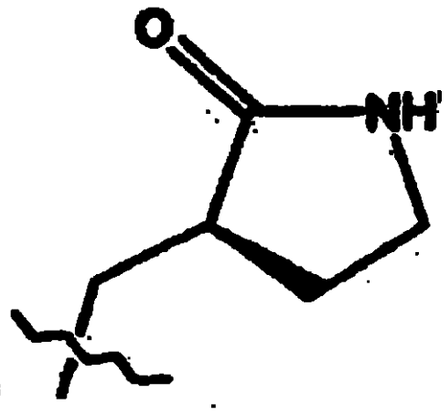
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comprende uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior y halógeno.

En modalidades especialmente preferidas de las Fórmulas I-a, I-b y I-c, R^9 es seleccionada de $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alquilo; $-CH_2NHC(O)CH_3$; y

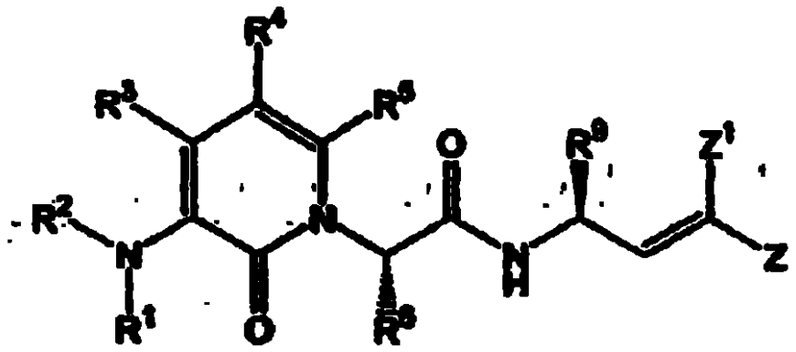


, donde n es 1 o 2.



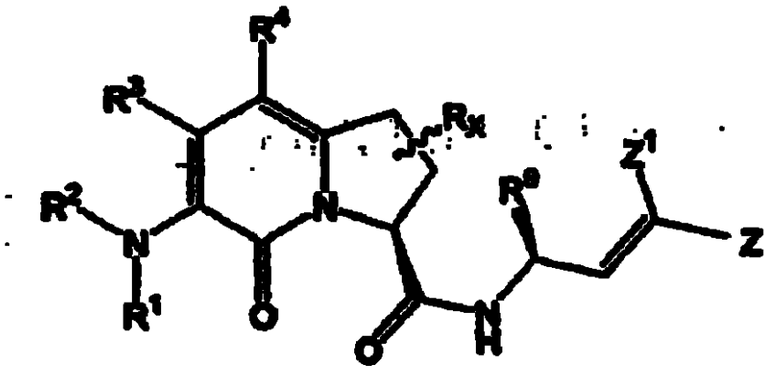
Más preferiblemente, R^9 es .

Las modalidades especialmente preferidas de esta invención comprenden compuestos de las Fórmulas I-a', I-b' y I-c' como sigue:



I-a'

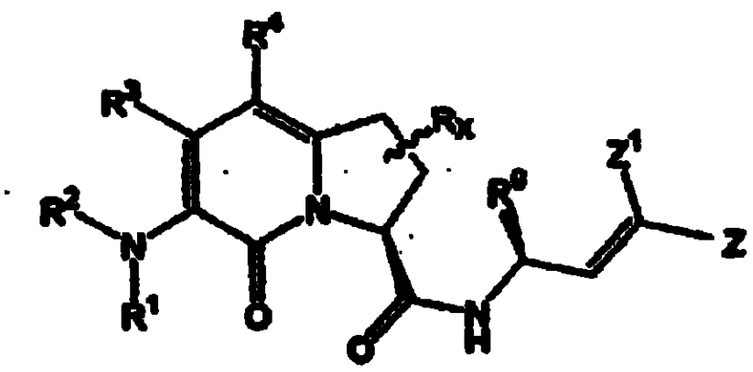
en la cual R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z y Z^1 son tal como se definieron previamente;



I-b'

en la cual R^1, R^2, R^3, R^4, R^9, R_x, Z y Z^1 son tal como se definieron previamente;

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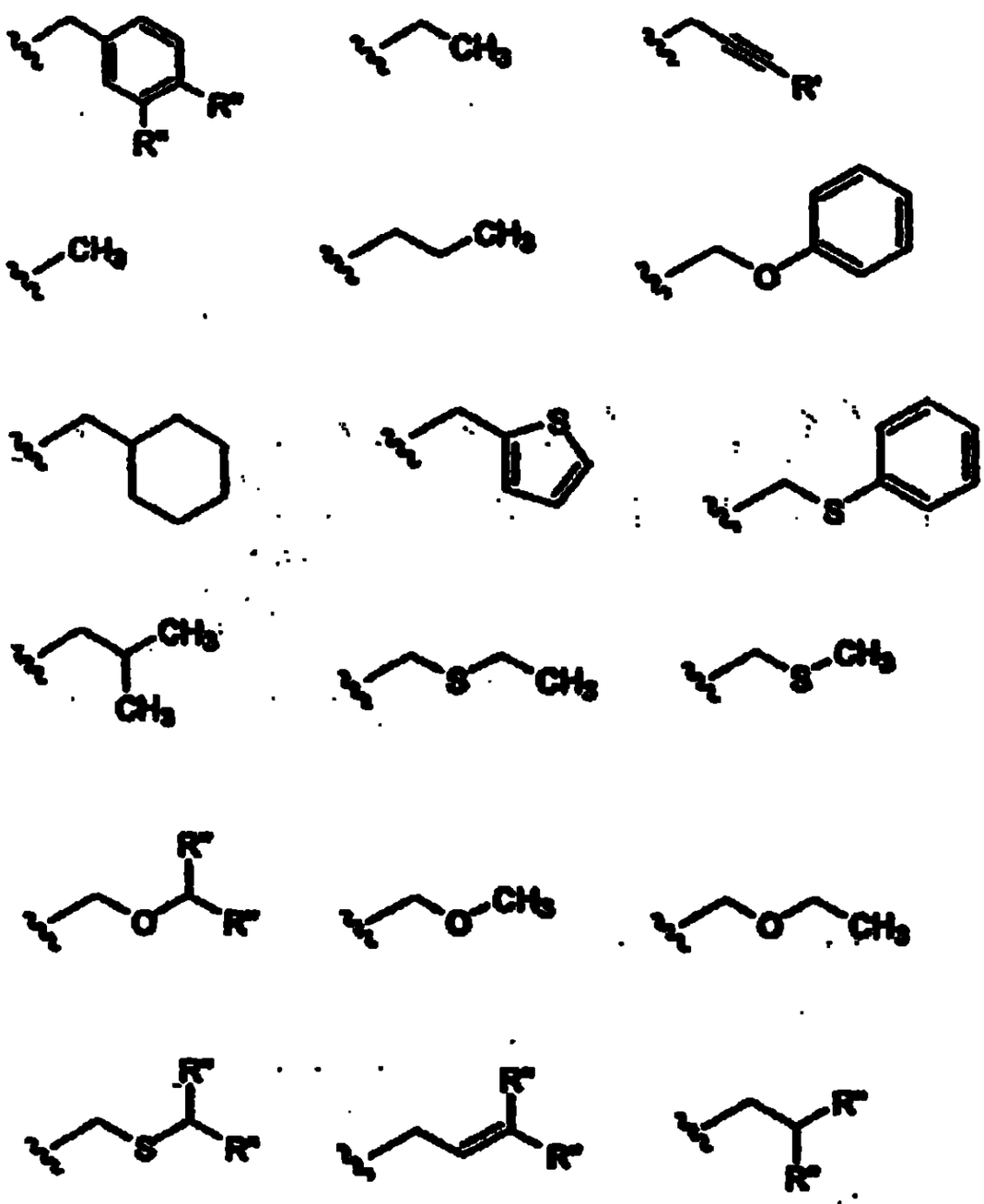


I-b'

en el cual R^4, R^5, R^8, R^9, R_y, Z y Z^1 son tal como se definieron previamente.

En modalidades especialmente preferidas de las Fórmulas I-a' y I-b', R^2 es bencilioxicarbonilo sustituido o no sustituido, arilioxicarbonilo, o heteroarilicarbonilo, más preferiblemente heteroarilicarbonilo, donde la mitad heteroarilo es un heterocicio de cinco-miembros que tienen de uno hasta tres heteroátomos seleccionados de O, N, y S. Más preferiblemente R^2 es heteroarilicarbonilo en el cual la mitad heteroarilo es un heterocicio de cinco-miembros que tiene por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxigeno (por ejemplo, 1,2-oxazolilo sustituido o no sustituido (es decir, isoxazolilo), 1,3-oxazolilo (es decir, oxazolilo), u oxadiazolilo (1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo); los oxadiazolilos preferidos no son sustituidos y monometil-sustituido 1,2,4-oxadiazolilo. En modalidades especialmente preferidas la mitad heteroarilo es 3-isoxazolilo o 5-isoxazolilo, ya sea sustituida o no sustituida con uno o dos sustituyentes seleccionados de metilo y halógeno, con cloro y fluoro siendo sustituyentes de halógeno preferidos.

En las modalidades especialmente preferidas de las Fórmulas I-a' y I-c', R^8 es seleccionada de:

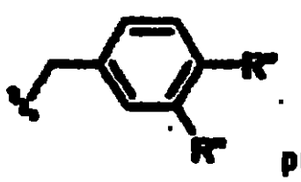
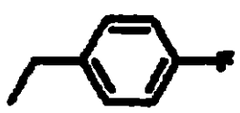


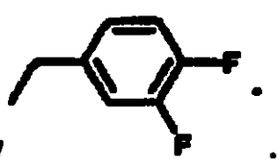
en la cual R' puede ser H o alquilo y R'' pueden uno o dos sustituyentes independientemente seleccionados de alquilo

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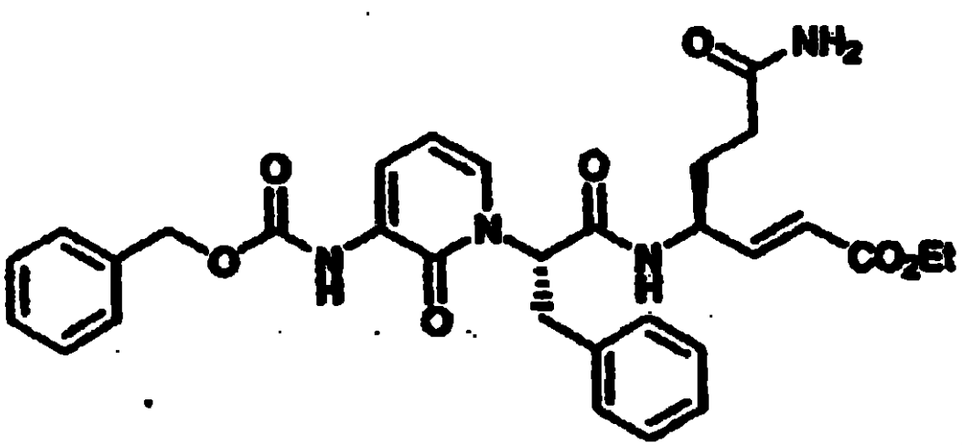
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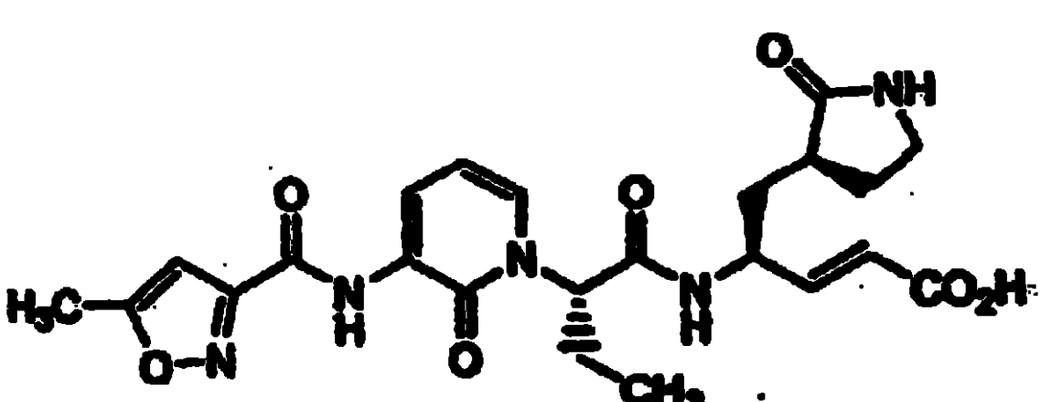
inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino, y halógeno.

Grupos  preferidos son 

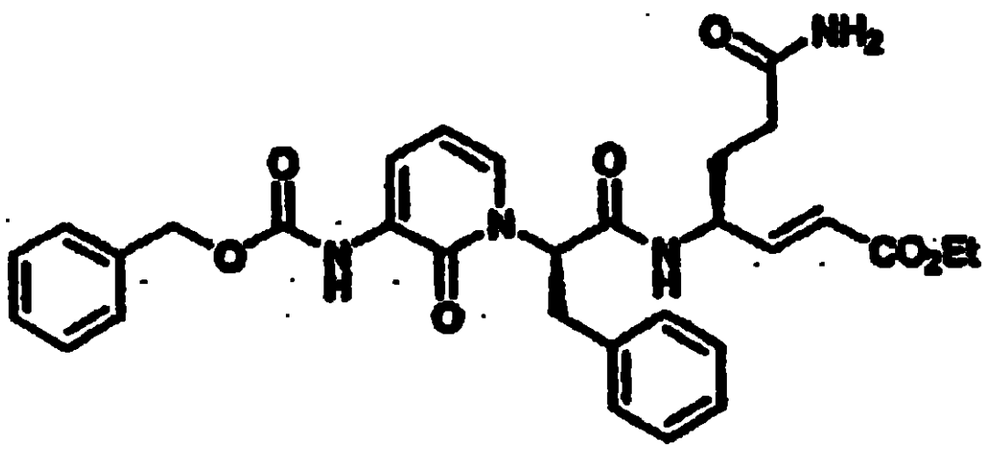
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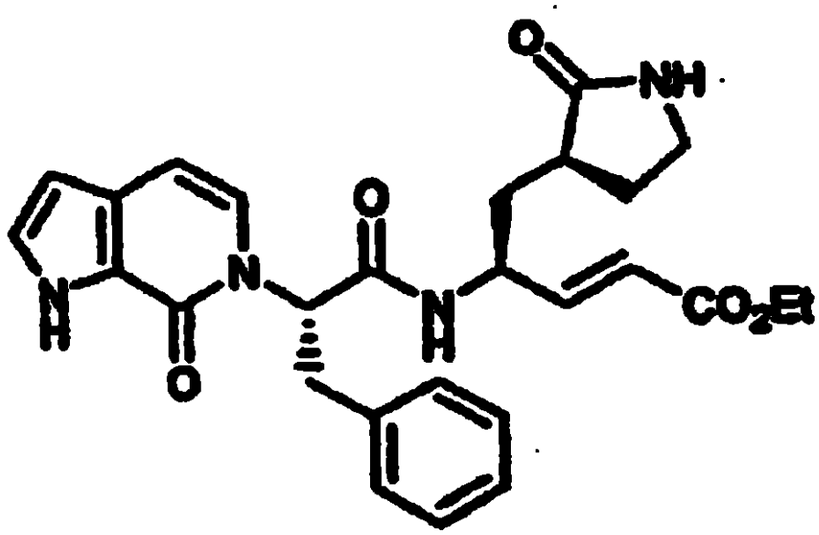
Los compuestos específicos preferidos incluyen aquellos de los Ejemplos abajo, especialmente:

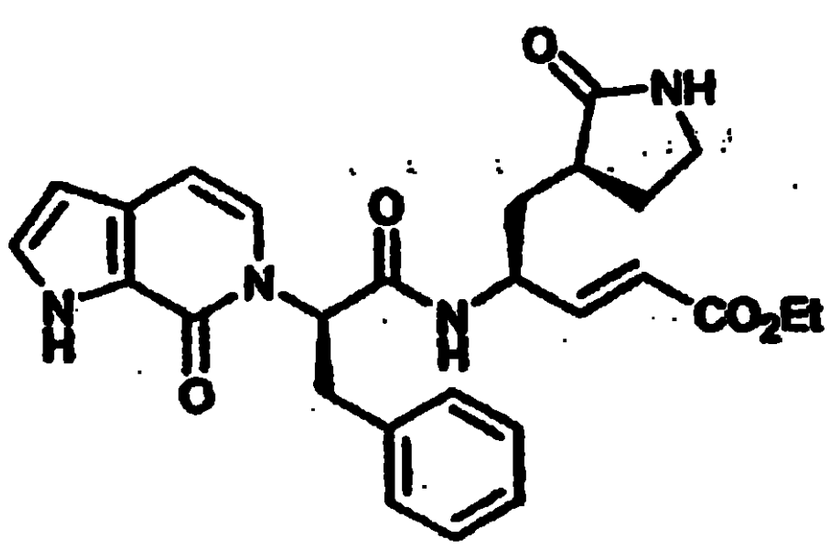




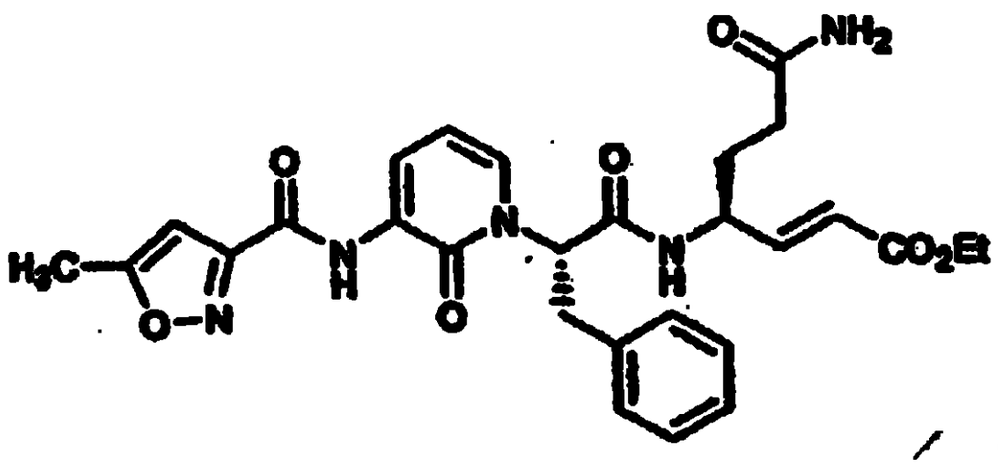
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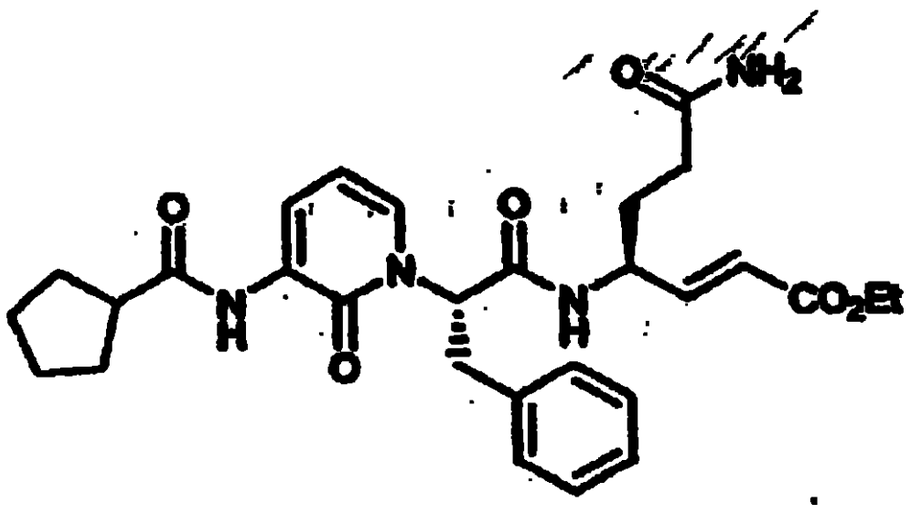


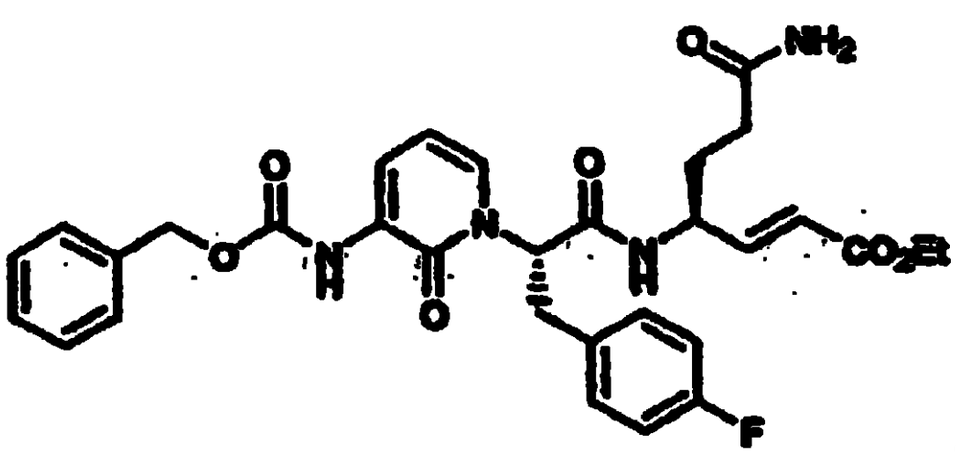




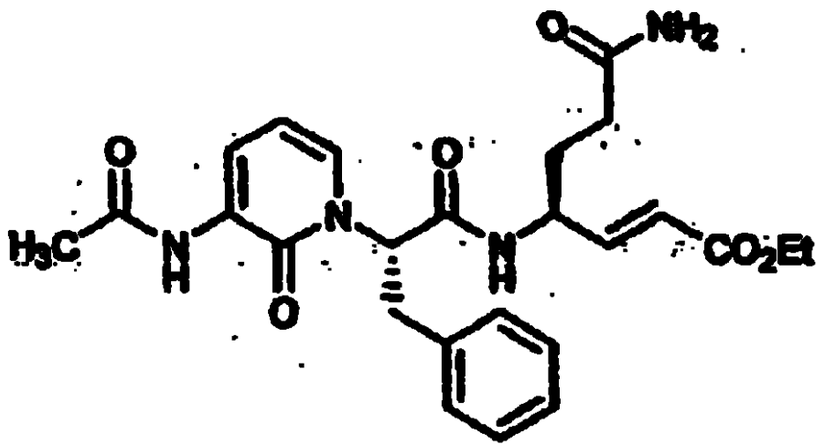
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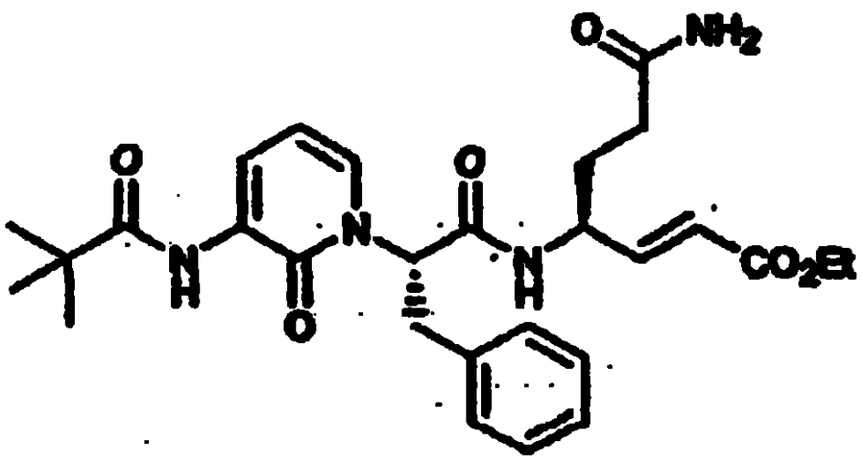


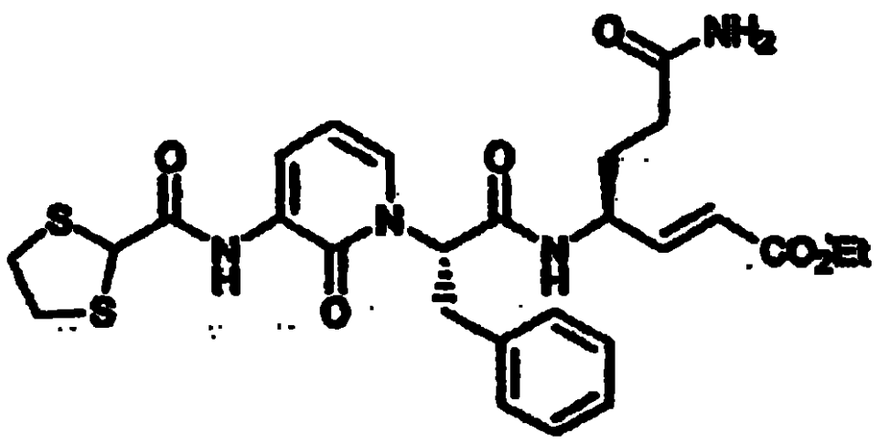




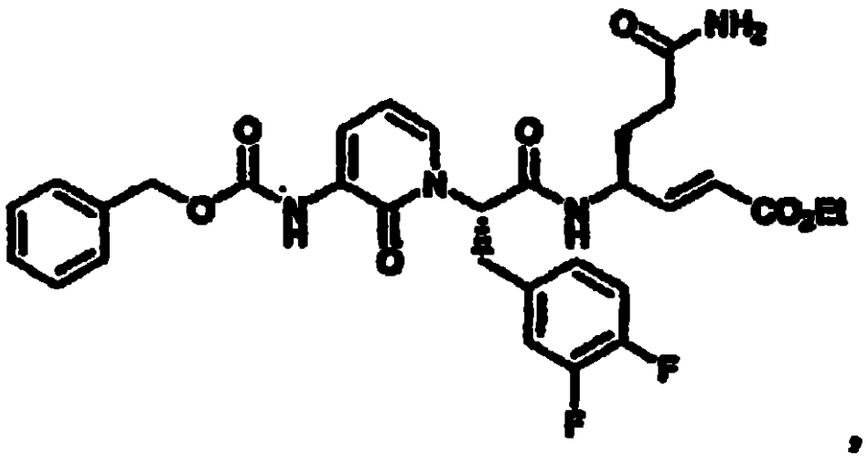
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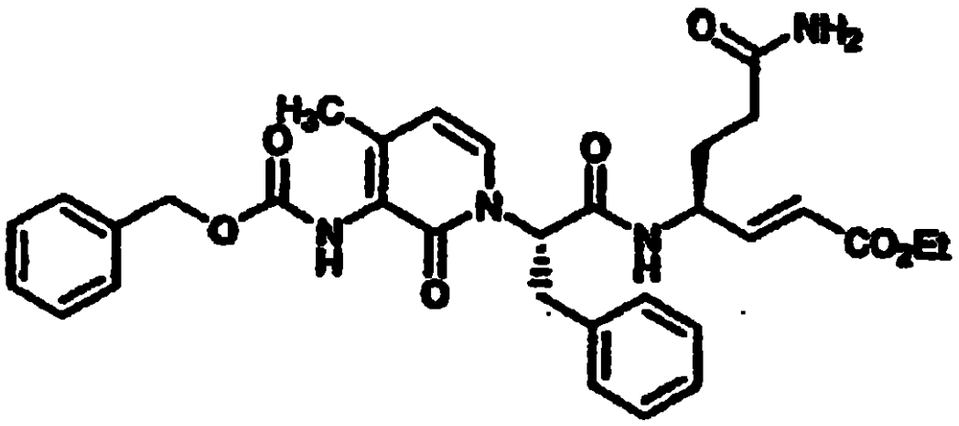


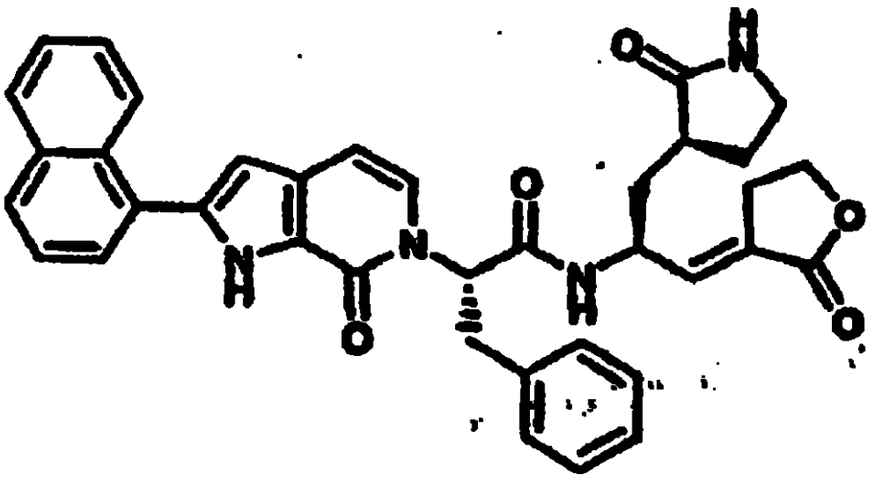




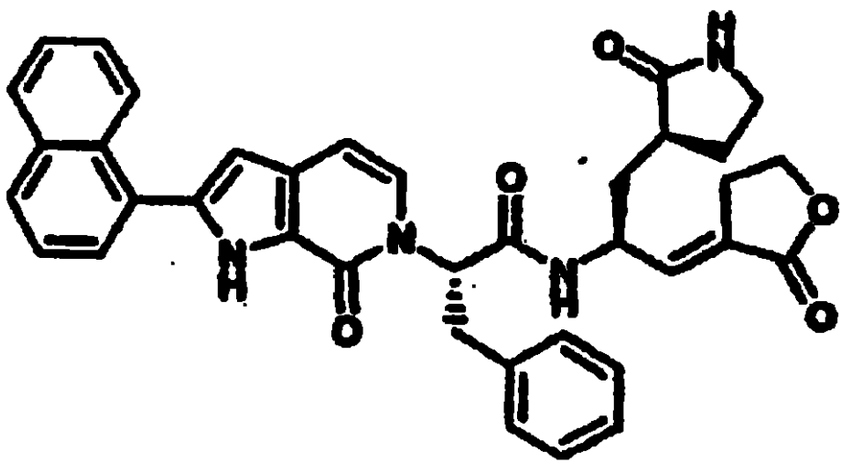
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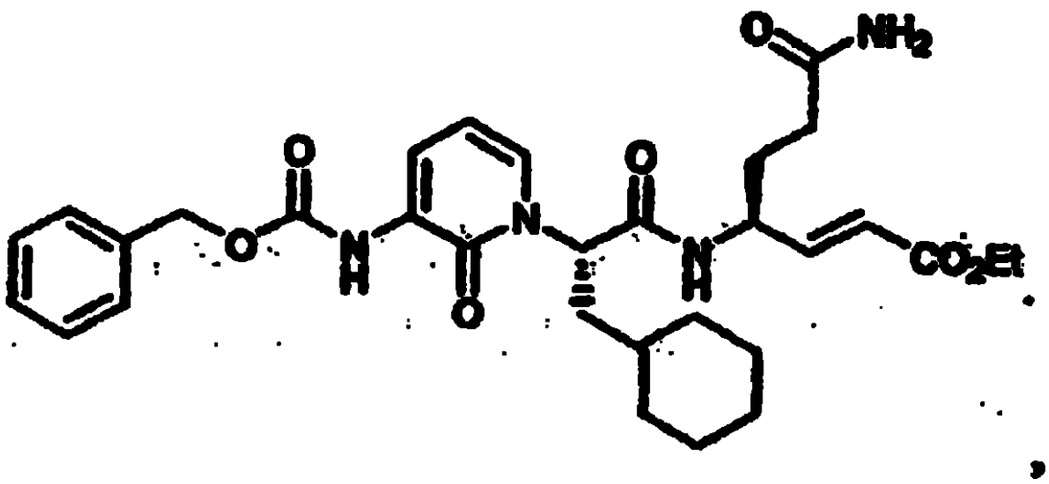


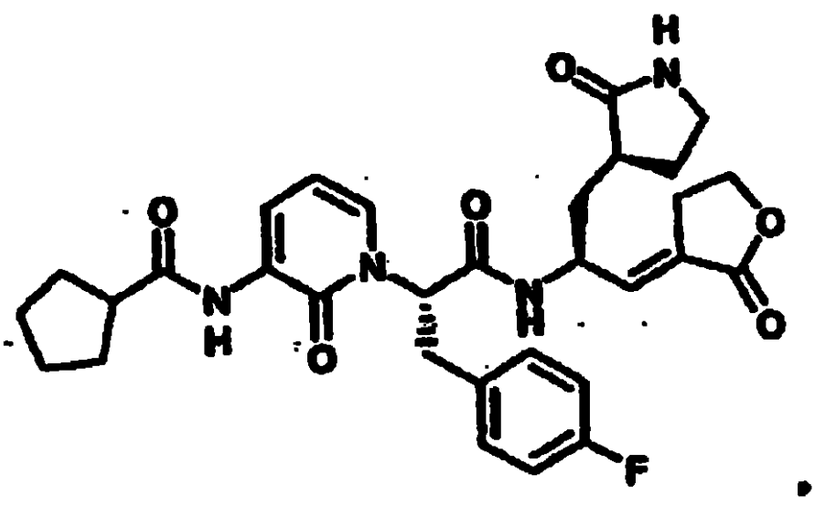




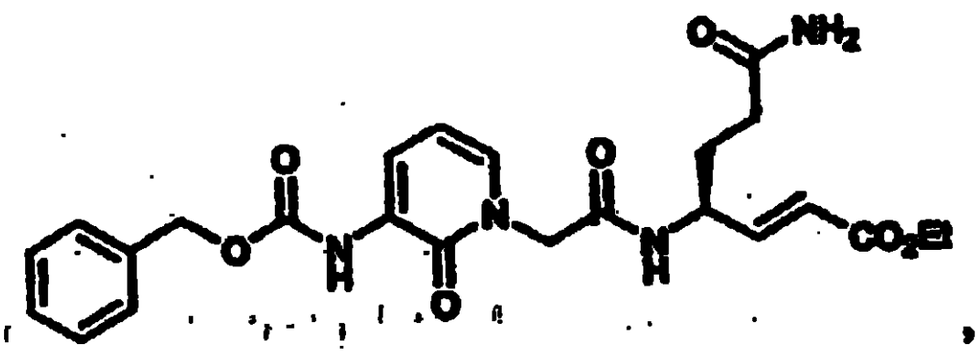
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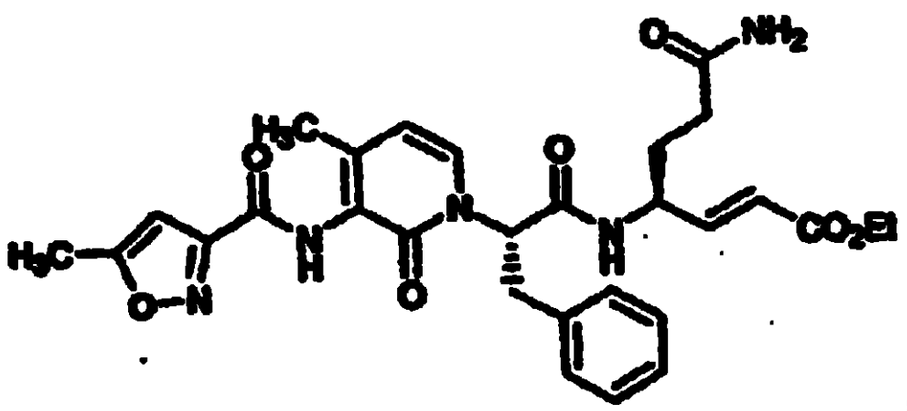


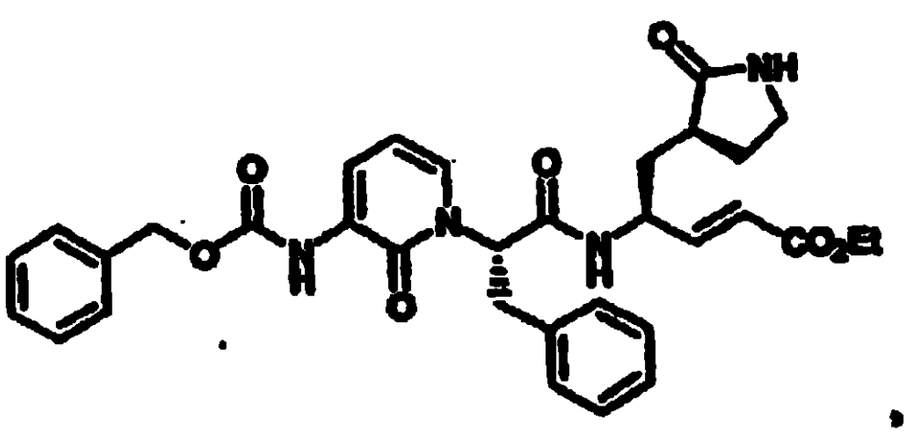


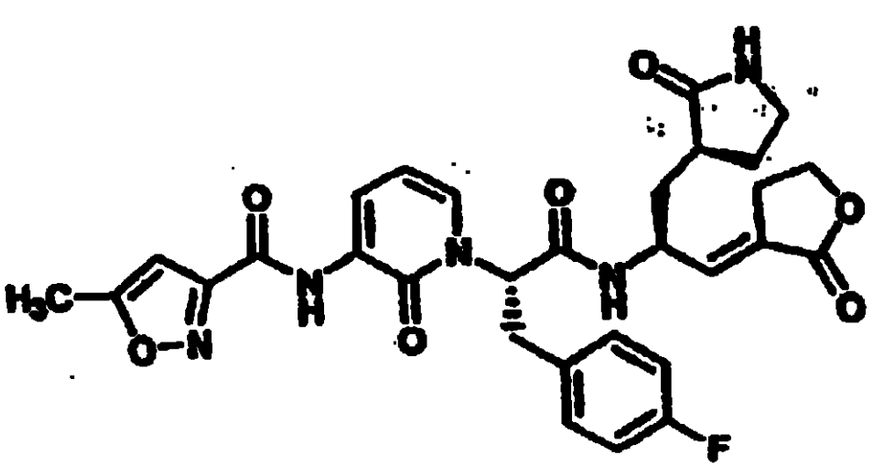


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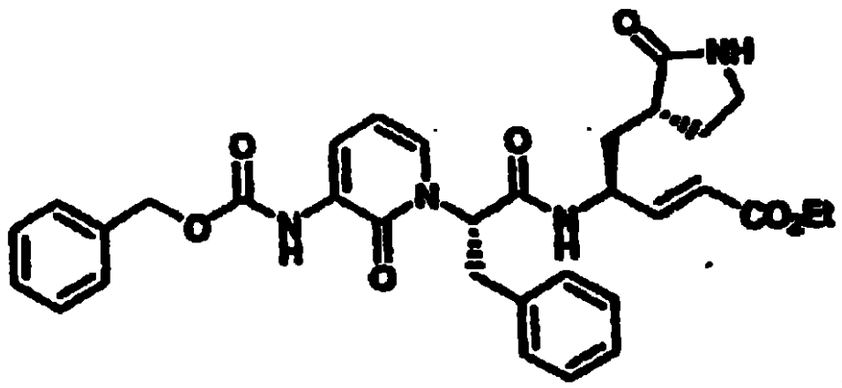


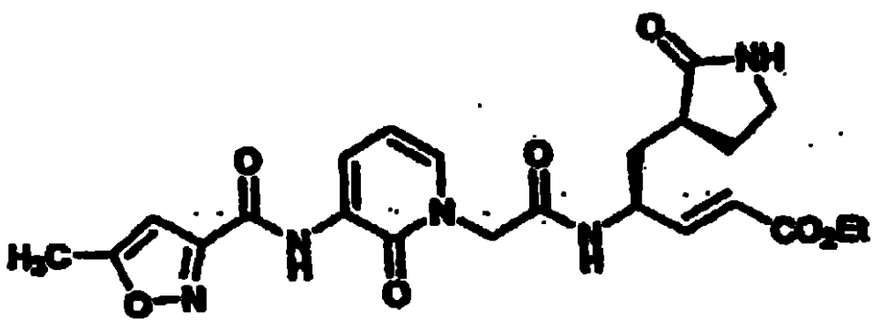


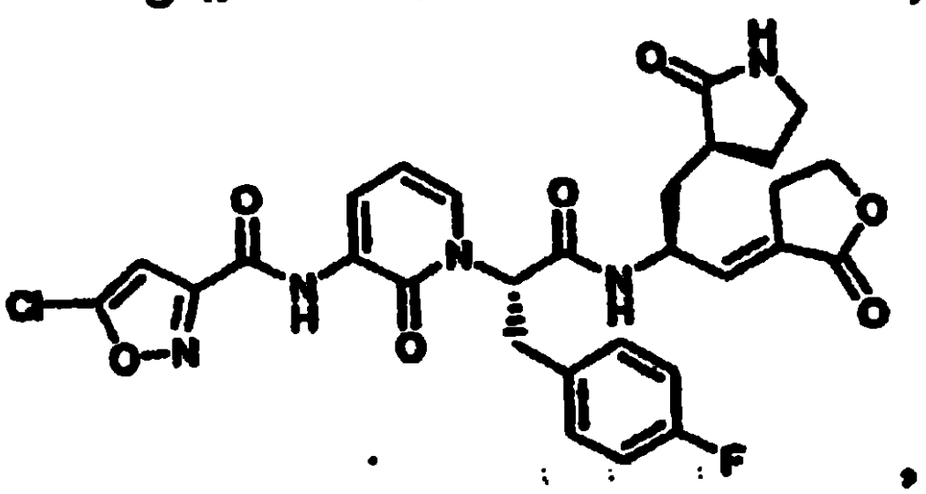


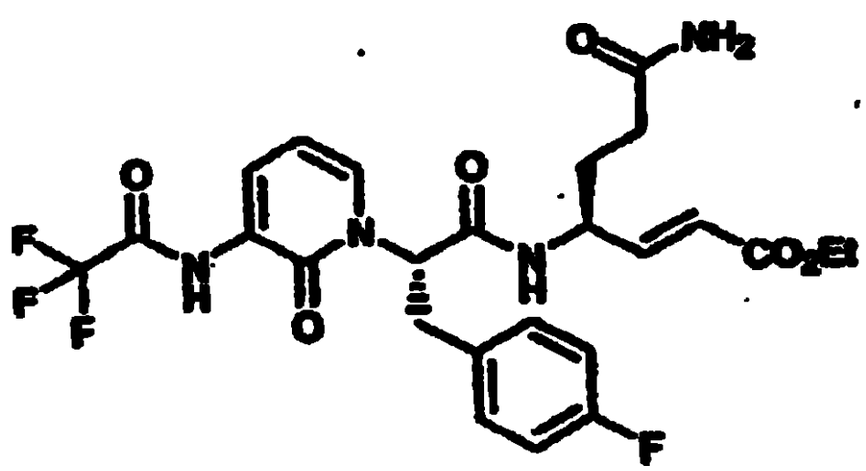


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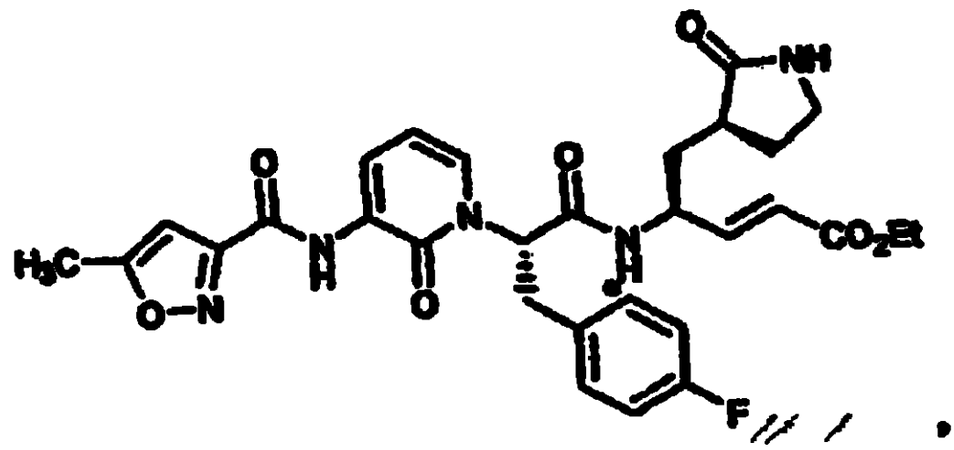


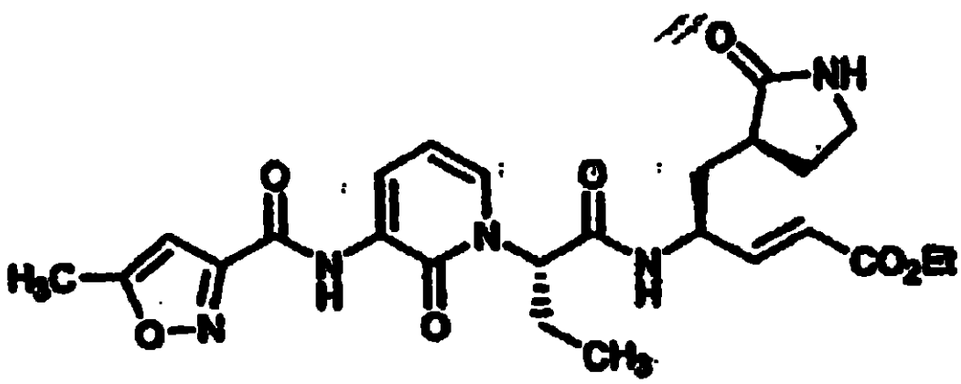


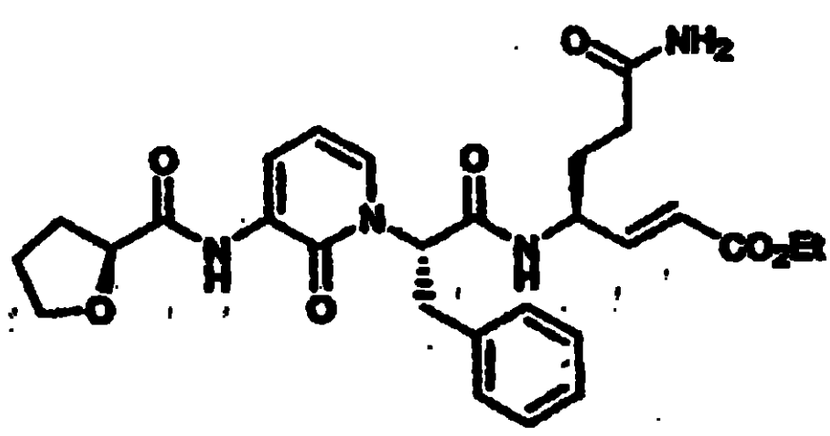


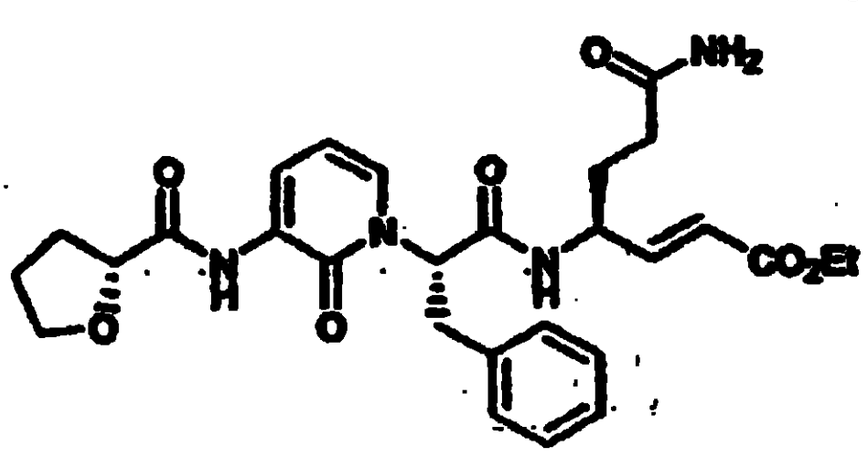


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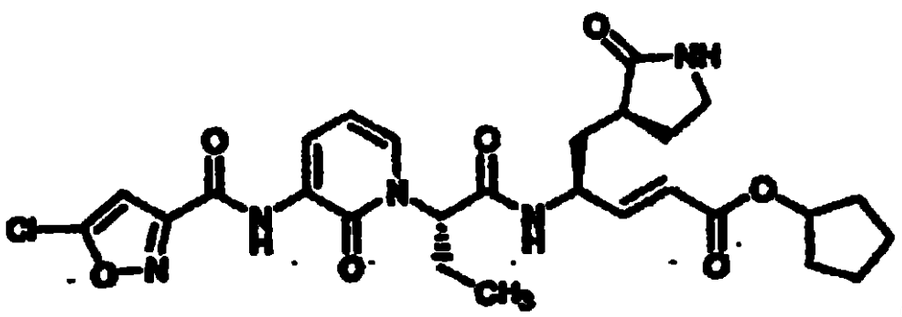


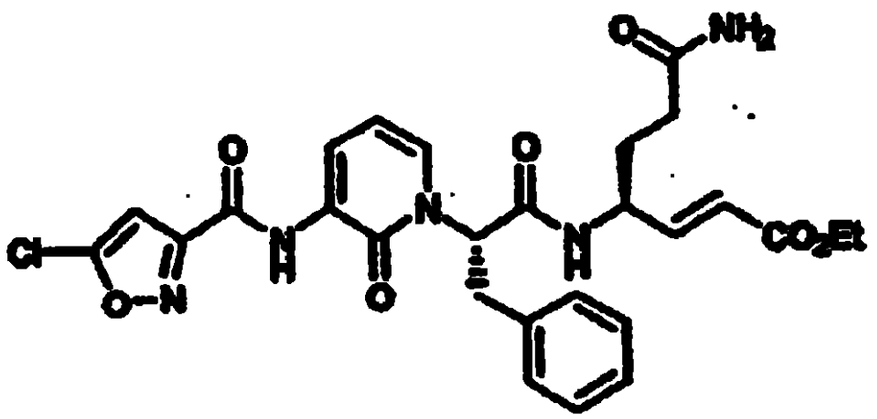


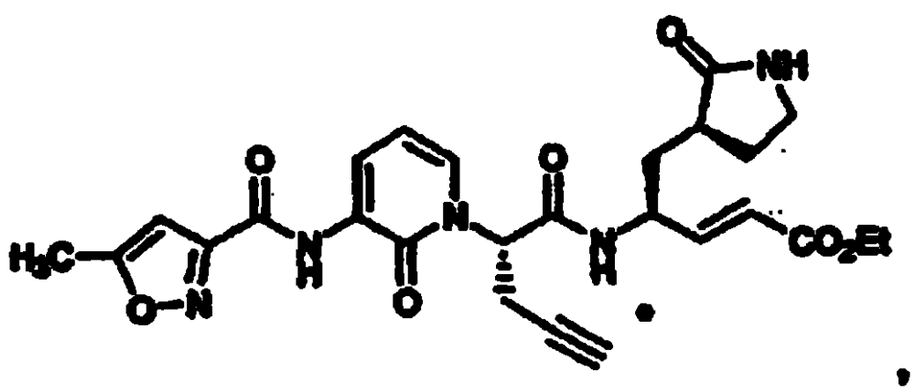


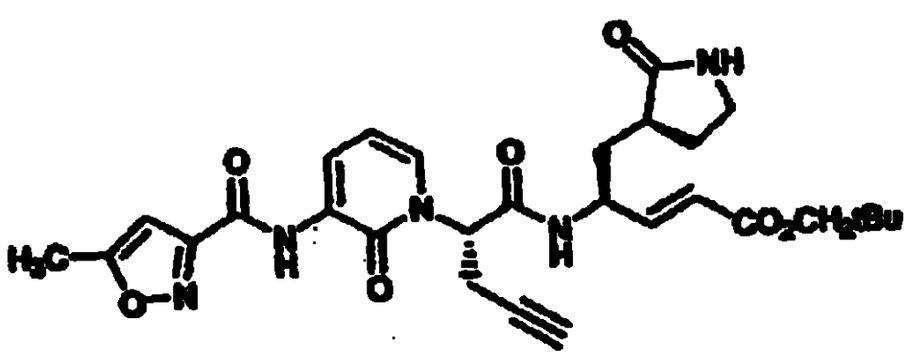


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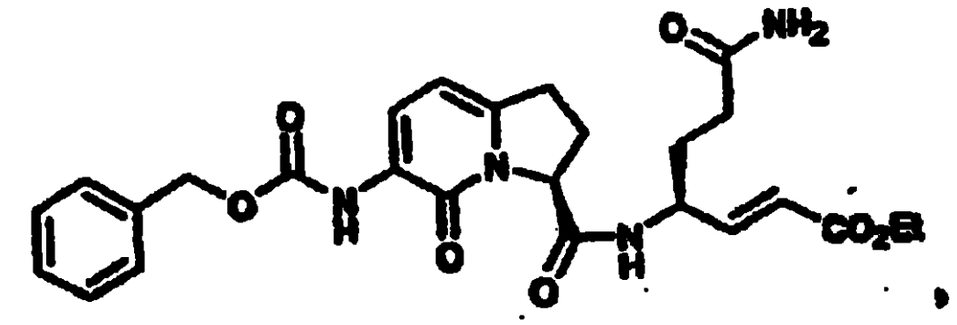


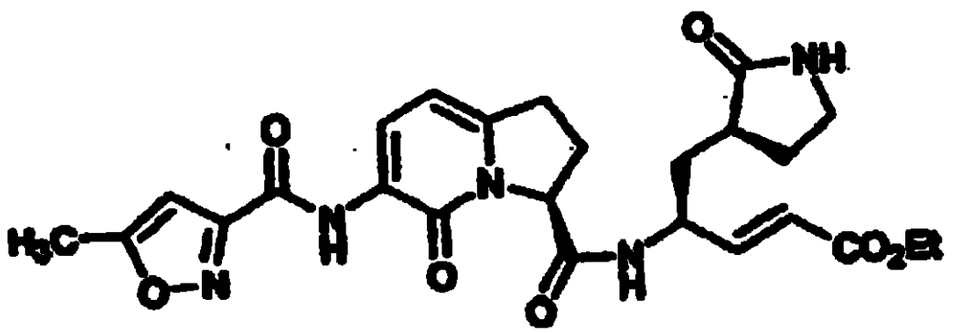


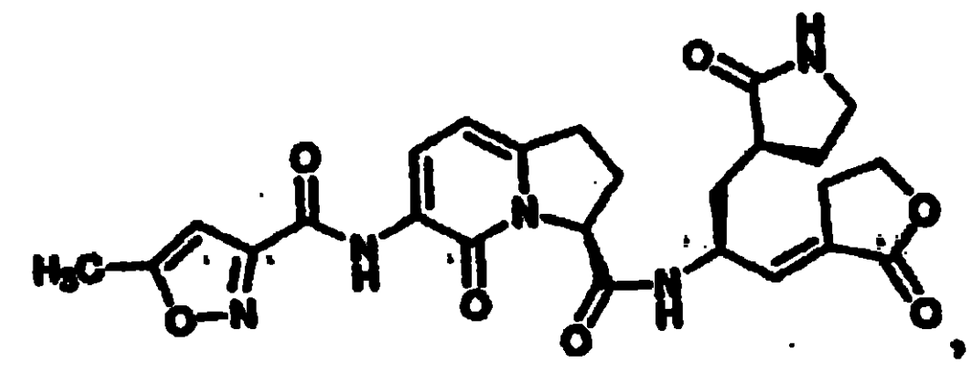


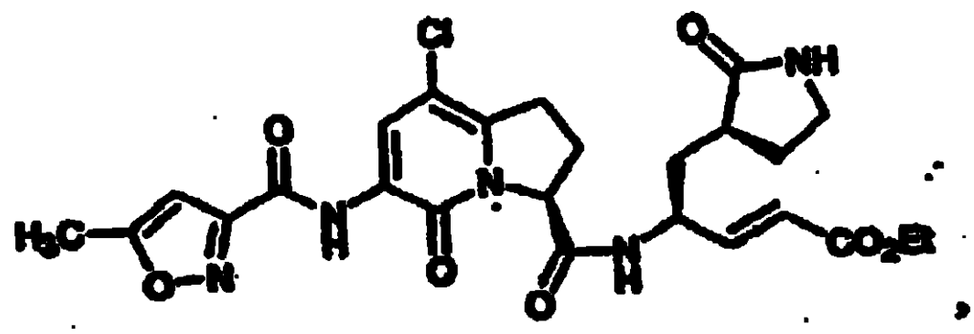
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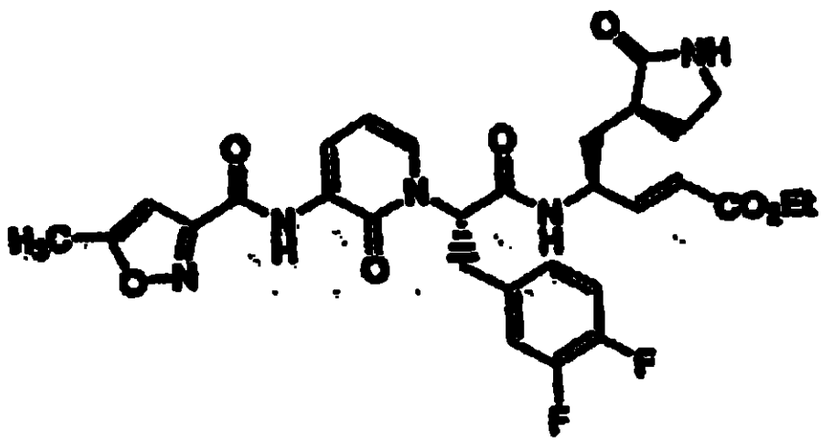


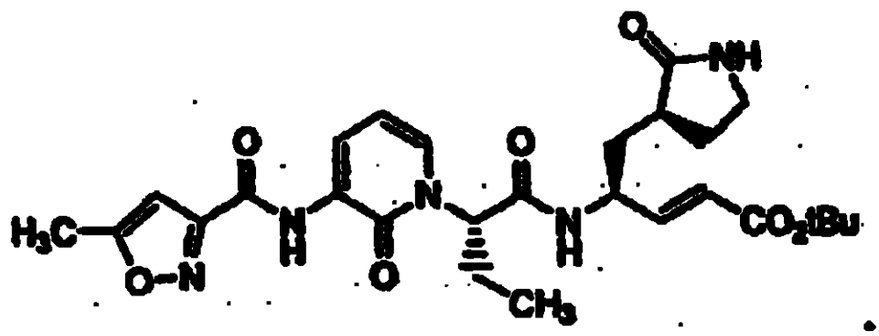






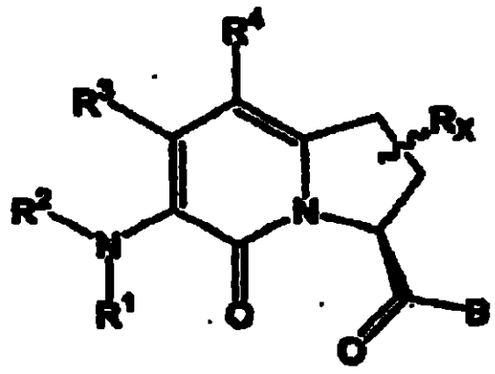
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y

La invención está también dirigida a los intermediarios de la Fórmula II, los cuales son útiles en la síntesis de ciertos compuestos de la Fórmula I:

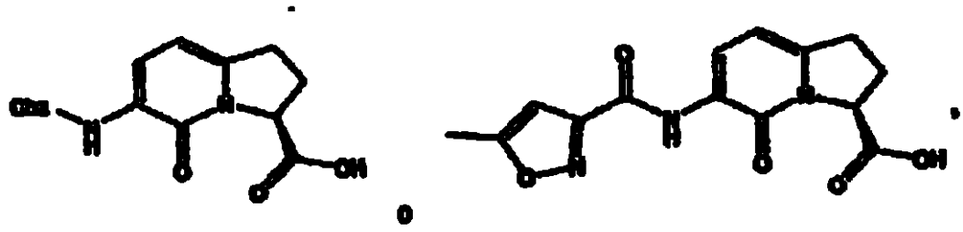


II

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en la cual las variables R^1, R^2, R^3, R^4 y R_x son como se han definido arriba, y B es H, $-OR^{24}$. Cuando R^1 y/o R^2 son independientemente grupos protectores de nitrógeno adecuable, cualquier grupo protector de nitrógeno adecuable conocido en el arte puede ser usado (ver, por ejemplo, Greene & Wuts, supra). Los sustituyentes adecuables R^1 y R^2 incluyen, pero no están limitados a, grupos protectores de carbamato tales como alquiloxicarbonilo (por ejemplo, Boc) y ariloxicarbonilo (por ejemplo, Cbz o FMOC), alquiloxicarbonilos (por ejemplo, metoxicarbonilo), alquilo o arilcarbonilo, alquilo sustituido, especialmente arilalquilo (por ejemplo, tritilo (trifenilmetilo), bencilo y bencilo sustituido) y similares. Preferiblemente, cuando R^1 y R^2 son independientemente grupos protectores de nitrógeno adecuados, el adecuable R^1 y sustituyentes R^2 incluyen, pero no están limitados a, Boc, y Cbz, FMOC, metiloxicarbonilo y tritilo. Cuando R^1 y R^2 tomados juntos son un grupo protector de nitrógeno adecuable, los sustituyentes adecuables R^1/R^2 incluyen ftalimido y una estabase (1,2-bis(dialquil))etileno). R^{24} puede ser H o un grupo protector adecuable para una mitad carbonilo. Los grupos protectores de carbóxilo adecuados son también bien conocidos en el arte, ejemplos de los cuales pueden encontrarse en Greene y Wuts, supra, e incluye, pero no están limitados a, grupos protectores donde R^{24} es alquilo, un arilo sustituido o no sustituido, alquilo y/o sililo sustituido de arilo (por ejemplo t-butildimetilsililo(TBS)), y similares.

La invención está también dirigida a sales farmacéuticamente aceptables de los compuestos de la Fórmula II. Los ejemplos preferidos de la Fórmula II útiles como intermediarios incluyen los siguientes:



y sales farmacéuticamente aceptables de éstos.

Los compuestos antipicornavirales de esta invención incluyen prodrogas, los metabolitos farmacéuticamente activos, y las sales farmacéuticas aceptables y solubles de éstos. En modalidades preferidas, los compuestos de la Fórmula I, prodrogas, sales farmacéuticamente aceptables, la actividad antirinoviral más preferiblemente, correspondiente a un EC_{50} menos de o igual a 100 μM en el ensayo de cultivo de célula H1-HeLa.

Una "prodroga" está destinada para significar un compuesto que es convertido bajo condiciones fisiológicas o por solvólisis o metabólicamente a un compuesto especificado que es un compuesto farmacéuticamente activo producido a través de metabolismo en el cuerpo de un compuesto especificado. Una "sal farmacéuticamente aceptable" está destinada para significar una sal que retiene la efectividad biológica de los ácidos y bases libres de un compuesto especificado y que no es biológicamente o de otra manera indeseable. Los ejemplos de sales farmacéuticamente aceptables incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, monohidrogenofosfatos, dihidrogenofosfato, metafosfatos, pirofosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, subacatos, fumaratos, maleatos, butino-1,4-dioatos, hexina-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos, sulfonatos silenosulfonatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-

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hidroxibutiratos, glicolatos, tartratos, metano-sulfonatos, propanosulfonatos, naftaleno-1-sulfonatos, naftaleno-2-sulfonatos, y mandelatos. Un "soluble" está destinado para significar una forma soluble farmacéuticamente aceptable de un compuestos especificado que retiene la efectividad biológica de tal compuesto. Los ejemplos de solubles incluyen compuestos de la invención en combinación con agua, isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético, o etanolamina. En el caso de compuestos, sales, o solubles que son sólidos, queda entendido por aquellos versados en el arte que los compuestos de la invención, sales, y solubles pueden existir en diferentes formas de cristal, todas las cuales están destinadas a estar dentro del alcance de la presente invención y fórmula especificadas.

La presente invención está también dirigida a un método de inhibir de actividad de proteasa picornaviral 3C, comprendiendo contactar la proteasa con una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable, prodroga, metabolito farmacéuticamente activo, o soluble de éstos. Por ejemplo, la actividad de proteasa picornaviral 3C puede ser inhibida en tejido de mamífero administrando un compuesto de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito farmacéuticamente activo, o soluble de éstos. Más preferiblemente, el presente método está dirigido a inhibir actividad de proteasa rinoviral. "Tratamiento" o "tratamiento" está destinado a significar por lo menos la mitigación de una condición de enfermedad en un mamífero, tal como un humano, que es aliviado por la inhibición de la actividad de poliovirus humano, coxsaquievirusos humanos, virusos de encefalomiocarditis, virus de meningitis, y virus de hepatitis A. Los métodos de tratamiento para la mitigación de una condición de enfermedad incluyen el uso de los compuestos de esta invención en cualquier forma convenientemente aceptable, por ejemplo, tal como un profiláctico. La actividad de los compuestos de la invención como inhibidores de actividad de proteasa picornaviral 3C puede ser medida por

cualquiera de los métodos adecuados conocidos por aquellos versados en el arte, incluyendo ensayos in vivo e in vitro. Como ejemplo de un ensayo adecuable para actividad de medida en el ensayo de cultivo de célula antiviral H1-HeLa descrito aquí en la presente.

La administración de los compuestos de la Fórmula I, y sus prodrogas, sales, metabolitos activos farmacéuticamente aceptables y solubles pueden ser llevados a cabo de acuerdo con cualquiera de los modos aceptados generalmente de administración disponibles para aquellos versados en el arte. Los ejemplos ilustrativos de modos adecuables de administración incluyen oral, nasal, parenteral, tópico, transdérmico, y rectal.

Un compuesto de la invención de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito activo, o soluble de éste puede ser administrado como una composición farmacéutica en cualquier forma farmacéutica reconocible para los artesanos versados como siendo adecuable. Las formas farmacéuticas adecuables incluyen sólidos, semisólidos, líquido, o formulaciones liofilizadas, tales como tabletas, polvos, cápsulas, supositorios, suspensiones, liposomas, y aerosoles. Las composiciones farmacéuticas de la invención pueden también incluir excipientes adecuados, diluyentes, vehículos, y portadores, así como también otros agentes farmacéuticamente activos, dependiendo sobre el uso intentado o modo de administración. En modalidades preferidas, las composiciones farmacéuticas de la invención son entregadas oralmente, o intranasalmente en la forma de suspensiones. Los métodos aceptables de preparar formas farmacéuticas adecuadas de las composiciones farmacéuticas pueden ser rutinariamente determinados por aquellos versados en el arte. Por ejemplo, las preparaciones farmacéuticas pueden ser preparadas siguiendo técnicas convencionales de la química farmacéutica involucrando etapas tales como mezcla, granulación, y compresión cuando sea necesario para formas de tableta, o

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mezcla, presentación, y disolución de los ingredientes como sea apropiado, para dar los productos deseados para administración oral, parenteral, tópica, intravaginal, intranasal, intrabronquial, intraocular, intraaural, y/o rectal.

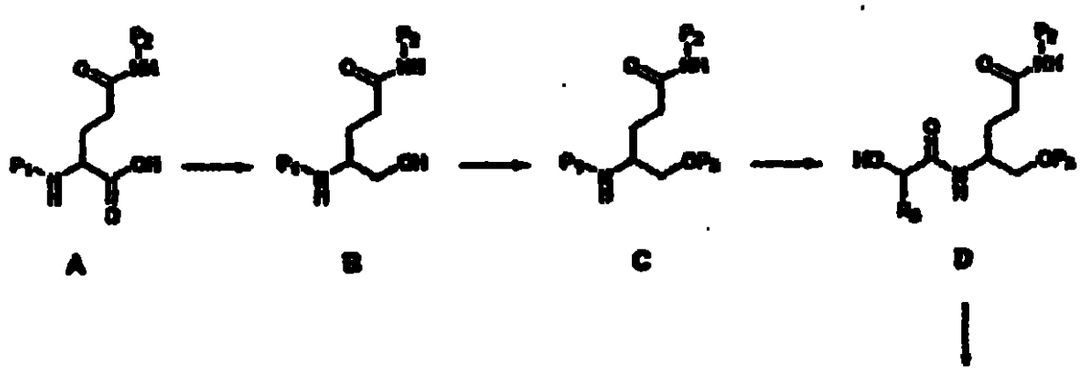
Los portadores, diluyentes, vehículos, o excipientes farmacéuticamente aceptables líquidos o sólidos pueden ser empleados en las composiciones farmacéuticas. Los portadores sólidos ilustrativos incluyen almidón, lactosa, dihidrato de sulfato de calcio, terra alba, sacarosa, talco, gelatina, pectina, acacia, estearato de magnesio, y ácido esteárico. Los portadores líquidos ilustrativos incluyen jarabe, aceite de maní, aceite de oliva, solución salina, y agua. El portador y diluyente pueden incluir un material de soltura prolongado, tal como monoestearato de glicerilo o diestearato de glicerilo, solo o con una cera. Cuando un portador líquido es usado, la preparación puede ser en la forma de un jarabe, elixir, emulsión, cápsula de gelatina blanda, líquido inyectable estéril (por ejemplo, solución), o una suspensión líquida acuosa o no acuosa. Una dosis de la composición farmacéutica contiene por lo menos una cantidad terapéuticamente efectiva del compuesto activo (es decir, un compuesto de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito activo, o soluble de ésta), y preferiblemente está hecha de una o más unidades de dosificación farmacéutica. La dosis seleccionada puede ser administrada a un mamífero, por ejemplo, un paciente humano, en necesidad de tratamiento medicado para inhibición de la actividad de proteasa picornaviral 3C, por cualquier método conocido o adecuables de administración de dosis, incluyendo: tópicamente, por ejemplo, como un ungüento o crema; oralmente; rectal, por ejemplo, como un supositorio; parenteralmente por inyección; o continuamente por infusión intraocular, intraaural, intrabronquial, intranasal, o intravaginal. Una "cantidad terapéuticamente efectiva" está destinada para significar la cantidad de un agente de la invención que, es administrado a un mamífero en necesidad de éste, es suficiente para efectuar

tratamiento para condiciones de enfermedad aliviadas por la inhibición de la actividad de una o más proteasas picornavirales 3C, tales como rinovirusos, poliovirus humano, coxsequievirusos humanos, virusos de encefalomiocarditis, menigovirus, y virus de hepatitis A. La cantidad de un compuesto dado de la invención que será terapéuticamente efectivo variará dependiendo sobre los factores tales como compuesto particular, la condición de enfermedad y la severidad de la misma, la identidad de un mamífero en necesidad de éste, dicha cantidad puede ser rutinariamente determinada por artesanos.

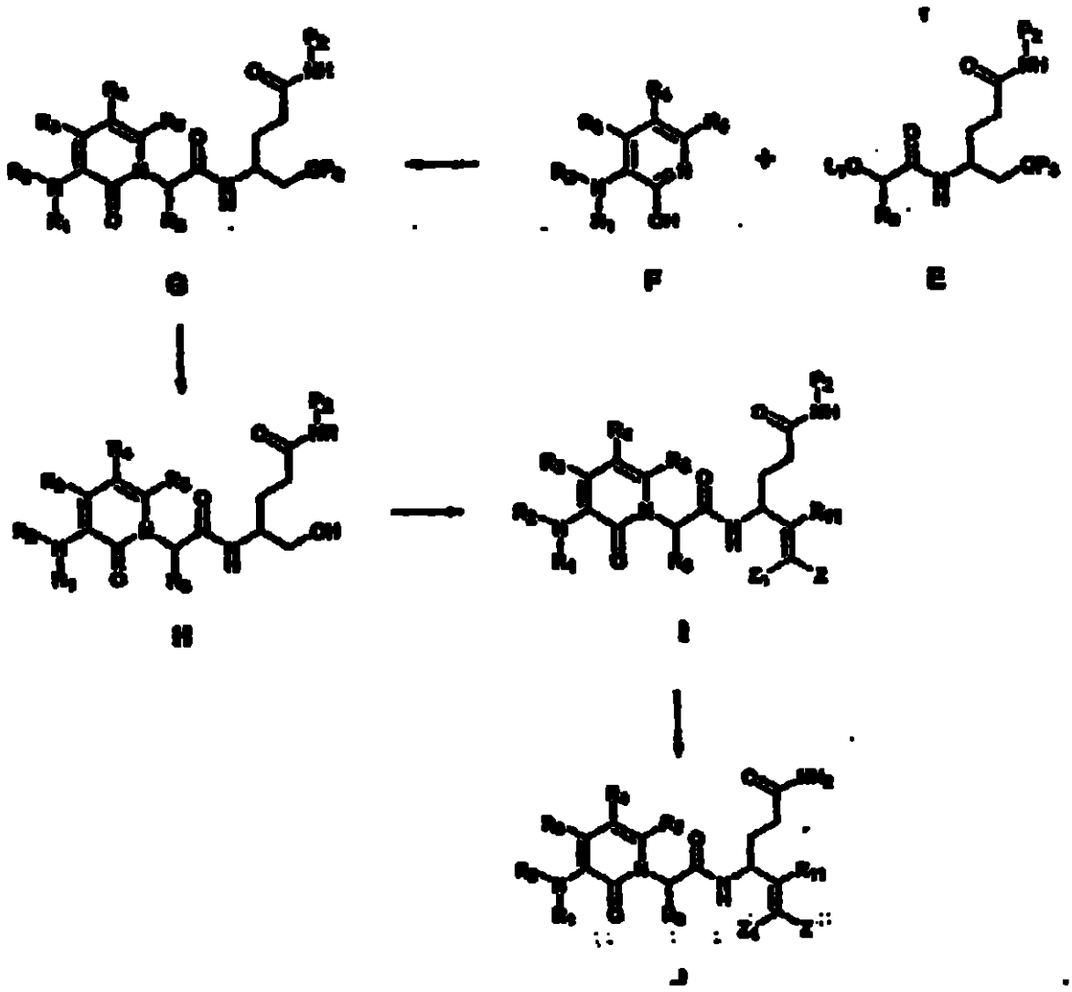
METODOS SINTÉTICOS GENERALES

Preferiblemente, los compuestos de la invención de la Fórmula I y II son preparados por los métodos de la presente invención, que incluyen los Métodos Generales mostrados abajo. Cuando la estereoquímica en no está especificada las estructuras químicas, ya sea en estereocentro puede ser utilizada. Aunque varios intermediarios están descritos y determinados como 2-hidroxipiridinas, queda entendido que tales entidades pueden también existir como los correspondientes tautómeros 2-piridina. Las siguientes abreciaciones también se aplican: Boc (tert-butoxicarbonilo), Ac (acetilo), Cbz (benciloxicarbonilo), DMB (2,4-dimetoxibencilo), TBS (tert-butildimetilzililo), TBDPS (tert-butildifenilzililo), Ms (metanosulfonato), Ts (toluenosulfonato), Bn (bencilo), y Tr (trifenilmetilo).

Método General 1



A B C D



En el Método General 1, un amino ácido A (comercialmente disponible o preparado por métodos descritos en la literatura química) donde P_1 es un grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac), y P_2 es un grupo protector apropiado para el nitrógeno de amida (por ejemplo, Tr), es reductivamente transformada en alcohol B. El compuesto B es secuencialmente convertido a compuestos C donde P_3 es un grupo protector apropiado para la funcionalidad de alcohol (por ejemplo, TBS). En este punto, el grupo protecto P_1 presente en C es removido y la amina resultante o sal de éste (no mostrada) está sometida a una unión amida formando reacción con un ácido α-hidroxicarboxílico (el cual incorpora R_8 y en la cual R_7 es H; tampoco mostrados) para proporcionar intermediario D. La presente funcionalidad de alcohol en D es entonces convertida a

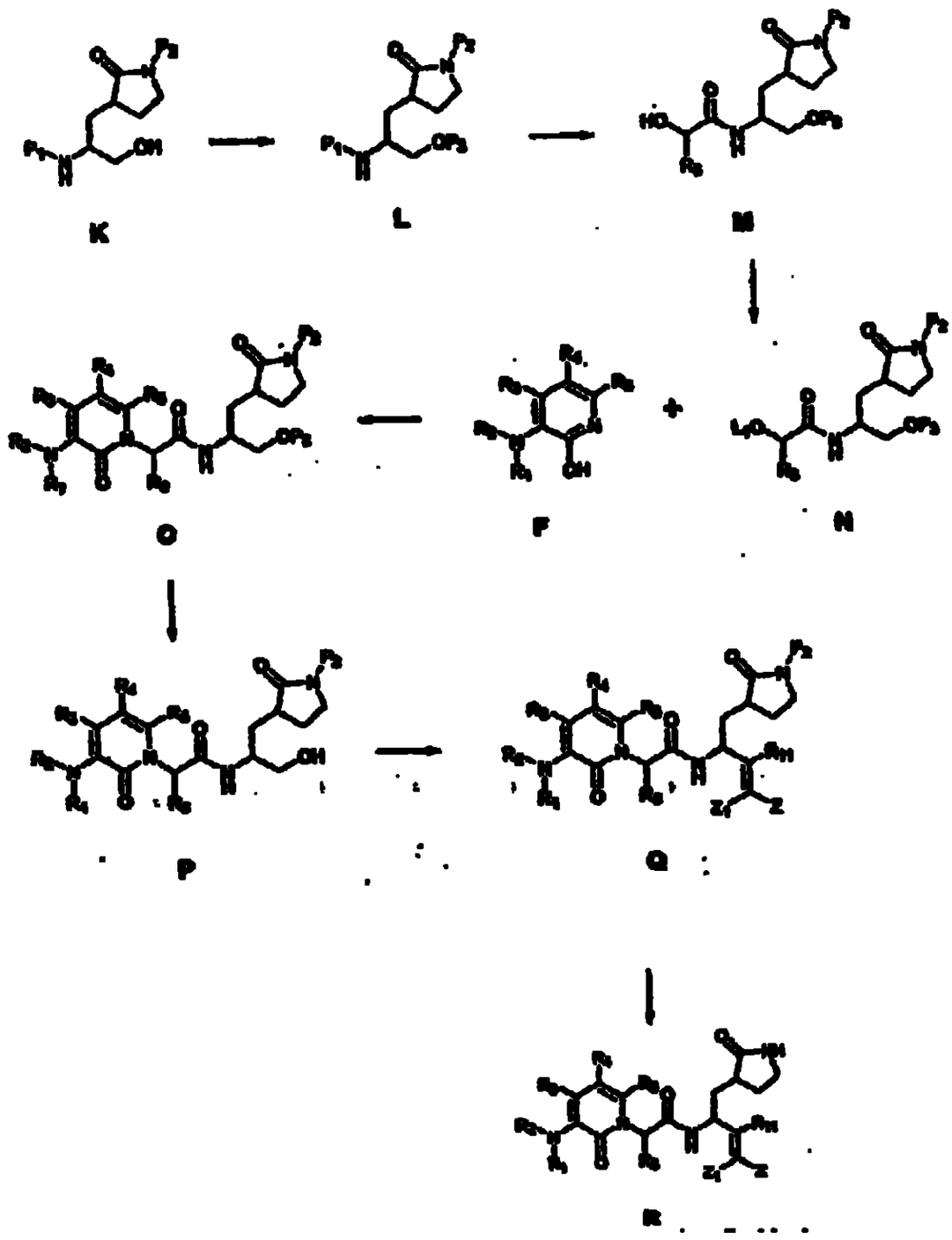
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un grupo de partida (por ejemplo, mesilato, tosilato) E y es acoplado con 2-hidroxipiridina F (el cual incorpora R_1, R_2, R_3, R_4 y R_5) para dar el intermediario G. Note que las mitades R_1 y R_2 presentes en F pueden ser grupos protectores apropiados para la funcionalidad de amina. El grupo protector P_3 es subsiguientemente removido de G y el alcohol resultante (H) es oxidado al correspondiente aldehido (no mostrado) y sometido a una reacción formadora de olefino para proporcionar el intermediario I (el cual incorpora R_{11}, Z, y Z_1). El grupo protector P_2 presente en I es entonces removido para dar el producto J. Si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, el/ellos puede ser removido de intermediarios G, H, I o producto J y reemplazado con un sustituyente diferente R_1 y/o R_2 para proporcionar intermediarios alternos G, H, I o productos J.

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Método General 2

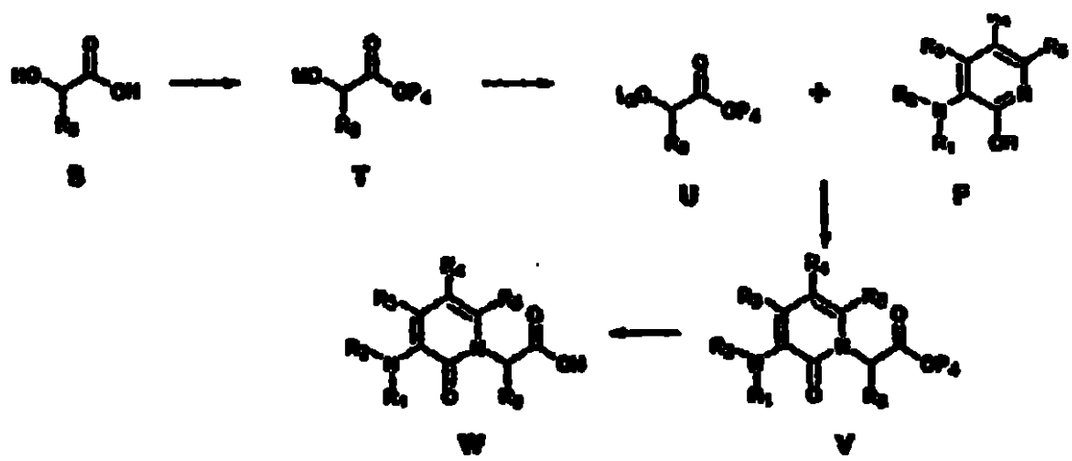


En el Método General 2, el alcohol de amino K (preparado por los métodos descritos en la literatura química), el cual incorpora R_8 y en el cual R_{10} es H, P_1 es un grupo protector apropiado para funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac), y P_2 es un

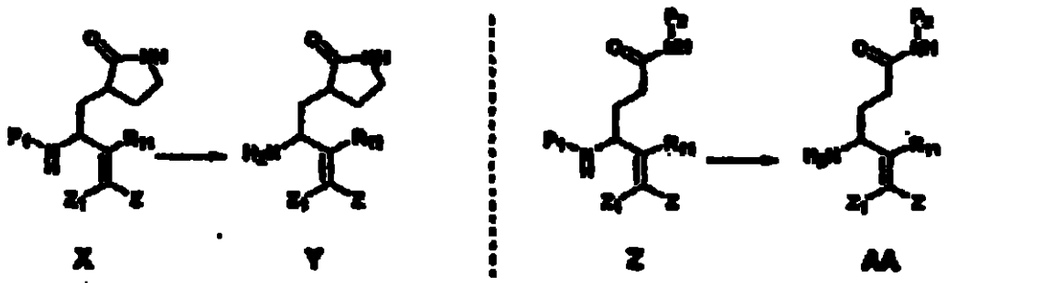
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grupo protector apropiado para el nitrógeno de amida (por ejemplo, DMB), es convertido a compuesto L donde P_3 es un grupo protector apropiado para la funcionalidad de alcohol (por ejemplo, TBDPS). El grupo protector P_1 presente en L es entonces removido y la amina resultante o sal de ésta (no mostrado) está sometida a una unión de amida formando reacción con ácido α-hidroxicarboxílico apropiado (el cual incorpora R_8 y en el cual R_2 es H; también no mostrado) para proporcionar intermediario M. La funcionalidad de alcohol presente en M es entonces convertida a un grupo de partida apropiado (por ejemplo, mesilato, tosilato) N y es acoplado con 2-hidroxipiridina F (la cual incorpora R_1, R_2, R_3, R_4 y R_5) para dar intermediario O. Note que las mitades R_1 y R_2 presentes en F pueden ser un grupo protector apropiado para la funcionalidad de amina. El grupo protector P_3 es subsiguientemente removido de O y el alcohol resultante (P) es oxidado para el correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para proporcionar intermediario Q (el cual incorpora R_{11}, Z, y Z_1). El grupo protector P_2 presente en Q es entonces removido para dar producto R. Si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, ellos pueden ser removidos de intermediarios O, P, o Q o producto R y reemplazado con un sustituyente diferente R_1 y/o R_2 para producir intermediarios alternos O, P, o Q o productos R.

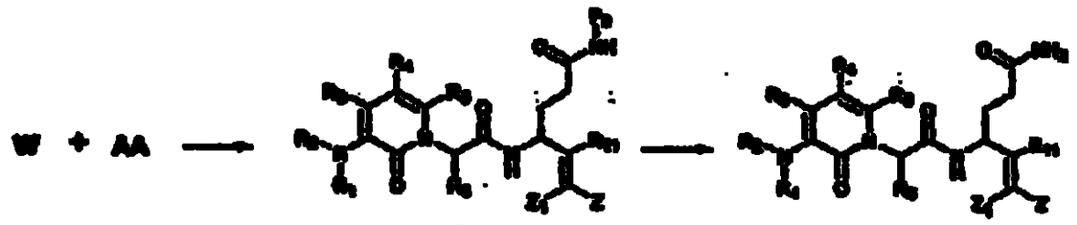
Método General 3



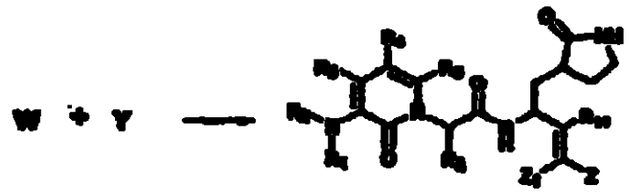
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X Y Z AA



I J



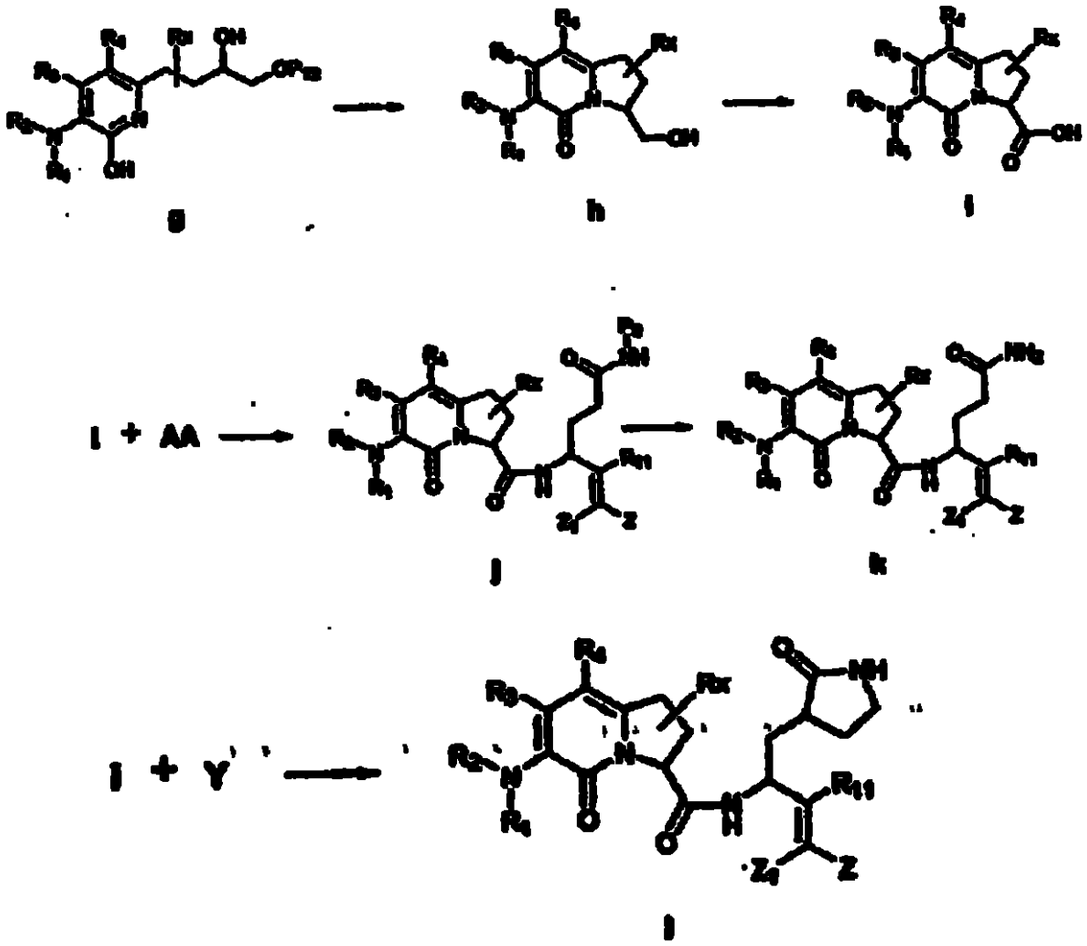
R

Un método alterno para preparar ya sea producto J o producto R está ilustrado en el Método General 3. Un ácido α-carboxílico S (ya sea comercialmente disponible o preparados por métodos descritos en la literatura química) el cual incorpora R_8 y el cual R_7 es H es convertido a α-hidroxiéster T donde P_4 es un grupo protector apropiado para el grupo funcional de ácido carboxílico (por ejemplo metilo, bencilo, o terf-butilo). La presente funcionalidad de alcohol en T es entonces convertida a un grupo de partida apropiado (por ejemplo, mesilato, tosilato, trifilato) U y es acoplado con 2-hidroxipiridina F (el cual incorpora R_1, R_2, R_3, R_4, y R_5) para dar intermediario V. Note que las mitades R_1 y R_2 presentes en F pueden ser un grupo protector apropiado para la funcionalidad de amina. El grupo protector P_4 es subsiguientemente removido de V para proporcionar ácido carboxílico W. Independientemente, los intermediarios X y Z_1 y en

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el cual P_1 es un grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac) y P_2 es un grupo protector apropiado para el nitrógeno de amida (por ejemplo, Tr), son convertidos a sus correspondientes aminas Y y AA (o sales de éstas), respectivamente. Las aminas AA y Y son entonces independientemente acopladas con ácido carboxílico W para proporcionar intermediario I y producto R, respectivamente. El grupo protector P_2 presente en el intermediario I es subsiguientemente removido para proporcionar J. Note que, aunque no está descrito en el Método General 3, el nitrógeno de lactam presente en el intermediario X puede ser protegido por un grupo protector adecuable (por ejemplo, DMB). Si tal mitad está presente en X, ésta puede ser removida después del acoplamiento de W con Y para proporcionar R.

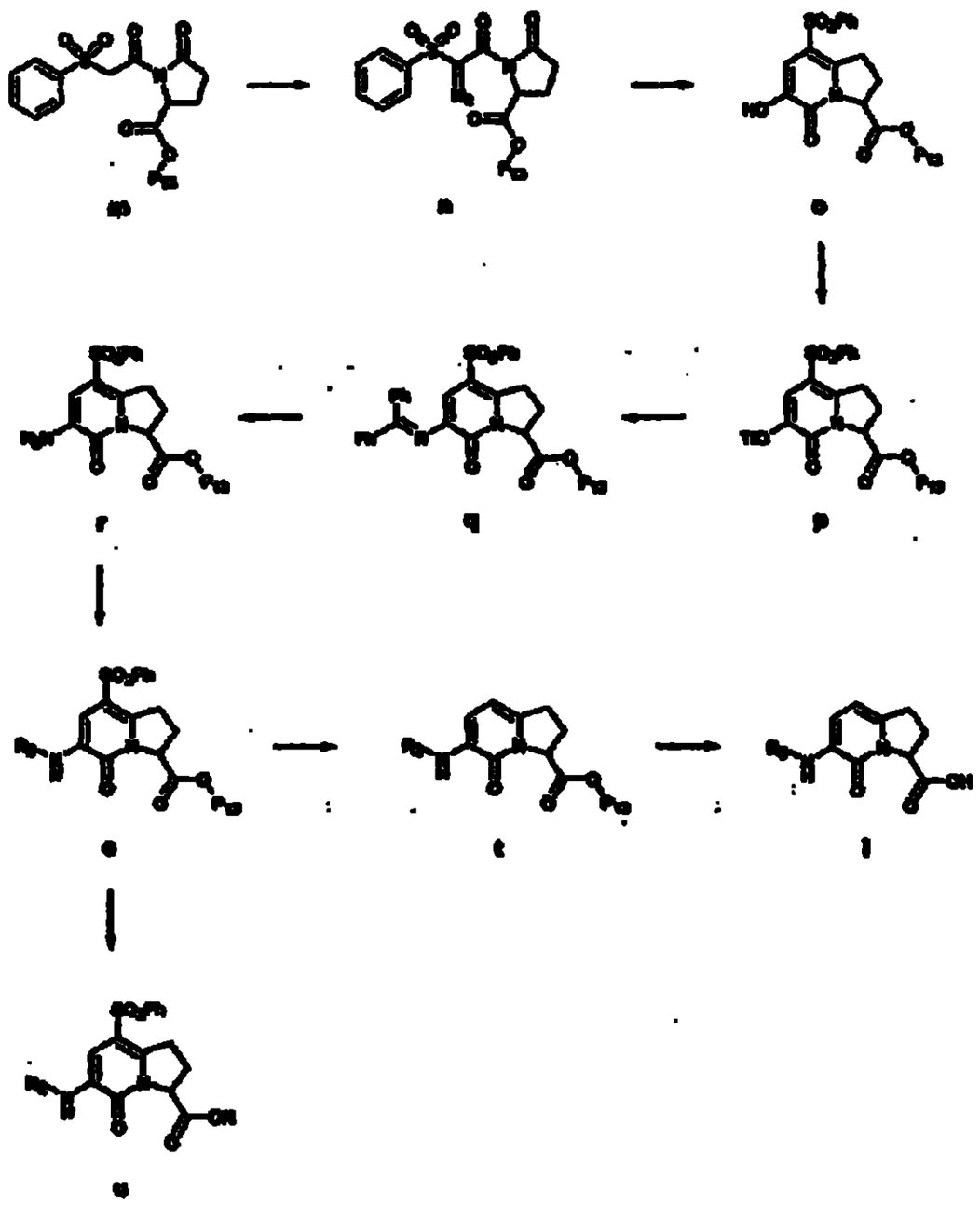
Método General 4



Un método para preparar de productos bicíclicos K y l está ilustrado en el Método General 4. Además, una piridina apropiada g (la cual incorpora R_1 R_2, R_3, y R_4, y el cual puede ser opcionalmente sustituido con R_x como se muestra (un ejemplo del cual puede ser preparado tal como se describió en el Método Específico 7 abajo) en el cual P_{11} y P_{12} son grupos protectores para la funcionalidad de alcohol (por ejemplo, éter de sililo, metilo) está sometido a un protocolo de desprotección/ciclisación intramolecular en el cual ambos P_{11} y P_{12} son removidos para dar piridona H. Note que las mitades R_1 y R_2 presentes en g pueden ser un grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz). La mitad de alcohol presente en h es entonces oxidada al correspondiente ácido carboxílico. Esta oxidación puede estar acompañada por vía de un intermediario de aldehído (no mostrada). Ácido carboxílico I es entonces independientemente acoplado con las aminas AA, y Y (o sales de ésta) (preparadas como se describió en el Método General 3 arriba) para proporcionar intermediario j: y producto l, respectivamente. El grupo protector P_2 presente en el intermediario j es subsiguientemente removido para proporcionar producto k. Note que, aunque no descrito en el Método General 4, el nitrógeno de lactam presente en el intermediario Y puede ser protegido con un grupo protector adecuable (por ejemplo, DMB). Si tal mitad está presente en Y, ésta puede ser removida después del acoplamiento de I con Y para proporcionar producto l. En adición, si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, éstos/ellos pueden ser removidos de intermediarios g, h, I, o j o productos k o l y reemplazados con un sustituyente diferente de R_1 y/o R_2 para proporcionar intermediarios alternos g, h, i, o j o productos k o l.

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Método General 5

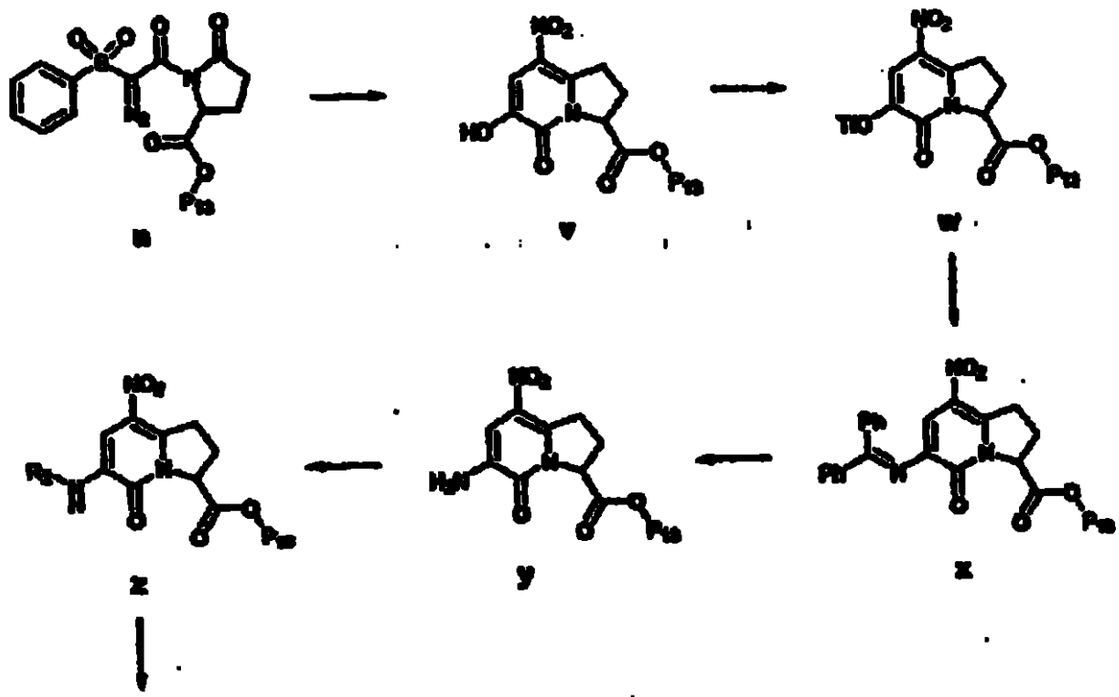


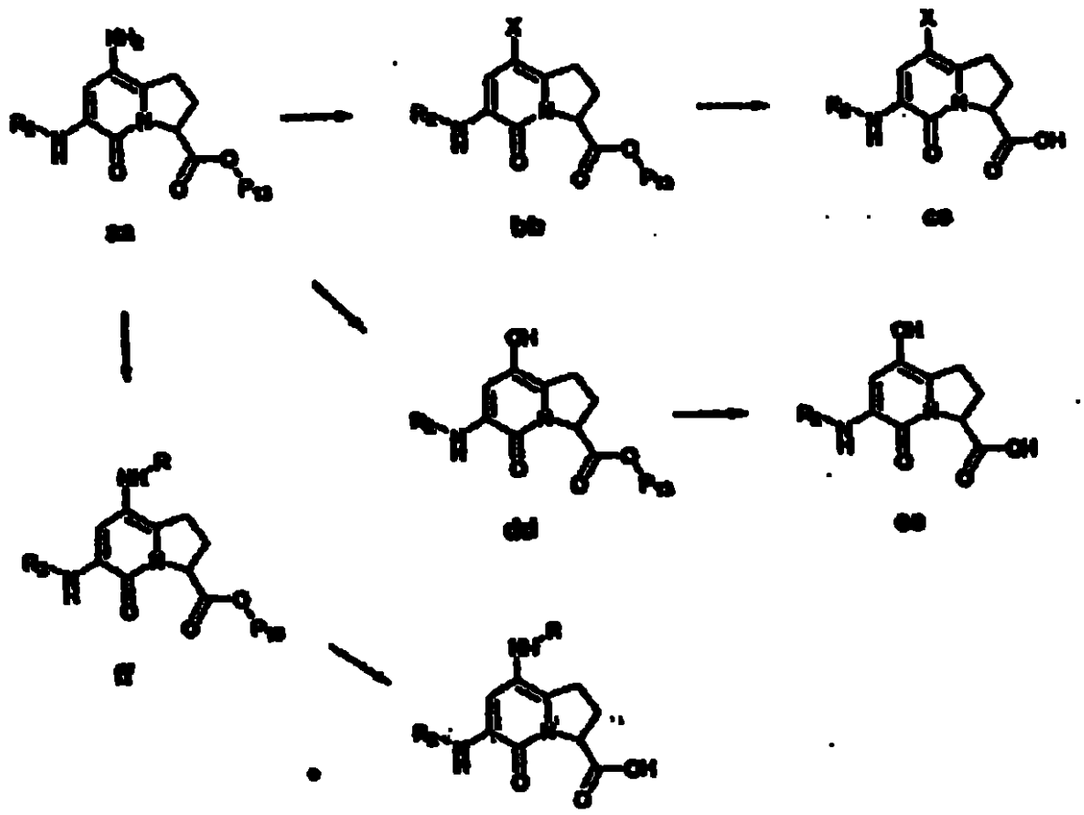
Un método alterno para preparar un tipo particular de intermediario I está ilustrado en el Método General 5. Además, el sulfono m (el cual puede ser preparado por el método descrito en Org. Lett., 1999, 1, 83) en el cual R_x es/son H y P_{13} es un grupo protector apropiado para la funcionalidad de ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de tert-butilo) es

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transformado en compuesto diazo n. Este intermediario está sometido a una reacción de ciclización catalizada de rodio que involucra sulfono de fenilvinilo para dar intermediario o (en el cual R_3 es H). El grupo hidróxilo presente en o es convertido al correspondiente sulfonato de trifluorometano (Otf) p, y este intermediario es además transformado a la amina r vía de la inmina q. La amina presente en r es derivada con una mitad apropiada para proporcionar intermediario s (el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario s está sometido a una reacción de desulfurización para dar el intermediario t y esta entidad es desprotegida para dar ácido carboxílico I (en el cual R_1, R_3, R_4 y R_x son H). Alternativamente, el intermediario s puede ser desprotegido para dar ácido carboxílico u (en el cual R_1, R_3, y R_x son H) el cual puede ser utilizado en lugar de I en el Método General 4.

Método General 6



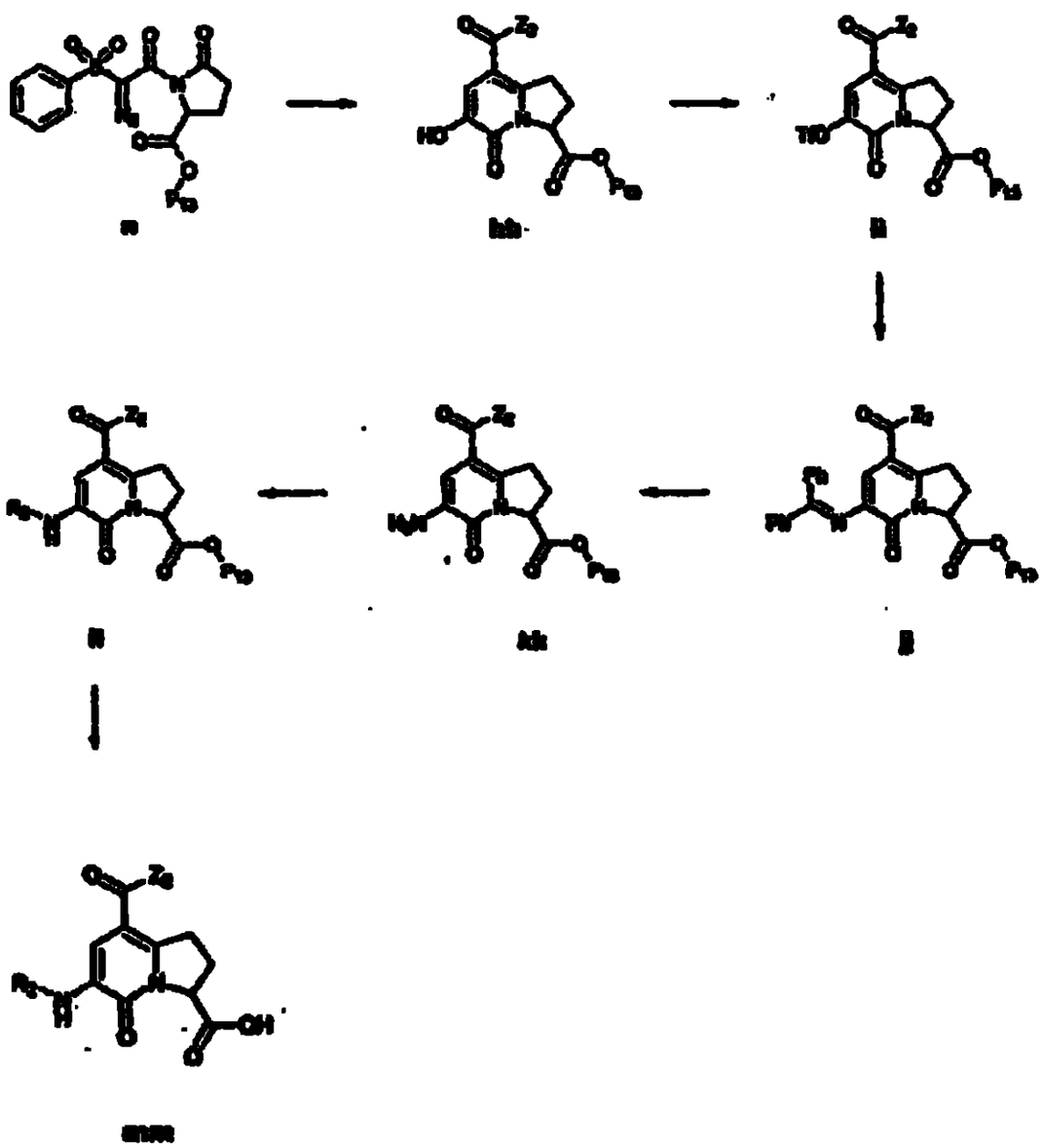


Un método adicional para preparar intermediarios relacionados con I está ilustrado en el Método General 6. Además, el compuesto diaso n (preparado en el Método General 5 arriba) en el cual R_x es/son H y en el cual P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de tert-butilo) está sometido a una reacción de ciclización catalizada de rodio involucrando nitroetileno para dar intermediario v (en el cual R_3 es H). El grupo hidróxilo presente en v es convertido al correspondiente sulfonato de trifluorometano (OTf) w, y este intermediario es además transformado a la amina y vía de la inmina x. La amina presente en y es derivada con una mitad apropiada para proporcionar intermediarios z (en el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario z es reducido para dar intermediario aa y está entidad es transformada a intermediario bb en el cual X es un halógeno. El intermediario w es subsiguientemente desprotegido para dar ácido carboxílico cc. Si se desea, el intermediario aa puede también ser transformado en

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intermediario t (Método General 5 arriba). Alternativamente, el intermediario aa es transformado a intermediario a dd el cual es subsiguientemente desprotegido para dar ácido carboxílico ee. Alternativamente, el intermediario aa es transformado a intermediario ff en el cual R es alquilo, acilo, sulfonilo, o acilioxi. El intermediario ff es subsiguientemente desprotegido para dar ácido carboxílico gg. Los ácidos carboxílicos cc, ee, y gg pueden cada uno ser utilizado en lugar de I en el Método General 4 arriba.

Método General 7

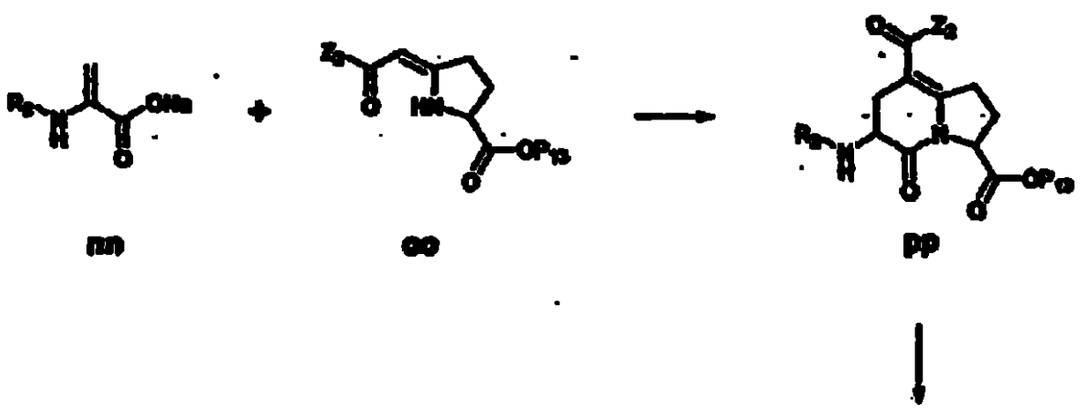


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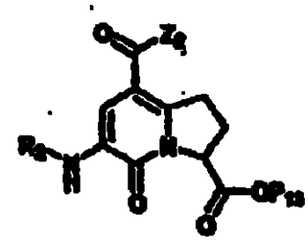
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Un método adicional para preparar intermediarios relacionados con i está ilustrado en el Método General 7. Además, el compuesto diazo n (preparado en el Método General 5 arriba) en el cual R_x es/son H y en el cual P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo o éster de terl-butilo) es sometido a una reacción de ciclización catalizada de rodio involucrando ésteres de acrilato o quetonas de vinilo para dar intermediario hh (en el cual R_3 es H y Z_2 es alquilo, arilo, alcoxi, y benciloxi). El grupo hidróxilo presente en hh es convertido al correspondiente sulfonato de trifluorometano (OTf) ii, y este intermediario es además transformado a la amina kk vía de la inmina jj. La amina presente en kk es derivada con una mitad apropiada para proporcionar intermediario ll (el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario ll es subsiguientemente desprotegido para dar ácido carboxílico mm el cual puede ser utilizada en lugar de i en el Método General 4 arriba. En cualquier punto en la secuencia de arriba, si Z_2 es alcoxi o benciloxi éste puede ser rearreglado para la correspondiente amina usando métodos establecidos y el contenido de intermediarios de amina puede ser utilizado como está descrito en el Método General 6. Por ejemplo, el intermediario ll (cuando Z_2 es OH) puede ser rearreglado a intermediario aa (Método General 6).

Método General 8



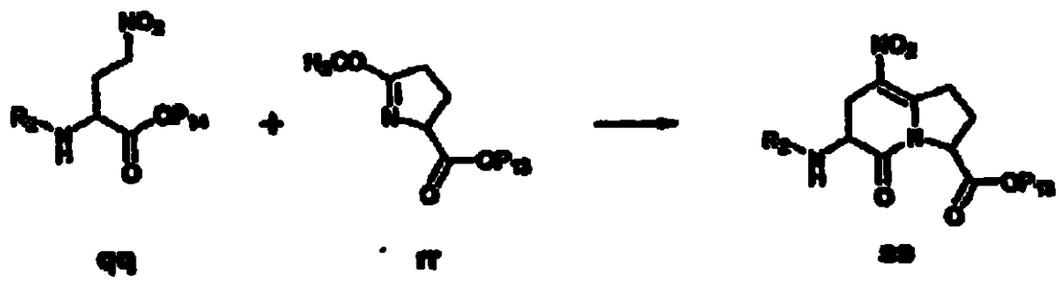
mm oo pp



II

Todavia otro método para preparar intermediario II está descrito en el Método General 8. Además la sal de sodio, del derivado α-dehidroalanina nn (el cual incorpora R_2 y en el cual R_1 es H) (el cual ya sea comercialmente disponible o puede ser preparado de serina por una variedad de técnicas de literatura) es condensado con intermediario oo (el cual puede ser preparado como está descrito en Tetrahedron Lett., 1989, 30, 3621) en el cual R_x es/son H y P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de terl-butilo) en el cual Z_2 es alquilo, arilo, alcoxi, o benciloxi para dar el intermediario pp. El intermediario pp es subsiguientemente oxidado (por una variedad de métodos de la literatura) para proporcionar el intermediario II el cual puede ser utilizado tal como se describió arriba en el Método General 7.

Método General 9

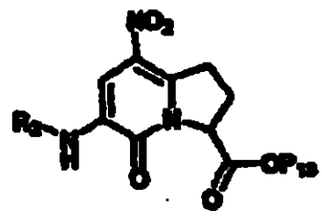


nn oo pp



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z

Un método alterno para preparar intermediarios z (del Método General 6 arriba) está descrito en el Método General 9. Además el compuesto nitro qq (preparado por analogía con el método descrito en: J. Chem. Soc., Perkin Trans. 1 1998, 1113) el cual incorpora R_2 y en el cual R_1 es H y P_{14} es un grupo protector adecuable para la funcionalidad del ácido carboxílico (por ejemplo, metilo o etilo) es condensado con intermediario rr (preparado de acuerdo con: J. Heterociclyc. Chem. 1992, 29, 1285) en el cual R_x es/son H y P_{13} es un grupo protector adecuable para la funcionalidad de ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o terl-butilo) para dar el intermediario es. El intermediario es es subsiguientemente oxidado (por una variedad de métodos de la literatura) para proporcionar intermediario z el cual puede ser utilizado tal como se describió en el Método General 6.

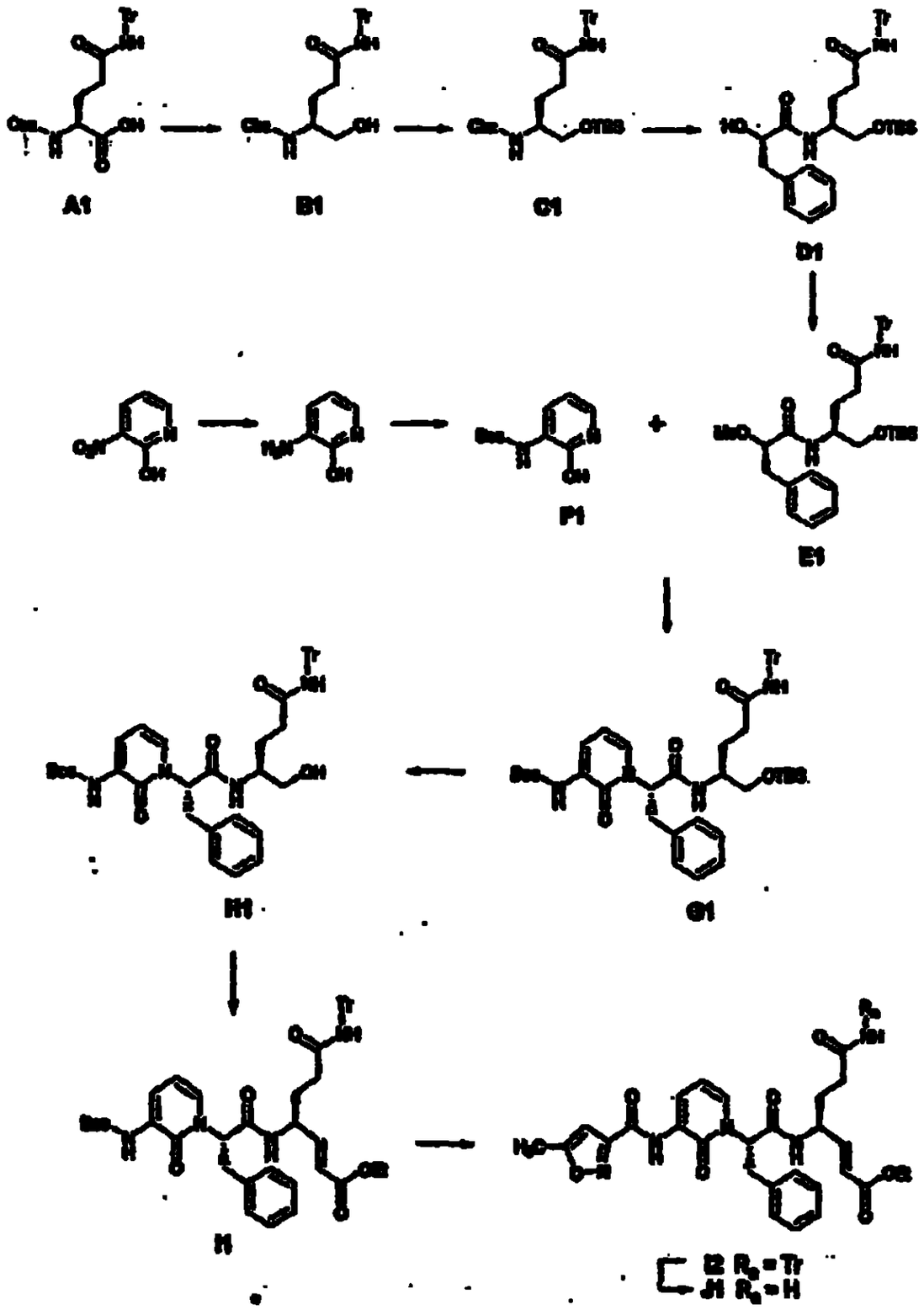
METODOS ESPECIFICOS

Los siguientes Métodos Específicos pueden también ser utilizados para preparar algunos de los compuestos descritos en esta invención.

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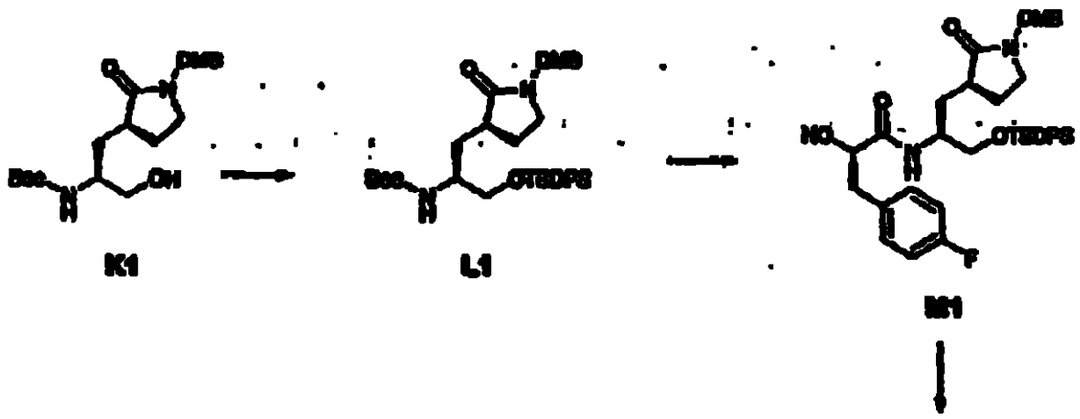
Método Específico 1

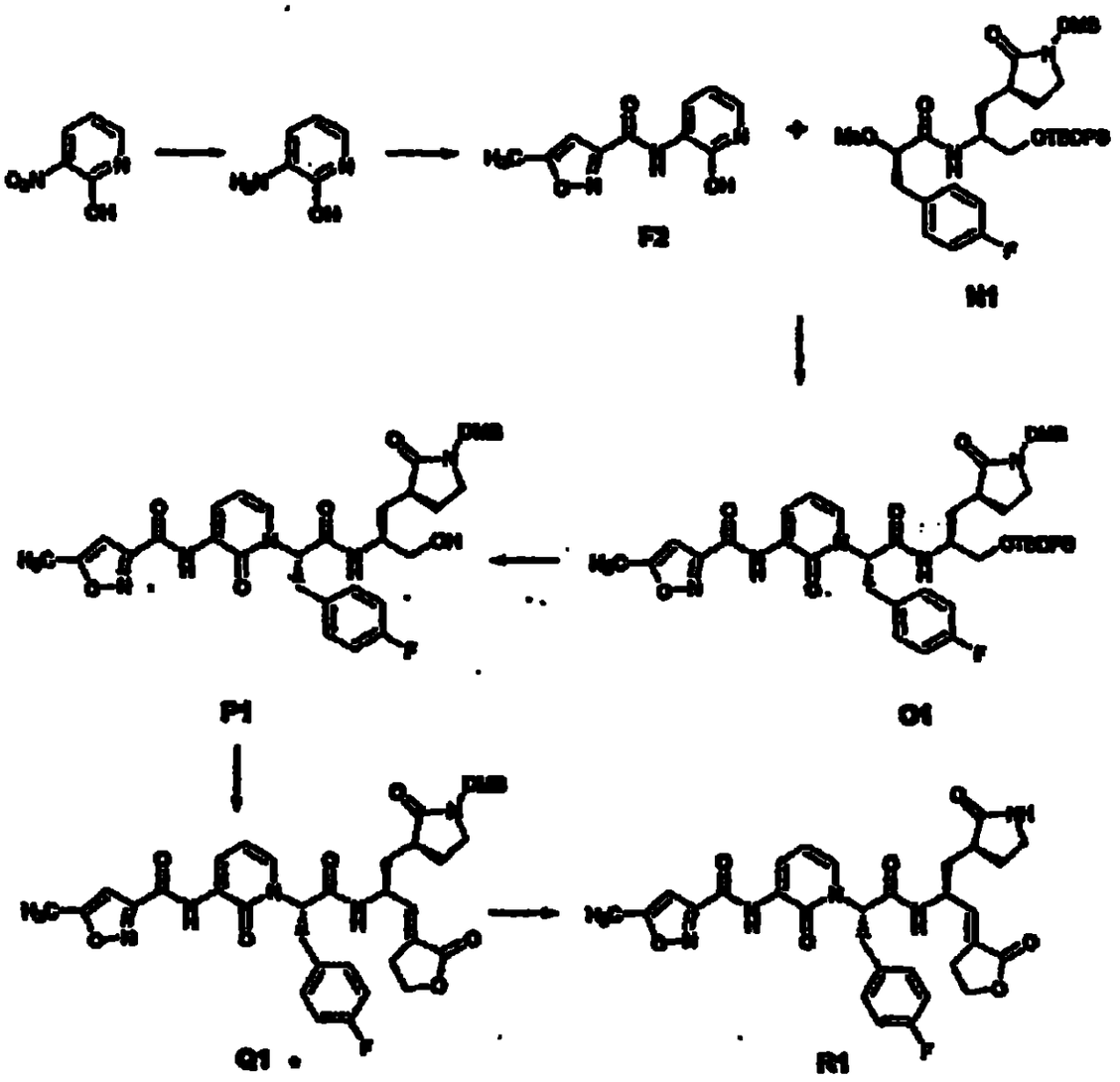


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El Método Específico 1 describe la preparación del compuesto específico J1 (compuesto 5). Además, comercialmente disponible el amino ácido A1 fue reducido a alcohol B1 el cual, a su turno, fue transformado en el compuesto C1. La mitad Cbz presente en C1 fue removida por hidrogenación y la amina resultante (no mostrada) fue acoplada con ácido D-3-fenilacético (comercialmente disponible) para proporcionar el intermediario D1. Esta última entidad fue subsiguientemente transformada al correspondiente metanosulfonato (mesilato) (E1) y fue acoplada con la sal de sodio de 2-hidroxipiridina F1 para proporcionar el intermediario G1. El 2-hidroxipiridina F1 fue preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reacción y subsiguiente protección Boc de la amina resultante. El grupo de protección sililo presente en G1 fue removido y el alcohol además obtenido (H1) fue oxidado para el correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario I1. La mitad Boc contenida en I1 fue entonces térmicamente desprotegida y la amina resultante (no mostrada) fue derivada de comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo para dar el intermediario I2. El grupo protector tritilo presente en I2 fue subsiguientemente removido bajo condiciones acídicas para completar la preparación del compuestos específico J1 (compuesto 5).

Método Específico 2

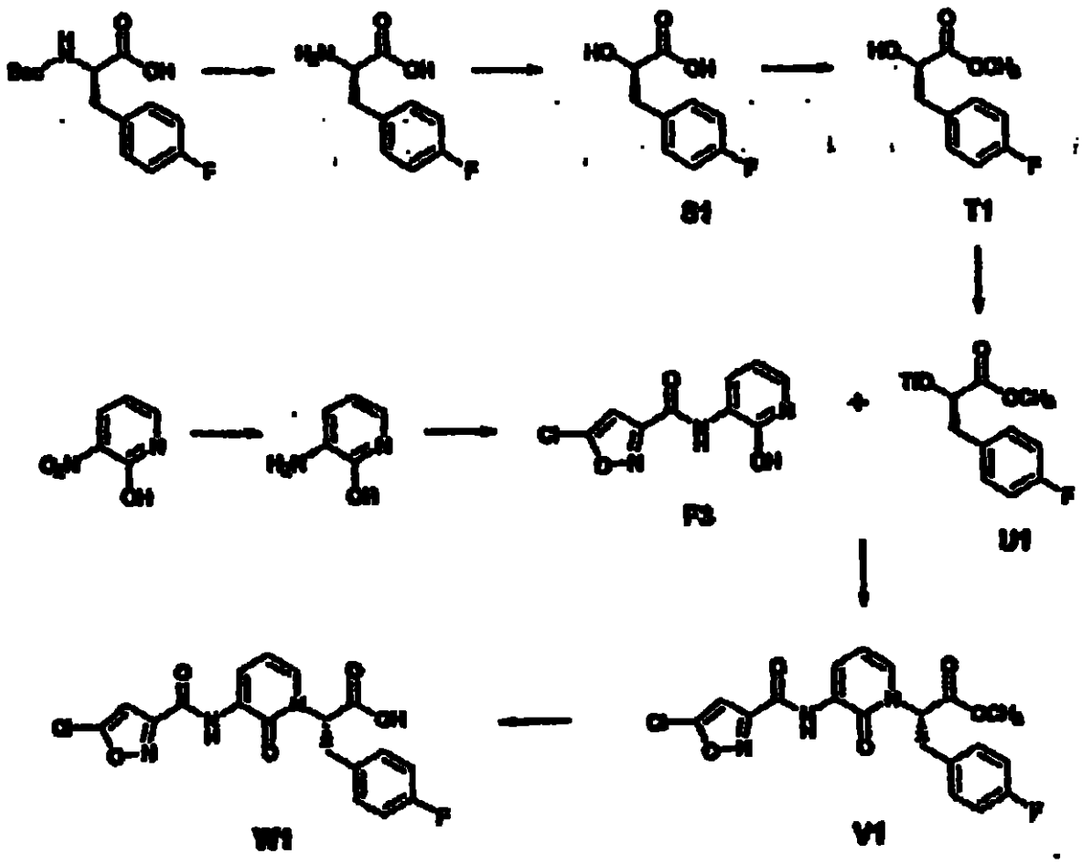




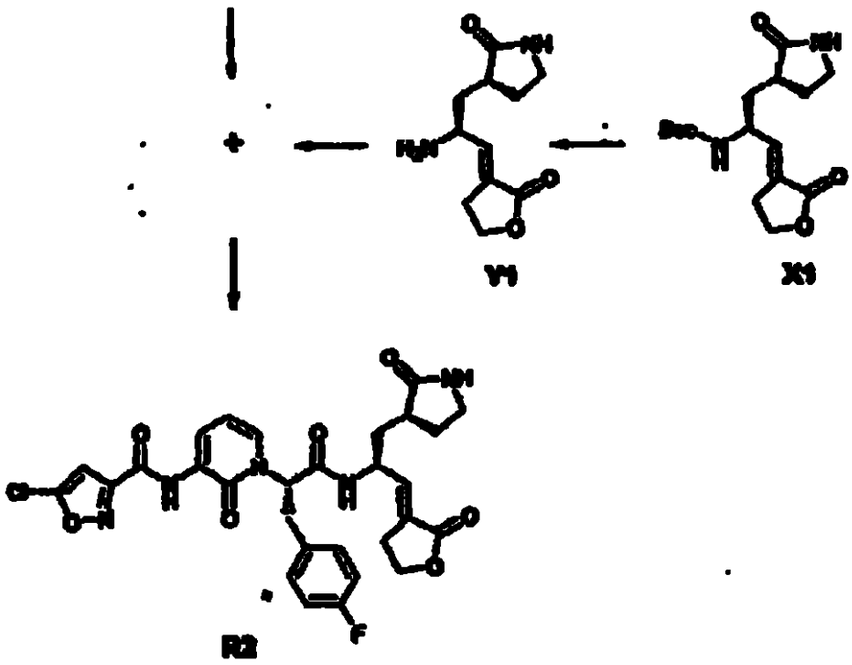
El Método Específico 2 describe la preparación del compuesto específico R_1 (compuesto 20). Además, el alcohol KI (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1999, 42, 1213) protegido para dar el intermediario LI. El grupo protector Boc presente en LI fue removido bajo condiciones acídicas y la sal de amina resultante (no mostrada) fue acopiada con (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (SI preparado tal como se describió en el Método Específico 3 abajo) para proporcionar el intermediario MI. Esta entidad última fue subsiguientemente transformada al correspondiente metanosulfonato (mesilato) (NI) y fue acopiada con la sal de sodio de 2-hidroxipiridina F2 para proporcionar el intermediario 01. El 2-

hidroxipiridina F2 fue preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con el comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo. El grupo protector sililo presente en O1 fue removido y el alcohol además obtenido (P1) fue oxidado al correspondiente aldehido (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario Q1. La mitad del compuesto DMB contenida en Q1 fue entonces desprotegida para completar la preparación del compuesto específico R1 (compuesto 20).

Método Específico 3



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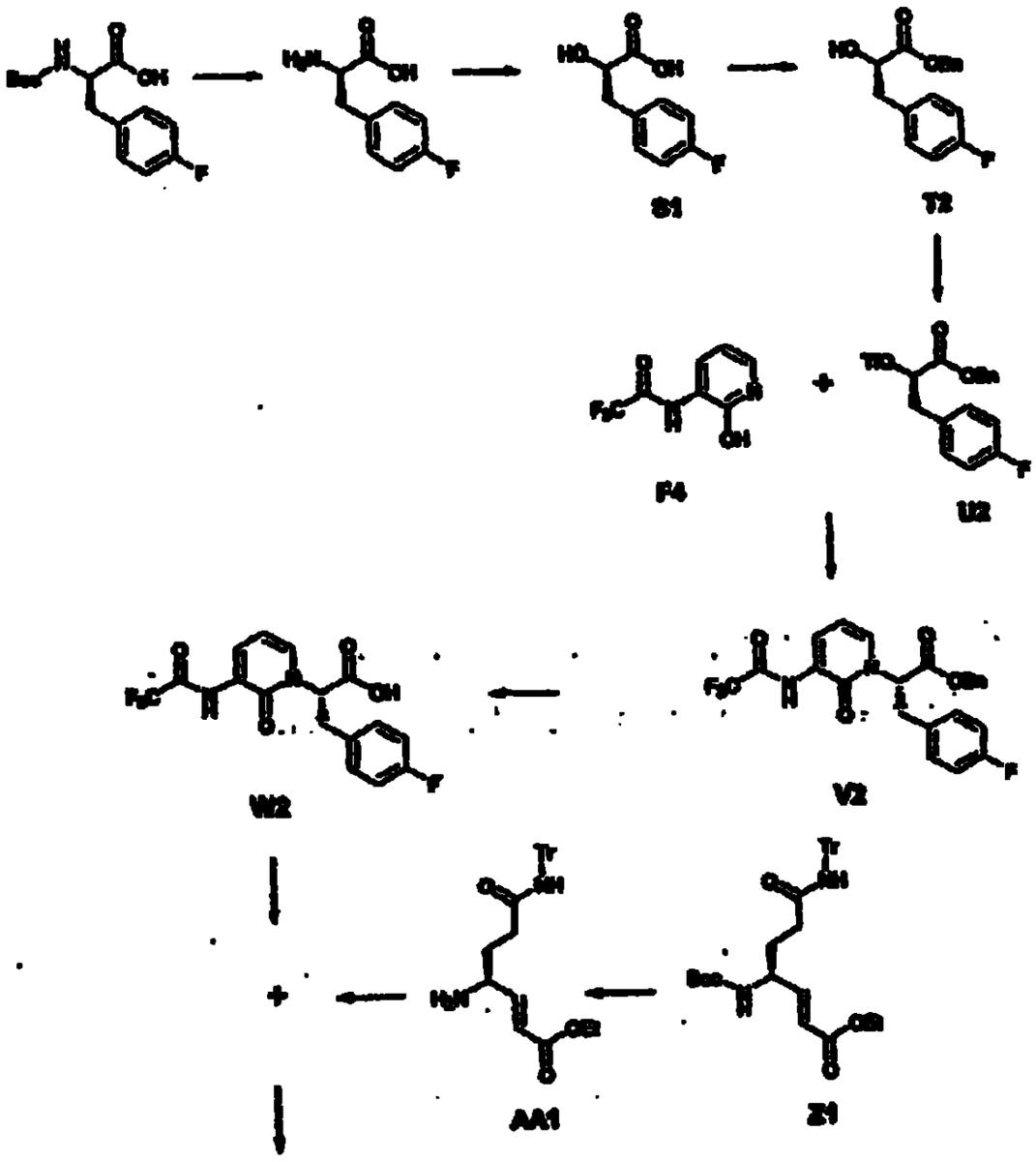


El método específico 3 describe la preparación del compuesto específico R_2 (compuesto 23). Además, el comercialmente disponible Boc-D-(4-F)PHe-OH fue desprotegido bajo condiciones acídicas y la sal de amina resultante fue sometida a un protocolo de desplazamiento/diazotización para proporcionar (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (S1). Este material fue subsiguientemente transformado en el correspondiente sulfonato de trifluorometano (triflato) U1 vía del éster de metilo T1 y fue acoplado con la sal de sodio de 2-hidroxipiridina F3 para proporcionar el intermediario V1. El 2-hidroxipiridina F3 fue preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con cloruro de 5-cloroisoxazol-3-carbonilo (preparado tal como se describió en la Sección Experimental de este trabajo. El ester de metilo presente en V1 fue subsiguientemente hidrolizado bajo condiciones básicas y el ácido carboxílico resultante (W1) fue acoplado con amina Y1 (o sal de ésta) para completar la preparación del compuesto específico R2 (compuesto 23). La amina Y1 (o sal de ésta) fue preparada por desprotección del

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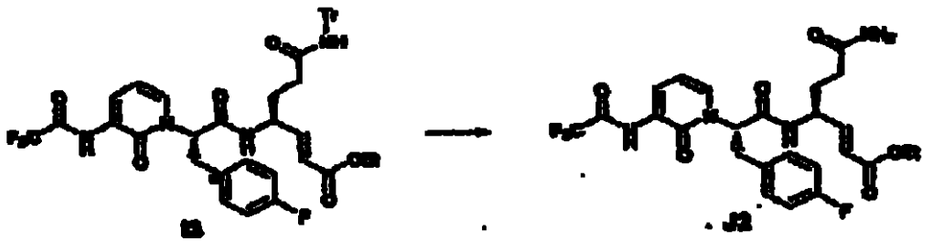
intermediario X1 (preparado de una manera análoga a aquella descrita en Baldwin y otros, J. Org. Chem. 1971, 36, 1441)

Método Específico 4



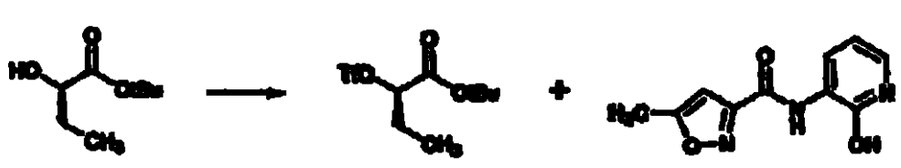
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El Método Específico 4 describe la preparación del compuesto específico J2 (compuesto 24). Además, (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (S1, preparado tal como se describió arriba en el Método Específico 3) fue transformado en el correspondiente sulfonato de trifluorometano (triflato) U2 vía del éster de bencilo T2 y fue acoplado con la sal de sodio de 2-hidroxipiridina F4 para proporcionar el intermediario V2. La 2-hidroxipiridina F4 fue preparada del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con anhídrido trifluoroacético. El éster de bencilo presente en V2 fue subsiguientemente removido por hidrogenación y el ácido carboxílico resultante (W2) fue acoplado con amina AA1 (o sal de ésta) para dar el intermediario I3. El grupo protector tritol presente en I3 fue entonces removido bajo condiciones acídicas para completar la preparación del compuesto específico J2 (compuesto 24). La amina AA1 (o sal de ésta) fue preparada por desprotección del intermediario Z1 (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1998, 41, 2806).

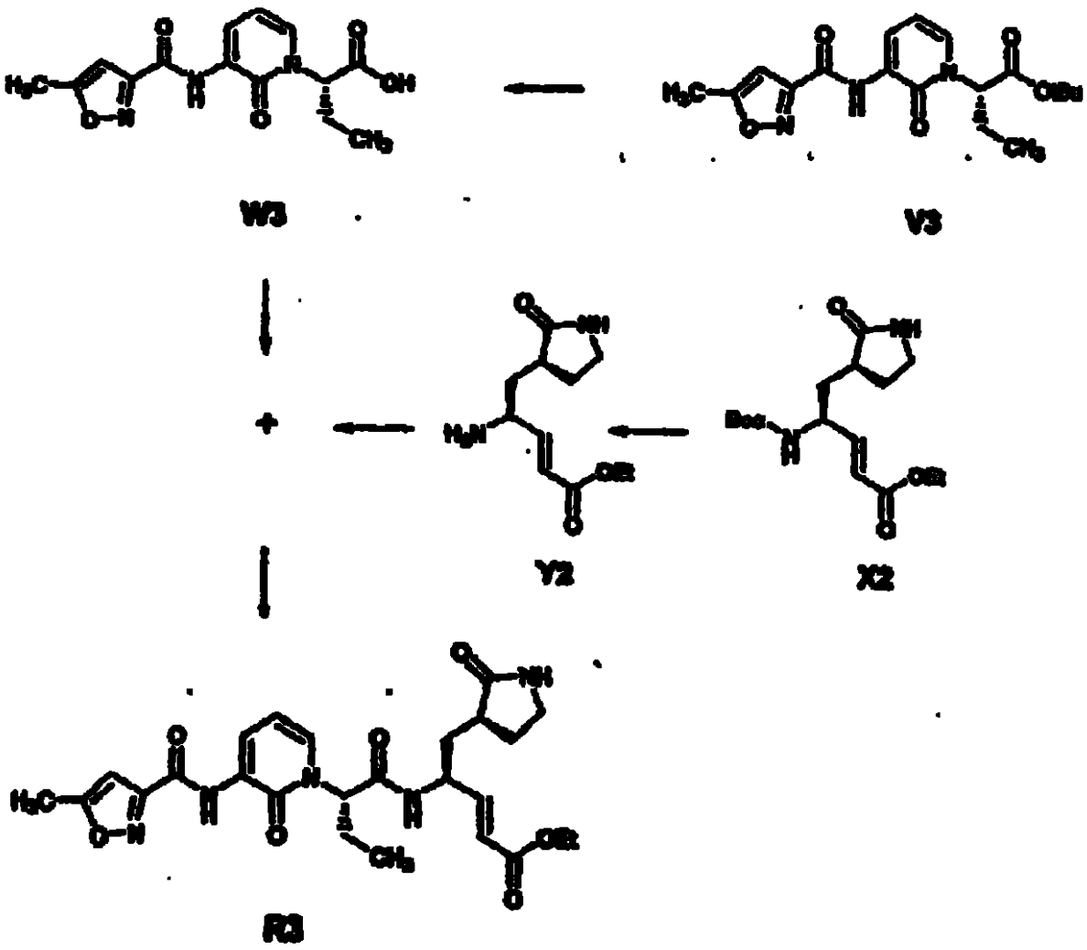
Método Específico 6



T3 U3 F2

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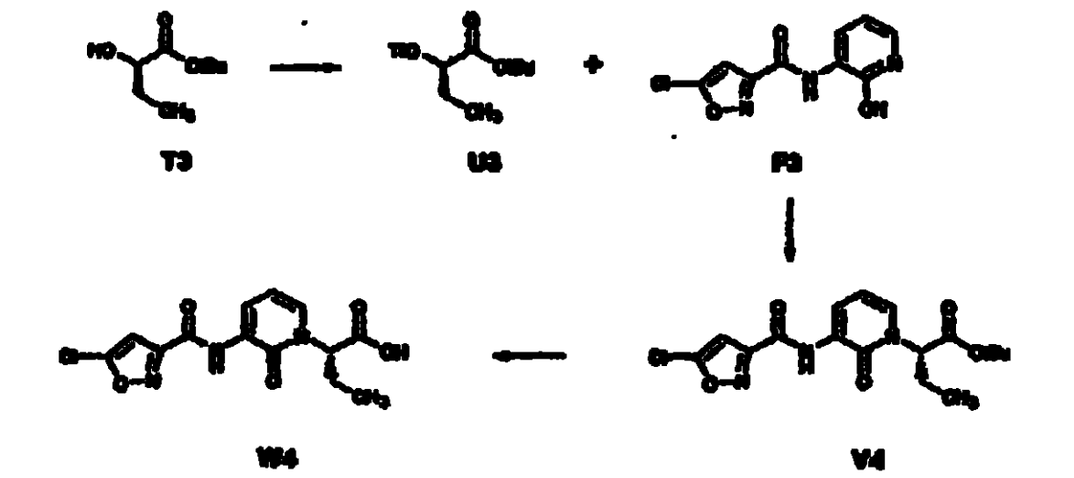


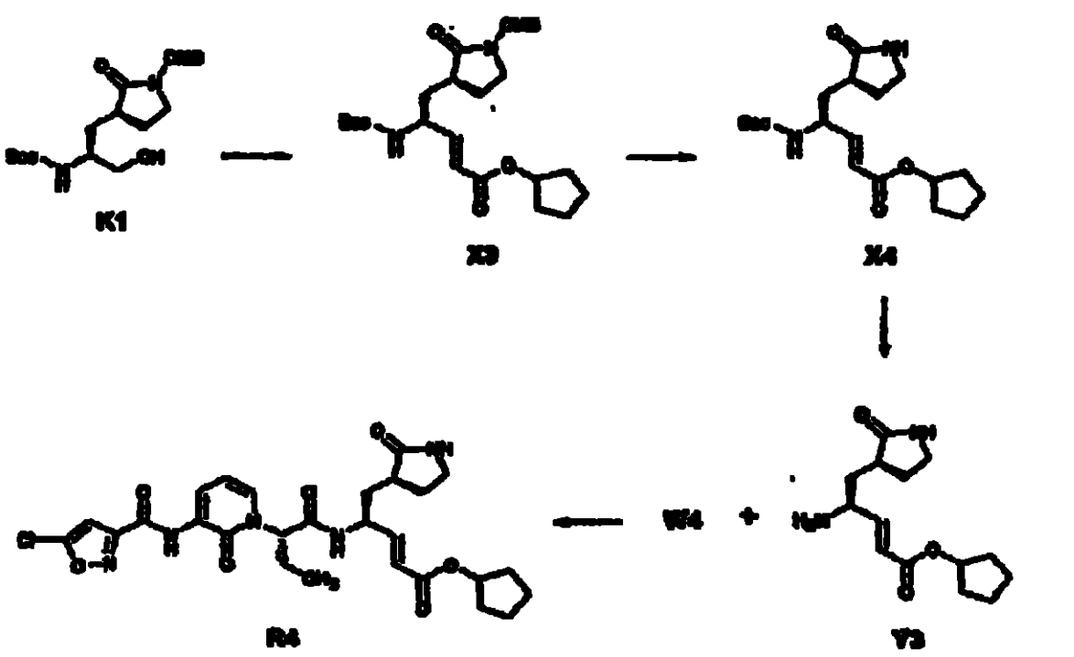
El Método Específico 6 describe la preparación del compuesto específico R3 (compuesto 26). Además, el disponible comercialmente tert-butilo (R)-2-hidroxibutirato (T3) fue transformado en el 2-hidroxipiridina F2 (preparada tal como se describió en el Método Específico 2) para proporcionar el intermediario V3. El éster de tert-butilo presente en V3 fue subsiguientemente hidrolizado bajo condiciones acídicas y el ácido carboxílico resultante (W3) fue acoplado con amina Y2 (o sal de ésta) para completar la preparación del compuesto específico R3 (compuesto 26). La amina Y2 (o sal de ésta) fue preparada por desprotección del intermediario X2, preparado de acuerdo con el método revelado en la solicitud co-pendiente, Solicitud de Patente Provisional de los E.U. No. 60/150,358, presentada en Agosto 24 de 1999, la revelación de la cual está incorporada aquí por referencia.

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Método Específico 6





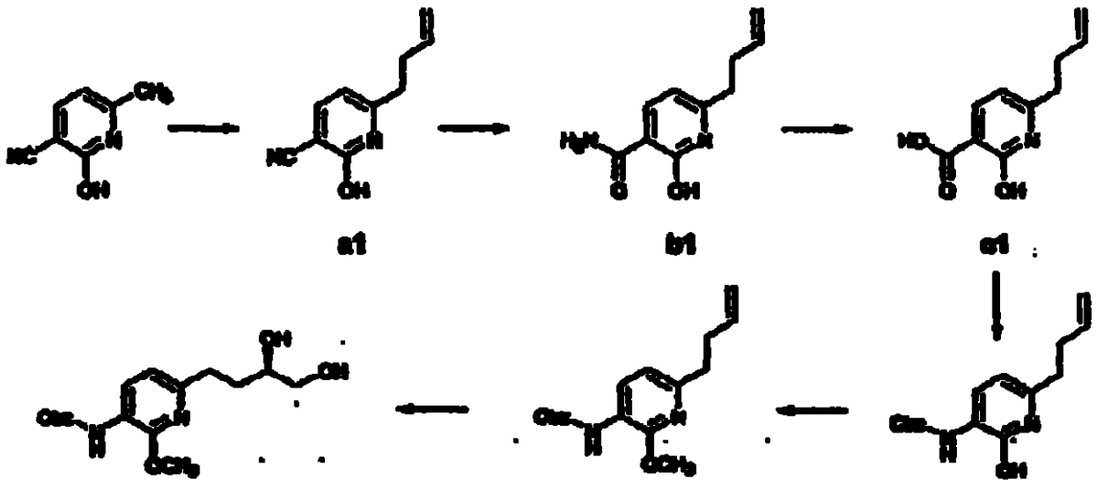
El Método Específico 6 describe la preparación del compuesto específico R4 (compuesto 29). Además, sulfonato de trifluorometano (triflato) U3 (preparado tal como se describió en el método Específico 5 arriba) fue acoplado con la sal de sodio de 2-hidroxipiridina F3 (preparada tal como se describió en el Método específico 3 arriba) para proporcionar el intermediario V4. El éster de terl-butilo presente en V4 fue subsiguientemente hidrolizado

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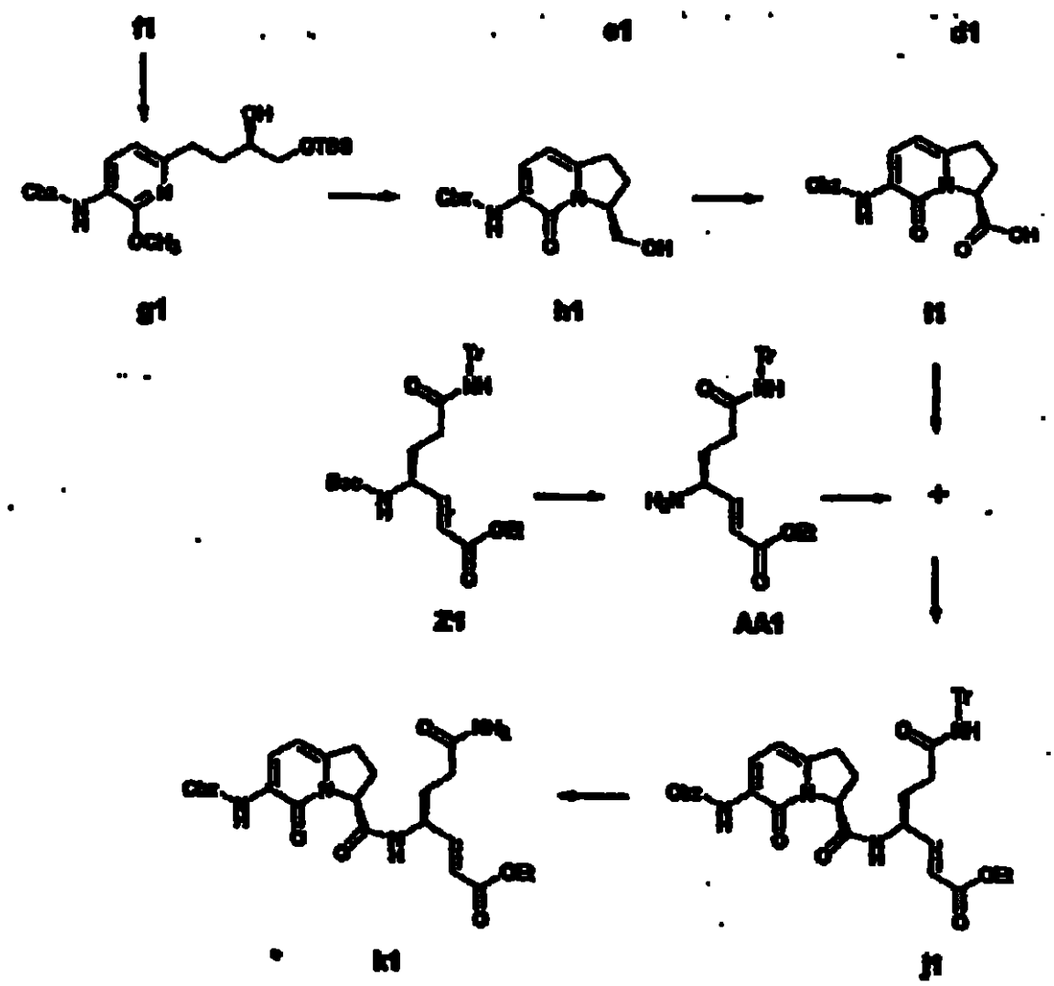
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bajo condiciones acídicas y el ácido carboxílico resultante (W4) fue acoplado con amina Y3 (o sal de ésta) para completar la preparación del compuesto específico R4 (compuesto 29). La amina Y3 (o sal de ésta) fue sintetizada de alcohol K1 (preparado como se describió en Dragovich, y otros, J. Med. Chem. 1999, 42, 1213) por el siguiente método. Alcohol K1 fue oxidado al correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario X3. La mitad DMB contenida en X3 fue entonces desprotegida para proporcionar el intermediario X4, y esta entidad fue desprotegida bajo condiciones acídicas para proporcionar amina Y3 (o sal de ésta).

Método Específico 7



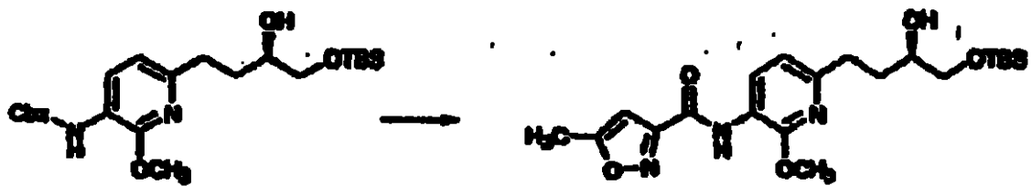
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El Método Específico 7 describe la preparación del compuesto específico K1 (compuesto 36). Además, el dianión del comercialmente disponible 2-hidroxi-6-metilnicotinonitrilo fue convertido a intermediario a1 por métodos relacionados a aquellos descritos en la literatura (Dejohn, D; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. J. Hterocilcic Chem. 1983, 20, 1295). La funcionalidad de nitrilo presente en este intermediario fue entonces convertida al correspondiente ácido carboxílico c1 vía de la amida primaria V1. El intermediario c1 fue sometido a un arreglo Curtius y el isocianato resultante fue enlazado con alcohol de bencilo para proporcionar carbamato d1. La mitad de hidróxilo contenida en d1 fue selectivamente metilada y el éter de metilo resultante (e1) fue sometido a una reacción de dihidroxilación asimétrica para dar diol

f1. Esta reacción de dihidroxilación asimétrica puede ser efectuada utilizando una variedad de aditivos quirales comerciales y no comerciales. La mitad de hidróxilo primario contenida en F1 fue selectivamente protegida como el correspondiente éter de tert-butildimetilsililo (g1). Este intermediario fue tratado con anhídrido trifluorometanosulfónico en la presencia de 2,6-lutidina a baja temperatura seguida por exposición a fluoruro de tetrabutilamonio para efectuar (i) ciclización intramolecular y (ii) desprotección de éter de sililo y proporcionar alcohol h1. El alcohol h1 fue oxidado al correspondiente aldehído (no mostrado), y este intermediario fue además oxidado al correspondiente ácido carboxílico i1. El ácido i1 fue acoplado con amina AA1 (o sal de ésta) para dar el intermediario j1. El grupo protector de tritilo presente en j1 fue entonces removido bajo condiciones acídicas para completar la preparación del compuesto específico k1 (compuesto 36). La amina AA1 (o sal de ésta) fue preparada por desprotección del intermediario Z1 (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1998, 41, 2806).

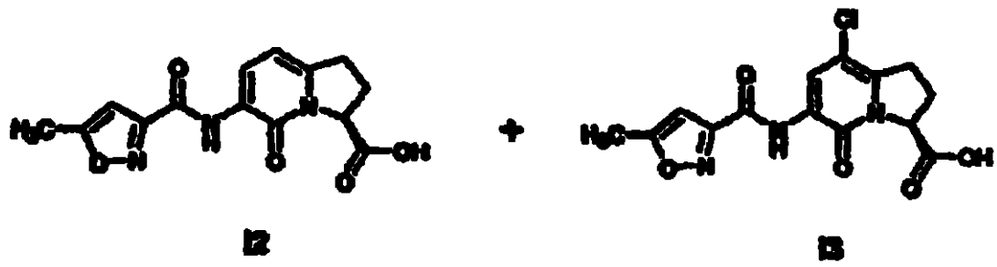
Método Específico 8



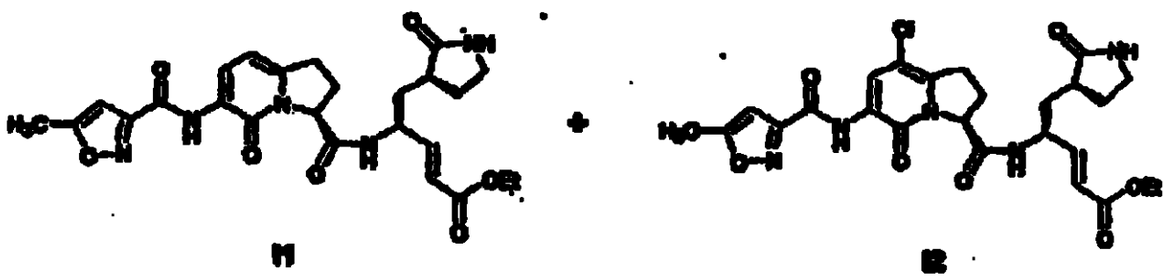
g1 g2

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I2 I3



I1 I2

El Método Específico 8 describe la preparación de los compuestos específicos 11 y 12 (compuestos 37 y 39, respectivamente). Además, la mitad Cbz presente en el intermediario g1 (preparada tal como se describió en el Método Específico 7 arriba) fue removida y la amina resultante (no mostrada) fue derivada con comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo para proporcionar el intermediario g2. Este intermediario fue convertido al compuesto específico 11 (compuesto 37) por un proceso análogo a aquél descrito en el Método Específico 7 para la conversión de intermediario g1 a intermediario j1 utilizando amina Y2 (Método Específico 5) donde fuere apropiado. Durante este proceso, una pequeña cantidad de intermediario I3 fue también generada "serendipituosly". Este intermediario fue transformado al compuesto específico I2 (compuesto 39) por un proceso análogo a aquél descrito en el Método Específico 7 para la conversión del intermediario g1 a intermediario j1 utilizando amina Y2 (Método Específico 5) donde fuere apropiado.

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EJEMPLOS

Los ejemplos de los procesos usados para hacer varios de los compuestos de las Fórmula I y II están estipulados abajo. Las estructuras de los compuestos de los siguientes compuestos fueron confirmadas por uno o más de lo siguiente: espectroscopia de resonancia magnética protón, espectroscopia infrarroja, microanálisis elemental y punto de derretimiento. El espectro de resonancia magnética protón (^{1}H NMR) fue determinado usando ya sea una UNITYplus Varian 300 o una operación de espectrómetro QE-300 General Electric a una fuerza de campo de 300 megahertz (MHz). Los traslados químicos son reportados en partes por millón (ppm, δ) campo debajo de un tetrametilciliano interno normal. Alternativamente, el espectro ^{1}H NMR fue referenciado para señales de solvente prótico residual como sigue: $CHCl_3$ = 7.26 ppm; DMSO = 2.49 ppm, C_6HD_5 = 7.15 ppm. Las multiplicidades periódicas son designadas como sigue: s, simple; d, doble; dd, doble de doble; t, triple; q, cuarto; br, resonancia amplia; m, múltiple. Las constantes acopladoras son dadas en Hertz. El espectro de absorción infrarroja (IR) fue obtenido usando un espectrómetro FTIR series 1600 de Perkin-Elmer. Los microanálisis elementales fueron llevados a cabo por Atlantic Microlab Inc., Norcross, GA y dieron resultados para los elementos declarados dentro ± 0.4% de los valores teóricos. La cromatografía de columna de destello fue llevada a cabo usando gel de Silice 60 (Merc Art 9385). La cromatografía analítica de capa delgada (TLC) fue llevada a cabo usando láminas prerrevestidas de Silice 60 F_{254} (Merc Art 5719). Los puntos de derretimiento fueron determinados sobre un aparato Mel-Temp y son incorrectos. Todas las reacciones fueron llevadas a cabo en frascos septum-sellados bajo una presión positiva ligera de argón a menos que de otra manera sea notado. Todos los reactivos comerciales fueron usados como recibidos de sus respectivos suministradores con las siguientes excepciones. Tetrahidrofurán (THF) fue destilado de quetilo de benzolferona de sodio anterior al uso. Diclorometano (CH_2Cl_2) fue destilado de hidruro de calcio anterior al uso. Et_2O se refiere a éter de dietilo. DMF se refiere a N, N-dimetilformamida.

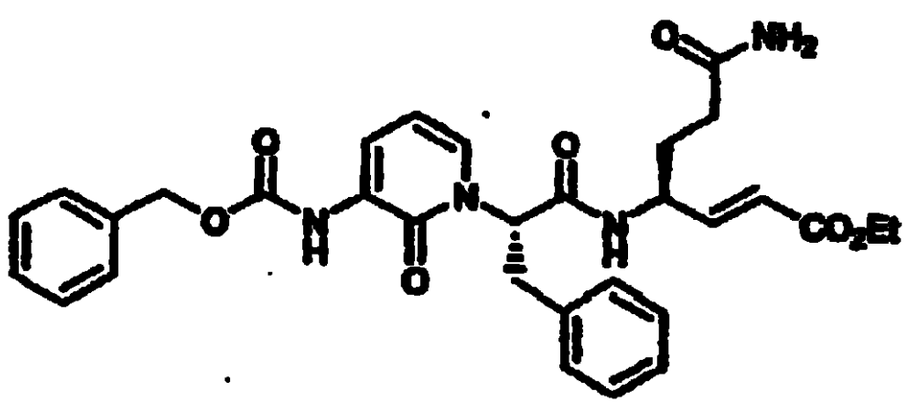
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DMSO se refiere a dimetilsulfóxido. MTBE se refiere a éter de metilo de tert-butilo. Otras abreviaciones incluyen: CH_3OH (metanol), EtOH (etanol), EtOAc (acetato de etilo), DME (éter de dimetilo de glicol etileno) Ac (acetilo), Me (metilo), Ph (fenilo), Tr (trifenilmetilo), Cbz (Benciloxicarbonilo), Boc (tert-butoxicarbonilo), TFA (ácido trifluoroacético), DIEA (N,N-diisopropiletilamina), TMEDA (N,N,N',N'-tetrametiletilenodiamina), AcOH (ácido acético), Ac_2O (anhídrido acético), NMM (4-metilmorfolina), HOBt (hidrato de 1-hidroxibenzotriazol), HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-hexafluorofosfato de tetrametil uronio], EDC [1-(3-dimetilaminopropil)-3-hidroxicloruro de etilcarbodiimide], DCC (diciorohexil-carbodiimida), DDQ (2,3-dicloro-5,6-diciano-1,4-benzoquinona), DMAP (4-dimetilaminopiridina), Gln (glutamina), Leu (leucina), Phe (fenilalanina), Phe (4-F) (4-flurorofenialanina), Val (valina), amino-Ala (2,3-ácido diaminopropiónico), y (S)-Pirrol-Ala [(2S, 3'S)-2-amino-3-(2'oxopirrolidin-3'-il)ácido propiónico]. Adicionalmente, "L" representa la configuración de amino ácidos que ocurren naturalmente.

EJEMPLO 1

Preparación del Compuesto 1:

trans-(2'S,4S)4-[2'-(3-Benzilloxicarbonilamino-2''-oxo-2''H-piridin-1''-il)-3'-fenilpropionilamino]-6-carbamoilhex-2-Ester de Etilo de Acido enóico



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Preparación del intermediario (2-hidroxipiridin-3-il)Ester de Bencilo de Acido carbámico

Una suspensión de 10% de paladio sobre carbono (0.20g) y 2-hidroxi-3-nitropiridina (3.00g, 21.4mmol, un equiv) en EtOH (100mL) fue sometida a una atmósfera de hidrógeno durante 4 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada y el filtrado evaporado para dar 2-hidroxi-3-aminopiridina la cual fue usada sin más purificación. Este material crudo fue agitado en THF (70mL) a 23°C. Cloroformato de bencilo (3.37mL, 23.6mmol, 1.1 equiv) y Na_2CO_3 (5.00g, 47.2mmol, 2.2 equiv) fueron agregados y la mezcla de reacción fue agitada durante 60 h entonces diluida con EtOAc (250mL) y lavada subsiguientemente con $NaHCO_3$ saturado y salmuera (50mL cada uno). La fase orgánica fue secada sobre $MgSO_4$, filtrada y concentrada. El residuo fue purificado por cromatografía de columna de destello (elución gradiente, 3→5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (3.69g, 71%) como un sólido blanco: ^1H NMR ($CDCl_3$) δ 5.21 (s, 2H), 6.33 (t, 1H, *J*=6.8), 7.00 (dd, 1H, *J*=6.8, 1.6), 7.31-7.43 (m, 5H), 7.80 (s, 1H), 8.12-8.17 (m, 1H), 12.97 (s, 1H).

Preparación del intermediario 5-(3-Benziloxicarbonilamino-2-oxo-2H-piridin-1-il)-6-fenil-4-[2-(tritilcarbamoil)etil]hex-2-Ester de Etilo de Acido enóico

(2-Hidroxipiridin-3-il)éster de bencilo de ácido carbámico fue convertido a el intermediario del título por vía de condensación con E1 (ver Ejemplo 5) por un proceso análogo aquel descrito en el Ejemplo 5 para la conversión de F1 a el intermediario I1: ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.2), 1.55-1.69 (m, 1H), 1.86-2.00 (m, 1H), 2.06-2.23 (m, 2H), 3.12 (dd, 1H, *J*=13.6, 7.8), 3.46 (dd, 1H, *J*=13.6, 8.2), 4.17 (q, 2H, *J*=7.2), 4.43-4.54 (m, 1H), 5.14 (d, 1H, *J*=12.1), 5.18 (d, 1H, *J*=12.1), 5.49-5.57 (m, 1H), 5.62 (dd, 1H, *J*=15.7, 1.7), 6.14 (t, 1H, *J*=7.3), 6.59-6.75 (m, 3H), 7.08-7.41 (m, 26H), 7.73 (s, 1H), 7.93-7.98 (m, 1H).

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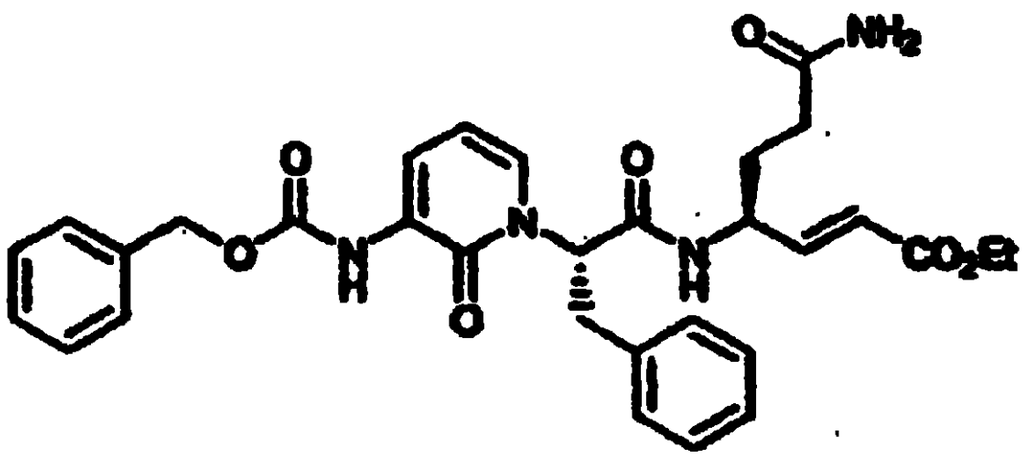
Preparación del Compuesto 1

El intermediario presedente fue convertido a compuesto 1 por un proceso análogo aquel descrito en el Ejemplo 5 para la conversión de I2 a producto J1: IR (cm^{-1}) 3298, 1713, 1655, 1590, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.1), 1.65-1.96 (m, 2H), 2.02-2.19 (m, 2H), 3.15 (dd, 1H, *J*=13.8, 7.6), 3.49 (dd, 1H, *J*=13.8, 8.3), 4.18 (q, 2H, *J*=7.1), 4.42-4.53 (m, 1H), 5.17 (s, 2H), 5.62-5.81 (m, 4H), 6.28 (t, 1H, *J*=7.2), 6.66 (dd, 1H, *J*=15.6, 5.4), 7.12-7.40 (m, 12H), 7.81 (s, 1H), 7.97-8.04 (m, 1H). Anal. $C_{31}H_{34}N_4O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 2

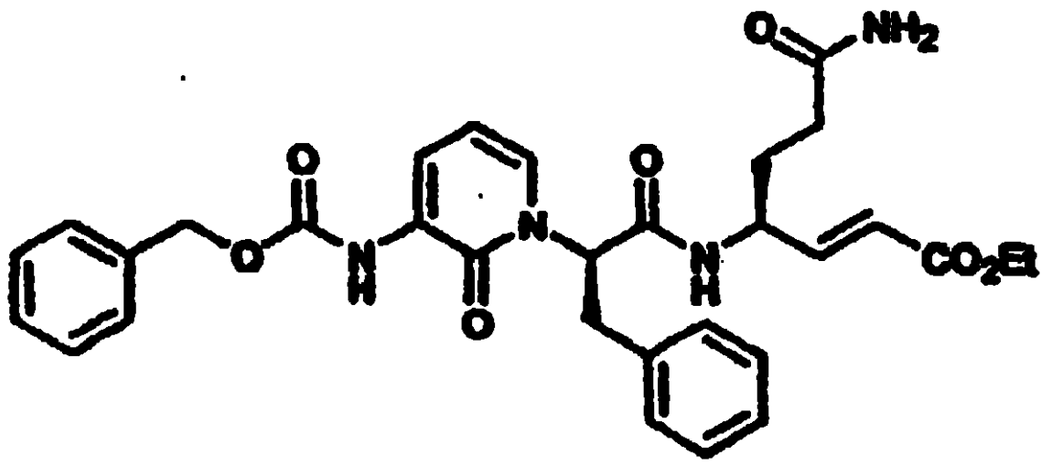
Preparación 1:1 mezcla del Compuesto 1 (arriba) y el Compuesto 2:

trans-(2'R,4S)-4-[2'-(3"-Benziloxicarboniiamino-2"-oxo-2"H-piridin-1"-il)-3'-feniipropioniiamino]-6-carbamoilhex-2-Ester de Etilo de Acido enóico



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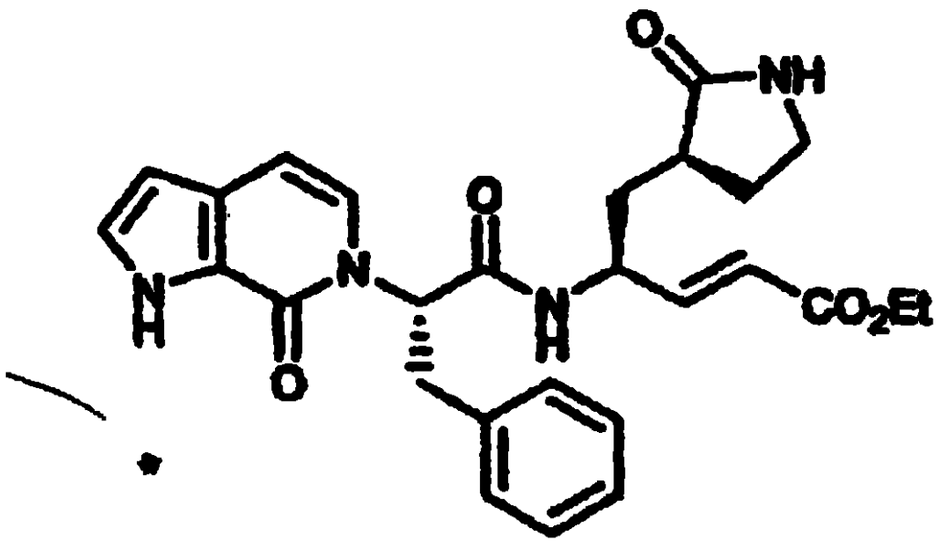
Los productos del título fueron preparados del comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico por un proceso análogo aquel descrito en el Ejemplo 22 para la conversión S1 a producto R2 utilizando intermediarios (2-hidroxipiridin-3-il)Ester de Bencilo de Acido carbámico (Ejemplo 1) y AA1 (Ejemplo 23) donde el apropiado: ^{1}H NMR ($CDCl_3$) (mezcla de isómeros) δ 1.20 (t, *J*=7.0), 1.29 (t, *J*=7.2), 1.64-2.25 (m), 3.08 (dd, *J*=13.6, 6.4), 3.14 (dd, *J*=13.6, 7.8), 3.41-3.62 (m), 4.09 (q,*J*=7.2), 4.18 (q, *J*=7.0), 4.39-4.50 (m), 5.16 (s), 5.59-5.82 (m), 6.12-6.22 (m), 6.25-6.34 (m), 6.65 (dd, *J*=15.6, 5.6), 6.70 (dd, *J*=15.6, 5.3), 7.10-7.41 (m), 7.47-7.58 (m), 7.79-7.86 (m), 7.97-8.07 (m).

EJEMPLO 3

Preparación del Compuesto 3:

trans-(2'S,3'''S,4S)-4-[2'-(7''-Oxo-1'',7''-dihidropirrol[2'',3''-c-piridin-6''-il)-3-fenilpropioniliamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Acido enóico

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Preparación del Intermediario (2S)-2-(2',2'-Dietiloxietilamino)-3-Ester de Etilo de Acido fenilpropiónico.

Una solución de ester de etilo de L-fenilalanina (8.37g, 46.8mmol, 1 equiv), acetal de dietilo de bromoacetaldehido (10.6mL, 70.1mmol, 1.5 equiv), y DIEA (16.2mL, 93.4mmol, 2.0 equiv) en DMF (100mL) fue calentada a 80°C durante 2 d. La solución resultante fue enfriada a 23°C, tomada en cloroformo (200mL), lavada con 10% de carbonato de potasio acuoso (3 x 50mL), secada sobre carbonato de potasio, y concentrada. La purificación del residuo por cromatografía de gel de sílice rindió 7.4g (54%) de producto. ^{1}H NMR ($CDCl_3$) δ 1.13-1.23 (m, 9H), 2.61 (dd, 1H, *J*=11.8, 5.9), 2.78 (dd, 1H, *J*=11.8, 5.9), 2.96-3.03 (m, 2H), 3.46-3.53 (m 1H), 3.55-3.70 (m, 4H), 4.18 (q, 2H, *J*=7.1), 4.57 (t, 1H, *J*=5.5), 7.19-7.33 (m, 5H).

Preparación del Intermediario (2S)-2-[(2,2-Dietoxietil)-(1H-pirrol-2-carbonil)-amino]-3-Ester de Etilo de Acido fenilpropiónico

Pirrol-2-ácido carboxílico (0.82g, 7.41mmol, 1.42 equiv) en CH_2Cl_2 (30mL) fue tratado con cloruro de oxalilo (1.0mL, 11.1mmol, 2.13 equiv), seguido por DMF (1 gota). La mezcla de reacción fue mantenida a 23°C toda la noche, entonces fue concentrada bajo

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presión reducida. El sólido resultante fue tomado en CH_2Cl_2 (30Ml), y fue tratado con intermediario precedente (1.60g, 5.2mmol, 1 equiv), y colidina (1.96mL, 14.8mmol, 2.85 equiv). La solución resultante fue mantenida 23°C toda la noche, entonces fue tomada en EtOAc (100mL), y lavada secuencialmente con ácido cítrico acuoso saturado (20mL), bicarbonato de sodio acuoso saturado (20mL), y salmuera (2 x 20mL). La capa orgánica fue secada sobre $MgSO_4$, entonces fue concentrada para rendir 2.18g del producto crudo. El producto fue purificado por cromatografía de gel de sílice para dar 1.42g (68%) de producto. ^1H NMR ($CDCl_3$) δ 1.15-1.30 (m, 9H), 3.24 (d, 2H, *J*=5.8), 3.75-4.43 (m, 2H),4.15-4.28 (m 6H), 4.50-4.57 (m, 1H), 5.05 (dd, 1H, *J*=13.6, 5.8), 6.22-6.24 (m, 1H), 6.56-6.59 (m, 1H), 6.94-6.96 (m, 1H), 7.19-7.33 (m, 5H), 9.76 (s, 1H).

Preparación del Intermediario (2S)-(7-Oxo-1,7-dihidropirrolo [2,3-c]piridin-6-il)-3-Ester de Etilo de Acido fenilpropiónico

Una solución del intermediario precedente (1.04g, 2.59mmol) en tolueno (30mL), fue tratada con PTSA (5mg), entonces calentada a reflujo durante 1 h. La solución fue tomada en EtOAc (100mL), lavada con bicarbonato de sodio acuoso saturado (30mL), luego salmuera (30mL), entonces concentrada. La purificación del residuo por cromatografía de gel de sílice dio 0.14g (18%) de producto. ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, *J*=7.1), 3.25 (dd, 1H, *J*=14.2, 9.8), 3.49 (dd, 1H, *J*=14.2, 5.7), 4.11 (q, 2H, *J*=7.1), 5.57 (dd, 1H, *J*=9.6, 5.7), 6.26 (t, 1H, *J*=2.3), 6.42 (d, 1H, *J*=7.2), 6.70 (d, 1H, *J*=7.2), 7.00-7.20 (m, 6H), 10.33 (s, 1H).

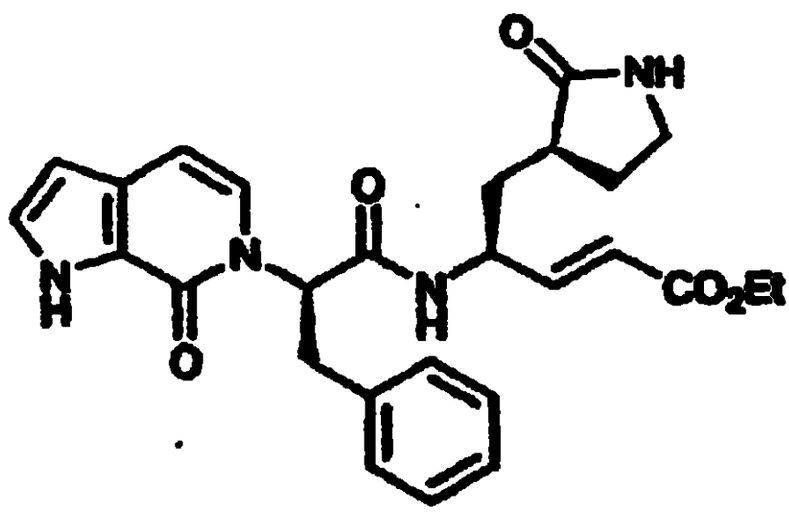
Preparación del Compuesto 3

Una solución del intermediario precedente (0.14g, 0.45mmol, 1 equiv) en 1:1 1.4-dioxano-agua (5mL) fue tratada con hidrato de LiOH (28mg, 0.68mmol, 1.42 equiv), y calentada a reflujo durante 30 min. La solución resultante fue tomada en acetato de etilo (50mL), lavada con ácido cítrico acuoso saturado (10mL), seguido por salmuera (2 x 15mL), secada sobre $MgSO_4$, entonces evaporada

para rendir 61mg del ácido correspondiente. Esta fue tomada en DMF (5mL), tratada con intermediario Y2 (Ejemplo 25, 49mg, 0.22mmol, 0.48 equiv), DIEA (0.07mL, 0.43mmol, 0.95 equiv), y HATU (82mg, 0.22mmol, 0.49 equiv), entonces mantenida a 23°C toda la noche. La solución fue tomada en acetato de etilo (30mL), lavada con salmuera (10mL), entonces evaporada. La purificación de residuo por cromatografía de gel de sílice rindió 0.12g (56%) de producto como una mezcla de 2:1 de 2S:2R diastereómeros (compuestos 3 y 4, respectivamente). Los diastereómeros fueron separados por fase reversa preparativa HPLC (acetonitrilo-H_2O gradiente). Compuesto 3: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.1), 1.42-1.65 (m, 2H), 1.90-2.10 (m, 2H), 2.20-2.35 (m, 1H), 2.82-2.95 (m, 1H), 3.05-3.25 (m, 2H), 3.53 (dd, 1H, *J*=13.8, 7.8), 4.17 (q, 2H, *J*=7.1) 4.45-4.58 (m, 1H), 5.76-5.90 (m, 2H), 6.32 (t, 1H, *J*=2.1), 6.63 (d, 1H, *J*=7.3), 6.69-6.78 (m, 2H), 7.08-7.35 (m, 7H), 8.11 (d, 1H, *J*=7.1), 11.22 (s, 1H).

EJEMPLO 4

Preparación del Compuesto 4: trans-(2'R,3'''S,4S)-4-[2'-(7''-Oxo-1'',7''-dihidropirrolo[2'',3''-c-piridin-6''-il)-3-fenilpropionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Eter de Etilo de Acido enóico



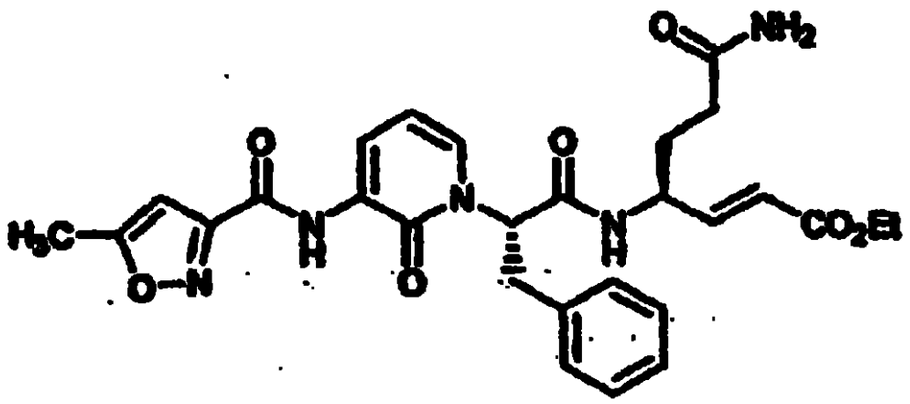
Ver preparación para el Ejemplo precedente: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, *J*=7.1), 1.42-1.52 (m, 1H), 1.58-1.70 (m, 1H), 1.90-

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2.28 (m, 3H), 3.12 (dd, 1H, *J*=13.3, 7.1), 3.20-3.28 (m, 2H), 3.57 (dd, 1H, *J*=13.3, 9.0), 4.07 (q, 2H, *J*=7.0), 4.45-4.58 (m, 1H), 5.80 (d, 1H, *J*=15.7), 6.04 (t, 1H *J*=7.7), 6.37 (t, 1H, *J*=2:3), 6.48 (s, br, 1H), 6.60-6.80 (m, 2H), 7.00-7.40 (m, 6H), 8.11 (d, 1H, *J*=7.8), 10.81 (s, 1H).

EJEMPLO 6

Preparación del Compuesto 6: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3"-[(5"'-metilisoxazol-3"'-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3-fenilpropionilamino)hex-2-Ester de Etilo de Acido enólico (J1)



Preparación del Intermediario (1S)-[1-Hidroximetil-3-(tritilcarbamoil)propil]Ester de Bencilo de Acido carbámico (B1)

4-Metilmorfolin (1.89mL, 17.2 mmol, 1 equiv) y cloroformato de etilo (165 mL, 17.3 mmol, 1equiv) fueron agregados para una mezcla de comercialmente disponible Cbz-Gln(Trt)-Oh (9.00 g, 17.2 mmol, 1equiv) en THF (23 mL) á –10°C. Después de la agitación 20 min, la reacción de mezcla fue filtrada y el filtrado fue agregado gota a gota para una suspensión de $NaBH_4$ (1.47 g, 38.9 mmol, 2.25 equiv) en H_2O (10 mL) a 0°C. La mezcla resultante fue dejada calentar a 23°C y agitada durante 5 h. Esta fue entonces enfriada de nuevo a 0°C, calmada por la cuidadosa agregación de 1 N HCl

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(30 mL) y entonces las partes por medio de MTBE (500 mL) y salmuera (2 x 100 mL). La fase orgánica fue secada bajo Na_2SO_4 y evaporada hasta proporcionar el intermediario titulado el cual fue usado sin además de la purificación.

Preparación del Intermediario (1S)-[1-(tert-Butildimetilsilanoximetil)-3-(tritilcarbamoil)propil]Ester de Bencilo de Ácido carbámico (C1)

Intermediario B1, preparado arriba, fue disuelto en DMF (10 mL). Imidazol (2.69 g, 39.5 mmol, 2.3 equiv) y tert-cloruro de butildimetilsilil (2.86 g, 19.0 mmol, 1.1 equiv) fueron agregados. La reacción de mezcla fue agitada toda la noche, entonces diluida con MTBE (500 mL) y lavado secuencialmente con 2.5% de $KHSO_4$, H_2O, y salmuera (100 mL cada una). La fase orgánica fue secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elusión de gradiente, 25→40% de EtOAc en hexanos) para proporcionar el intermediario titulado (7.6 g, 71%) como un sólido amorfo blanco: IR (cm^{-1}) 3307, 1708, 1660, 1496, 1249; ^1H NMR ($CDCl_3$) δ -0.01-0.05 (m, 6H), 0.89 (s, 9H), 1.76-1.93 (m, 2H), 2.29-2.40 (m, 2H), 3.56-3.77 (m, 3H), 5.03-5.16 (m, 3H), 7.00 (s, 1H), 7.18-7.39 (m, 20H); Anal. $C_{38}H_{46}N_2O_4Si$; C, H, N.

Preparación del Intermediario (2'R, 4S)-5-(tert-Butildimetilsilanoxi)-4-(2'-hidroxi-3'fenilpropionilamino)Tritilamida de Acido pentanóico (D1)

El intermediario C1 de arriba.(7.6 g, 12 mmol, 1 equiv) y 10% de paladio sobre carbono (0.45 g) fueron suspendidos en EtOH (140 mL) e hidrogenado a 50 psi toda la noche. La mezcla de racción fue filtrada a través de Whatmn papel #3, el papel fue lavado con EtOH (120 mL) y los filtrados combinados fueron evaporados. El residuo fue combinado con D-3-ácido fenilactico (1.42 g, 12.2 mmol, 1 equiv), iPr_2NEt (4.25 mL, 24.4 mmol, 2 equiv) y HATU (4.64 g, 12.2

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mmol, 1 equiv) en DMF (35 mL) a 0°C. Después de la agitación 1 h, la mezcla de reacción fue dejada calentar a 23°C y agitada 20 min más. Entonces 5% de $KHSO_4$ (80 mL) y MTBE (600 mL) fueron agregados y las fases fueron separadas. La fase orgánica fue lavada con H_2O (80 mL) y salmuera (70 mL9, secada bajo Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (50% EtOAc en hexanos) para proporcionar el intermediario titulado como una sopa blanca (4.85 g, 62%): IR (cm^{-1}) 3394, 3295, 1666, 1649, 1519, 1255, 1114, 1085; ^1H NMR ($CDCl_3$) δ -0.03-0.02 (m, 6H), 0.85 (s, 9H), 1.70-1.89 (m, 2H), 2.18-2.42 (m, 3H), 2.83 (dd, 1H, *J*=10.0, 3.1), 3.83-3.94 (m, 1H), 4.17-4.23 (m,-1H), 6.79 (d, 1H, *J*=8.7), 7.09 (s, 1H), 7.17-7.32 (m, 20H); Anal. $C_{39}H_{46}N_2O_4Si \cdot 0.30H_2O$: C, H, N.

Preparación del intermediario (1'S,2R)-Ácido metanosulfónico 1-[1'-(tert-butildimetilsilaniloximetil)-3'-(tritilcarbamoil) propilcarbamoil]-2-Ester feniletilo (E1)

Intermediario D1 de arriba (1.96 g, 3.08 mmol, 1 equiv) y iPr_2Net (0.752 mL, 4.32 mmol, 1.4 equiv) fueron disueltos en CH_2Cl_2 (30 mL) y enfriado a −10°C. Cloruro Metanosulfonilo (0.286 mL, 3.70 mmol, 1.2 equiv) fue agregado gota a gota, lentamente, con agitación vigorosa. Después de 30 min, la mezcla de reacción fue diluido con CH_2Cl_2 (200 mL), lavado con salmuera (50 mL), secada bajo Na_2SO_4 y evaporada para proporcionar el intermediario titulado el cual fue usado sin más purificación.

Preparación del Intermediario (2-Hidropiridin-3-il)Ester de tert-Butilo de ácido carbámico (F1)

Una suspensión de 10% de paladio sobre carbono (0.35 g) y 2-hidroxi-3-nitropiridina (5.00 g, 35.7 mmol, 1 equiv) en EtOH (170 mL) fue sujetado a una atmósfera de hidrógeno durante 16 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado

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para dar 2-hidroxi-3-aminopiridina el cual fue usado sin más purificación. Este material crudo fue agitado en THF (100 mL) a 23°C. Dicarbonato de di-tert-butilo (7.79 g, 35.7 mmol, 1 equiv) fue agregado y la mezcla de reacción fue calentada a reflujo durante 4 h. Más dicarbonato de di-tert-butilo (6.0 g, 27 mmol, 0.8 equiv) fue agregado y la mezcla de reacción fue calentada a reflujo durante toda la noche. El solvente fue evaporado y el residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 50→60% EtOAc en hexanos) para proporcionar el intermediario del título como un sólido blanco (6.48 g, 83%): IR (cm^{-1}) 3225,1725, 1649, 1514; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.33 (dd, 1H, J= 7.4,6.6), 7.01 (dd, 1H, J= 6.6,1.8), 7.66 (s, 1H), 8.11 (d, 1H, J= 7.1), 12.61 (s, IH); Anal. $C_{10}H_{14}N_2O_3$: C, H, N.

Preparación del Intermediario (1''S,2'S)-(1-{1'-[1''-(tert-Butildimetilsilanilloximetilo)-3''-(tritilcarbamoil)propilcarbamoil]-2'-feniletil}-2-oxo-1,2-dihidropiridin-3-il)- Ester de tert-Butilo de ácido carbámico (G1).

El intermediario F1 de arriba (0.838 g, 3.99 mmol, 1.3 equiv) fue agitado en THF (20 mL). Hidruro de sodio (60% de dispersión en aceite mineral, 0.148 g, 3.70 mmol, 1.2 equiv) fue agregado. Después de la agitación de 20 min, una solución del intermediario E1 de arriba (1 equiv basado sobre D1) en THF (15 mL) fue agregado. La mezcla resultante fue calentada a reflujo durante 40 h, pero la cromatografía de capa delgada mostró la reacción para ser solamente 50% completa. En un frasco separado, más hidruro de sodio (60% de dispersión en aceite mineral, 0.111 g, 2.78 mmol, 0.9 equiv) fue agregado a una suspensión de F1 (0.647 g, 3.08 mmol, 1 equiv) en THF (10 mL). Después de la agitación de 20 min, esta mezcla fue agregada a vasija de reacción original y la mezcla resultante fue calentada a reflujo durante 21 h. Después de la agitación a 23°C durante la semana, la mezcla de reacción cruda fue diluida con MTBE (600 mL) y lavada con una mezcla de salmuera y 10% de $KHSO_4$ (3:1, 80 mL) y salmuera (80 mL),

entonces secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 30→35% EtOAc en hexanos) para proporcionar el intermediario deseado G1 como una espuma blanca (1.98 g, 77%): IR (cm^{-1}) 3389, 3307, 1725, 1678, 1649, 1590, 1502; ^1H NMR ($CDCl_3$) δ -0.02-0.04 (m, 6H), 0.86 (s. 9H), 1.52 (s, 9H), 1.55-1.88 (m, 2H), 2.08-2.14 (m, 2H), 3.19 (dd, 1H, *J*= 13.7,8.1), 3.39-3.51 (m, 2H), 3.53 (dd, 1H, *J*=14.2,7.8), 3.82-3.93 (m, 1H), 5.60-5.67 (m, 1H). 6.17 (t, 1H. *J*=7.3), 6.44 (d, 1H, *J*=8.3), 7.04 (s, 1H), 7.12-7.36 (m, 21H), 7.59 (s, 1H), 7.94 (d, 1H, *J*=7.1); Anal. $C_{49}H_{60}N_4O_6Si$: C, H, N.

Preparación del intermediario (1"S,2'S)-(1-{1'-[1"-Hidroximetil- 3"-(tritilcarbamoil)propilcarbamoil]- 2'-feniletil}-2-oxo-1,2-dihidropiridin-3-il)-Ester de tert-Butilo de ácido carbámico (H1)

El intermediario G1 de arriba (1.92g, 2.32 mmol, 1 equiv) fue disuelto en una mezcla de CH_3CN (30 mL) y H_2O (3 mL) en un tubo plástico. Trihidrofluoruro de trietilamina (21 gotas) fue agregada y la solución de reacción fue agitada durante toda la noche. Esta fue entonces diluida con EtOAc (750 mL), lavada con salmuera (3 x 80 mL), secada sobre $MgSO_4$ y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario trans-(2'S,4'S)-4-[2'-(3"-tert-Butoxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3"-fenilpropionilamino]-6-tritilcarbamoil)hex-2- Ester de Etilo de Acido enóico (I1)

El intermediario H1 de arriba (1 equiv basado sobre G1) fue disuelto en CH_2Cl_2 (20 mL). Comercialmente disponible Dess-Martin Periodinane (1.09 g, 2.55 mmol, 1.1 equiv) fue agregado. Después de la agitación de 2 h, el solvente fue evaporado y el residuo fue suspendido en tolueno y de nuevo evaporado (70 mL, entonces 2% mL) para dar una espuma amarilla. Una mitad de este material (1.16 mmol basada sobre G1) fue disuelta en THF (17 mL). (Carbetoximetileno) trifenilfosforano (0.563 g, 1.62 mmol, 1.4 equiv)

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fue agregado y la mezcla de reacción fue calentada a reflujo durante 1 h y entonces agitada a 23°C toda la noche. Después de la evaporación del solvente, el residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 40→50% EtOAc en hexanos) para proporcionar el intermediario del título (0.710 g, 77%): IR (cm^{-1}) 3378, 3284, 1719, 1649, 1596, 1508, 1267; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.47 (s, 9H). 1.54-1.69 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.22 (m, 2H), 3.12 (dd, 1H, *J*= 13.7,7.7), 3.47 (dd, 1H, *J*= 13.7,8.1), 4.17 (q, 2H, *J*= 7.1), 4.43-4.54 (m, 1H), 5.51-5.58 (m, 1H), 5.64 (dd, 1H, *J*= 15.7,1.6), 6.12 (t, 1H, J= 7.2), 6.60-6.68 (m, 3H), 7.08-7.31 (m, 21H), 7.51 (s, 1H), 7.90 (d, 1H, *J*= 7.1); Anal. $C_{47}H_{50}N_4O_7 \cdot 0.50H_2O$: C, H, N.

Preparación del intermediario trans-(2'S,4S)-4-(2'-{3"-[(5"'-metilisoxazol-3"'-carbomil)amino]-2"-oxo-2"H-piridin-1"-il}-3"-fenilpropioniiamino)-6-(tritilcarbamoil)hex-2-Ester de Etilo de Acido enóico (I2)

El intermediario I1 de arriba (0.088 g, 0.11 mmol, 1 equiv) fue calentado (neto) a entre 190 y 200°C durante 65 minutos, entonces dejado enfriar proporcionando la amina cruda como un residuo oscuro la cual fue disuelta en CH_3CN (2 mL) y enfriada a 0°C. 5-metilisoxazol-3-cloruro de carbonilo (0.033 g, 0.23 mmol, 2 equiv) y 4-metilmorfolina (0.025 mL, 0.23 mmol, 2 equiv) fue agregada y la mezcla de reacción fue dejada calentar hasta 23°C. Después de la agitación de 40 min, una mezcla de 10% de $KHSO_4$ y salmuera (1:1, 15 mL) y EtOAc (70 mL) fue agregado. Las fases fueron separadas y la fase orgánica fue lavada con salmuera, secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (60% EtOAc en hexanos) para proporcionar el intermediario del título (0.049 g, 55%): IR (cm^{-1}) 3331, 1678 (br), 1590, 1525; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.58-1.72 (m, 1H), 1.87-2.03 (m, 1H), 2.10-2.26 (m, 2H), 2.48 (s, 3H), 3.15 (dd, 1H.J= 13.7, 7.8), 3.47 (dd, 1H, J== 13.7, 8.1), 4.17 (q, 2H, *J*^ 7.1), 4.43-4.55 (m, 1H), 5.54-5.61 (m, 1H), 5.65 (dd, 1H,J= 15.8,1.5), 6.17 (t, 1H, J= 7.3), 6.45 (s, 1H), 6.65 (dd, 1H,J= 15.8, 5.4), 6.72

(s, 1H), 6.84 (d, 1H, *J*- 8.0). 7.08-7.32 (m., 22 H), 8.35 (dd, 1H, J= 7.3,1.5), 9.49 (s, 1H); Anal. $C_{47}H_{48}N_5O_7 \cdot 0.25H_2O$: C, H, N.

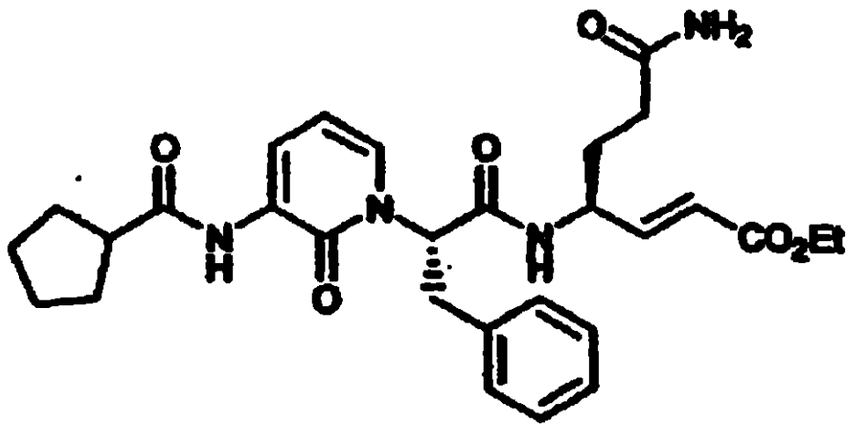
Preparación del Producto J1 (Compuesto 6)

El intermediario I2 de arriba (0.047 g, 0.059 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (3 mL). Triisopropilsilano (0.036 mL, 0.176 mmol, 3 equiv) y TFA (2 mL) fue agregado. La solución amarilla brillante fue agitada 25 min, entonces diluida con CCl_4 (3 mL) y todos los volátiles fueron evaporados. El residuo fue purificado por cromatografía de columna de destello (3% CH_3OH en CH_2Cl_2) para dar el producto deseado J1 (0.028 g, 85%): IR (cm^{-1}) 3342,1666 (br), 1590,1531,1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.17-2.24 (m, 2H), 2.48 (s, 3H), 3.18 (dd, 1H, *J*= 13.7,7.8), 3.50 (dd, 1H, *J*= 13.7,8.1), 4.19 (q, 2H, *J* = 7.1), 4.43-4.54 (m, 1H), 5.68 (dd, 1H, *J* = 15.7,1.3), 5.74-5.82 (m, 1H), 6.00 30 (s, 1H), 6.19 (s, 1H), 6.32 (t, 1H, *J*= 7.3), 6.46 (s, 1H), 6.69 (dd, 1H, *J*= 15.7,5.5), 7.13-7.30(m, 5H), 7.48 (dd, 1H, 7=7.3, 1.6), 7.62(d, 1H,*J*= 7.6), 8.39 (dd, 1H,*J*=7.3, 1.6),9.46(s, 1H); Anal. $C_{28}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 6

Preparación del Compuesto 6: trans-(2'S,4S)-6-Carbamoil-4-{2'-[3''-ciclopentanocarbonilamino-2''-oxo-2''H-piridin-1''-il]-3'-fenilpropionilamino}-hex-2-Ester de Etilo de Acido enóico

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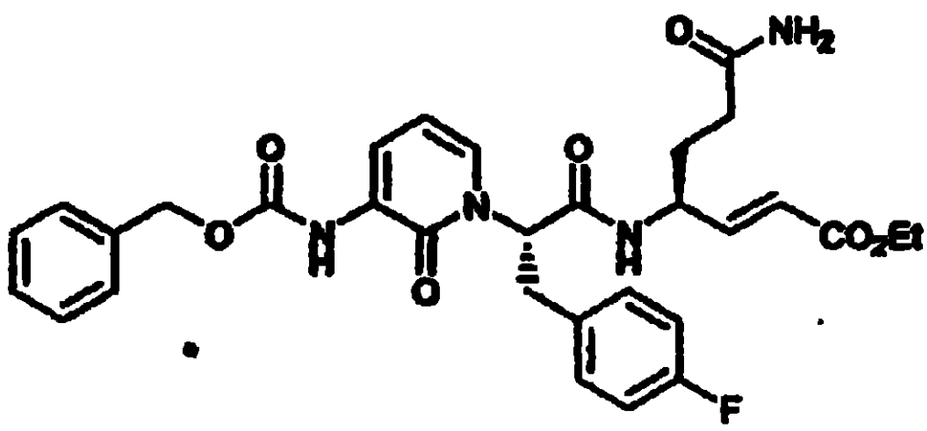


El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a quel descrito en el Ejemplo 6 para la conversión de I1 a producto J1 utilizando intermediario de cloruro de ciclopentanocarbonilo donde el apropiado: IR(cm^{-1}) 3319, 1713, 1666, 1590, 1514; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, 7= 7.1), 1.55-2.02 (m, 10H), 2.04-2.22 (m, 2H)2.68-2.80 (m, 1H), 3.16 (dd, 1H,J= 13.7,7.7), 3.51 (dd, *J*= 13.7,8.1), 4.19 (q, 2H, *J*= 7.1), 4.45-4.56 (m, 1H), 5.57-5.74 (m, 4H), 6.29 (t, 1H, *J*= 7.4), 6.68 (dd, 1H, *J*= 15.8,5.5), 7.10-7.32 (m. 7H), 8.30(s, IH),8.35(dd, 1H, .7=7.4,1.7); Anal. $C_{29}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 7

Preparación del Compuesto 7: trans-(2'S,4S)-4-[2'-(3"-Benciloxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3'-(4"'-fluorofenil) propionilamino]-6-carbamoilhex-2-Ester de Etilo de Acido enóico

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Preparación del intermediario trans-(2'S,4S)-4-[2'-(3"-Benciloxicarbonylamino-2"-oxo-2"H-piridin-1"-il)-3'-(4"'-fluorofenil)propionilamino]-6-(tritilcarbamoil)hex-2-Ester Etilo de Ácido enóico

El intermediario C1 (Ejemplo 5) fue convertido al intermediario del título por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de C1 a intermediario I1 utilizando S1 (Ejemplo 22) donde fuere apropiado: IR (cm^{-1}) 3283, 1722, 1651, 1604, 1513; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, *J*= 6.9), 1.62-1.71 (m, 1H), 1.94-2.01 (m, 1H), 2.17-2.24 (m, 2H), 3.06-3.13 (m. 1H), 3.43-3.50 (m, 1H), 4.21 (q, 2H, *J*= 6.9), 4.50-4.57 (m, 1H), 5.16-5.25 (m, 2H), 5.52 (t, 1H, *J*= 8.1), 5.63 (dd, 1H, *J*= 15.6,1.5), 6.18 (t, 1H, *J*= 7.2), 6.65 (s, br. 1H), 6.69 (dd, 1H, *J*= 15.6,5.4), 6.84 (d, 1H, *J*= 8.4), 6.96 (t, 2H, *J*= 8.4), 7.09-7.18 (m, 7H), 7.21-7.33 (m, 12H), 7.38-7.42 (m, 4H), 7.76 (s, br. 1H), 7.99 (d, 1H, *J*= 7.5); Anal. $C_{50}H_{47}N_4O_7 \cdot 0.50H_2O$: C, H, N.

Preparación del Compuesto 7

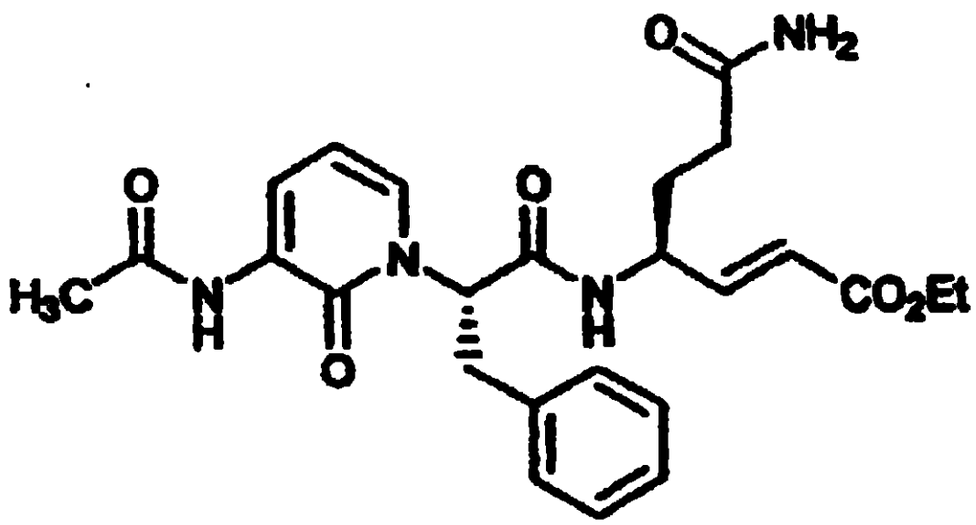
El intermediario precedente fue convertido a compuesto 7 por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de I2 a producto J1: mp = 99-101 °C; IR (cm^{-1}) 3308, 1714, 1650, 1511, 1198; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, *J*=6.9), 1.72 -1.82 (m, 1H), 1.86-1.96 (m, 1H), 2.10-2.18 (m, 2H), 3.10-3.17 (m, 2H), 3.10-3.17 (m. 2H), 3.46-3.53 (m, 1H), 3.63-3.74 (m, 2H), 4.22

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(q, 2H, *J*= 6.9), 4.48-4.57 (m, 1H), 5.21 (s, 2H), 5.58-5.65 .(m, 2H), 5.91-5.97 (m, 1H), 6.19-6.22 (m, 1H), 6.35 (t, 1H, *J*= 7.2), 6.69 (dd, 1H, J= 15.6, 5.1), 6.98 (t, 2H, *J*= 8.7), 7.13-7.18 (m, 2H), 7.36-7.40 (m, 5H), 7.85 (s, br. 1H), 8.06-8.09 (m, 1H); Anal. $C_{33}H_{33}N_4O_7 \cdot 1.25H_2O$: C, H, N.

EJEMPLO 8

Preparación del Compuesto 8: trans-(2'S,4S)-4-[2'-(3"-Acetilamino-2"-oxo-2"H-piridm-1"-il)-3'-fenipropioniiamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enoico



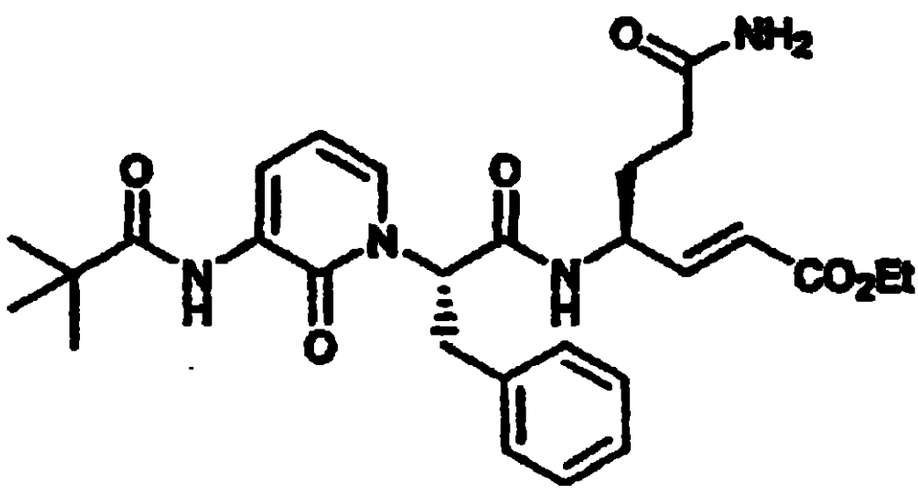
El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a aquel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando intermediario cloruro de acetilo donde fuere apropiado: IR (cm^{-1}) 3307, 1708, 1666, 1643, 1590, 1519; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H,J= 7.1), 1.70-1.86 (m, 2H), 2.05-2.24 (m, 5H), 3.15 (dd, 1H,J= 13.7, 8.1), 3.50 (dd, 1H, J= 13.7,7.8), 4.19 (q, 2H, *J*= 7.1), 4.45-4.56 (m, 1H), 5.66-5.77 (m, 2H), 5.82 (s, 1H), 5.94 (s, 1H), 6.28 (t, 1H, *J*= 7.2), 6.69 (dd, 1H, 7= 15.7,5.6), 7.10-7.29 (m, 5H). 7.32-7.45 (m, 2H), 8.28-8.36 (m, 2H); Anal. $C_{28}H_{30}N_4O_8 \cdot 0.50H_2O$: C, H, N.

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EJEMPLO 9

Preparación del Compuesto 9: trans-(2'S,4S)-6-Carbamoil-4-{2'-[3"-(2"',2"'-dimetilpropioniiamino)-2"-oxo-2"H-piridin-1"-il]-3'-fenilpropioniiamino}hex-2-Ester de Etilo de Ácido enóico



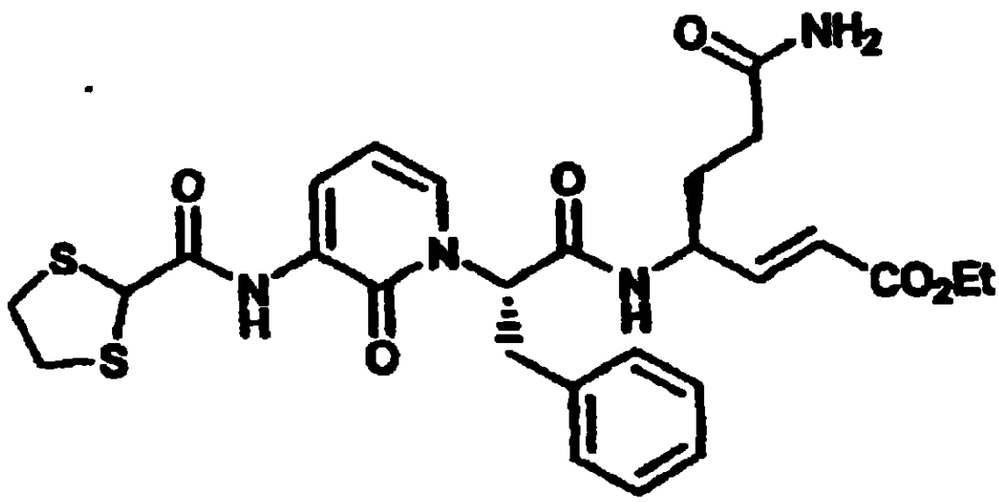
El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a aquel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando intermediario cloruro de 2,2-dimetilpropionilo donde fuere apropiado: IR (cm^{-1}) 3378, 3307, 3213, 1713, 1666, 1643, 1590, 1514, 1273; ^1H NMR ($CDCl_3$) δ 1.18-1.37 (m, 12H), 1.67-1.98 (m, 2H), 2.05-2.20 (m, 2H), 3.17 (dd, 1H,J= 13.6, 7.7), 3.50 (dd, 1H,^= 13.6,8.2), 4.19 (q, *2H,J*= 7.1), 4.43-4.54 (m, 1H), 5.62-5.72 (m, 2H), 5.81-5.92 (m, 2H), 6,29 (t, 1H,J= 7.2), 6.66 (dd, 1H, J= 15.8,5.7), 7.13-7.39 (m, 7H), 8.33-8.38 (m, 1H), 8.59 (s, 1H); Anal. $C_{28}H_{38}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 10

Preparación del Compuesto 10: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3"-[([1"',3"']ditiolano-2"'-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3'-fenilpropioniiamino)hex-2-Ester de Etilo de ácido enóico

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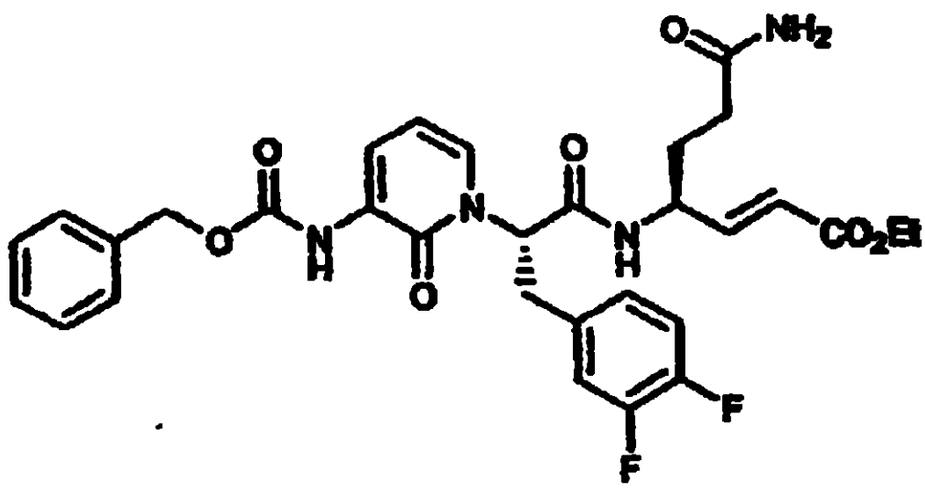


El compuesto del título fue preparado de i1 (Ejemplo 5) por un proceso análogo a quel descrito en el Ejemplo 6 para la conversión de I1 a producto J1 utilizando el intermediario cloruro [1,3]ditiolano-2-carbonilo (preparado tal como se describió en *Helv. Chim. Acta* 1975, *58*, 2509) donde fuere apropiado: IR (cm-l) 3295, 1672 (br), 1590, 1519 (br), 1273; ^{1}HNMR (CDC_3) δ 1.30 (t, 3H, *J*= 7.1), 1.66-2.22 (m, 4H), 3.17 (dd, 1H, *J*= 13.7,7.8), 3.28-3.45 (m, 4H), 3.52 (dd, 1H, *J*= 13.7, 8.1), 4.19 (q, 2H, *J*= 7.1), 4.43-4.55 (m, 1H), 5.01 (s, 1H), 5.66 (dd, 1H, *J*= 15.8,1.5), 5.67 (s, 1H), 5.86 (s, 2H), 6.29 (t, 1H, *J*= 7.3), 6.67 (dd, 1H, *J*= 15.8, 6.5), 7.12-7.40 (m, *7H)*, 8.31 (dd, 1H, *J*= 7.3,1.6), 9.57 (s, 1H); Anal. $C_{27}H_{32}N_4O_7S_4 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 11

Preparación del Compuesto 11: trans-(2'S,4S)-4-[2'-(3"-Benciloxicarboniiamino-2"-oxo-2"H-piridin-1"-il)-3'-(3"',4"'-difluorofenil)propioniiamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico

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Preparación del intermediario (2R)-3-(3',4'-Difluorofenil)-2-Ácido hydroxipropiónico

Boc-D-3,4-Difluorofenilalanina (3.05 g, 11.0 mmol, 1 equiv) fue disuelto en 1,4-dioxano (10 mL), y una solución de HCl en 1,4-dioxano (4.0 M, 10 mL) fue agregada. La reacción fue agitada a 23 °C durante 5 h, entonces el solvente fue removido bajo presión reducida. El residuo fue disuelto en 1 M H_2SO_4 (22 mL), enfriado a 0 °C y 2 N $NaNO_2$ (22 mL) fue agregado vía de adición de tunel bajo argón. La mezcla de reacción fue agitada a 0 °C durante 3 h y calentada a temperatura ambiente toda la noche. La mezcla resultante fue extractada con MTBE (3 x 40 mL), secada sobre Na_2SO_4 y concentrada. El residuo fue recristalizado de éter/éter de petróleo para proporcionar el intermediario del título (1.29 g, 58%) como un sólido casi blanco. ^1H NMR (DMSO-d_6) δ 0.82-0.86 (m, 2H), 1.10-1.27 (m, 4H), 1.40-1.48 (m, 2H), 1.63-1.78 (m, 5H), 3.95-4.00 (m, 1H).

Preparación del Compuesto 11

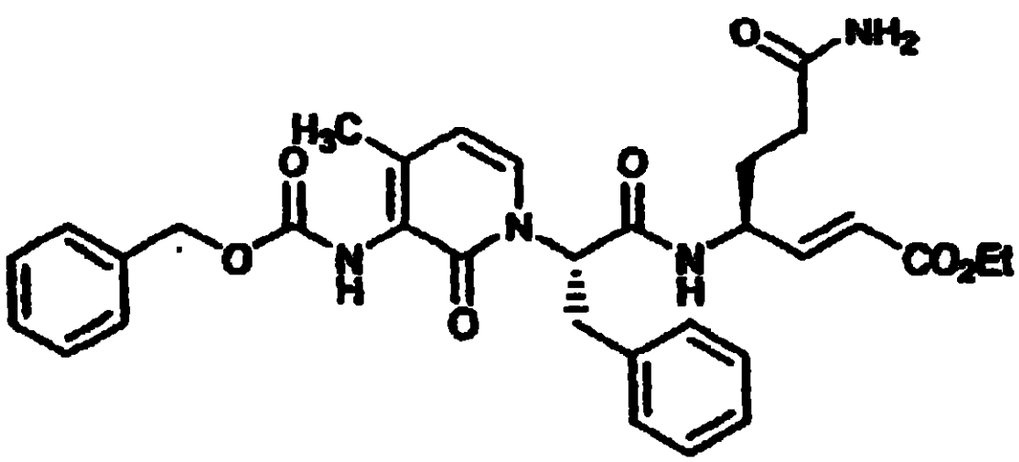
El intermediario C1 (Ejemplo 5) fue convertido a compuesto 11 por un proceso análogo como aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando (2R)-3-(3',4'-difluorofenil)-2-ácido hidroxipropiónico (Ejemplo 11) donde fuere apropiado: mp = 176-178°C; IR (cm^{-1}) 3298, 1661, 1516, 1266;

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^{1}HNMR (CDC_3) δ 1.32 (t, 3H,*J*=7.2), 1.74-1.95 (m,2H), 2.12-2.20 (m,2H), 3.05-3.12 (m, 1H), 3.42-3.50 (m. 1H),4.21 (q,2H,J= 7.2), 4.45-4.56 (m, 1H), 5.21 (s, 2H), 5.58-5.71 (m, 3H), 6.07-6.10 (m, 1H), 6.32-6.34 (m, 1H), 6.71 (dd, 1H, *J*= 15.6, 5.1), 6.88-6.91 (m, 1H), 6.99-7.11 (m, 2H), 7.30-7.33 (m, 1H), 7.36-7.39 (m, 5H), 7.53 (s, br. 1H), 7.86 (s, br. 1H), 8.04 (s, br. 1H); Anal. $C_{31}H_{32}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 12

Preparación del Compuesto 12: trans-(2'S,4S)-4-[2'-(3"-Benciloxicarboniiamino-4"-metil-2"-oxo-2"H-piridin-1"-il)-3'-fenilpropioniiamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico



Preparación del Intermediario (2-Hidroxi-6-metilfenil)Ester de Bencilo de ácido carbámico

Una suspensión de 10% de paladio sobre carbono (0.045 g) y 2-hidroxi-4-metil-3-nitropiridina (0.600 g, 3.89 mmol, 1 equiv) en EtOH (20 mL) fue sometida a una atmósfera de hidrógeno durante 16 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-4-metil-3-aminopiridina el cual fue

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usado sin más purificación. Este material crudo fue agitado en THF (18 mL) a 23°C. Cloroformato de bencilo (0.611 mL, 4.28 mmol, 1.1 equiv) y Na_2CO_3 (0.907 g, 8.56 mmol, 2.2 equiv) fueron agregados y la mezcla de reacción fue agitada durante 60 h, pero el TLC mostró que la reacción fue solamente 25% completa. La mezcla de reacción fue calentada a reflujo durante 24h. Más cloroformato de bencilo (0.611 mL, 4.28 mmol, 1.1 equiv) y Na_2CO_3 (0.454 g, 4.28 mmol, 1.1 equiv) fue agregado. La mezcla de reacción fue calentada a reflujo durante 24 h más, dejada enfriar, diluida con EtOAc (200 mL, lavada con la mitad de salmuera saturada (2 x 40 mL), secada sobre $MgSO_4$, filtrada y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 3→5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.383 g, 35%) como un sólido blanco: ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 3.3L.3.35 (m, 2H), 5.06 (s, 2H), 6.83 (d, 1H, J= 6.7), 7.17 (d, 1H, J= 6.7), 7.28-7.39 (m, 5H); Anal. $C_{14}H_{14}N_2O_3$: C, H, N.

Preparación del Compuesto 12

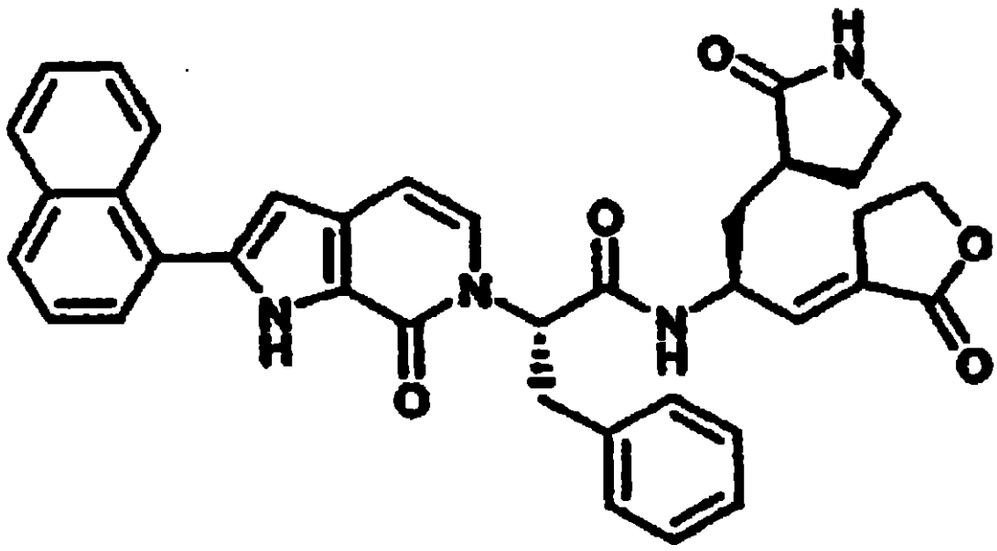
El intermediario precedente fue convertido a compuesto 12 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico y C1 (Ejemplo 5) donde fuere apropiado: IR cm^{-1}) 3284, 1684 (br), 1596, 1327, (br), 1308, 1267, 1237; ^{1}HNMR (CDC_3) δ 1.29 (t, 3H, *J*= 7.1), 1.55-1.68 (m, 1H), 1.82-2.07 (m, 4H), 2.14 (s, 3H), 3.08 (dd, 1H, *J*= 13.6,7.1), 3.47 dd, *J*= 13.6, 8.8), 4.17 (q, 2H, *J*= 7.1), 4.41-4.52 (m, 1H), 5.06 (d, 1H, *J*= 12.3), 5.12 (d, H, *J*= 12.3), 5.59 (dd, 1H, *J*= 15.7,1.6), 5.67-5.74 (m, 1H), 5.90 (s, 1H), 6.02 (s, 1H), 6.17 d, 1H, *J*= 7.3), 6.68 (dd, 1H, *J*= 15.7, 5.1), 7.01 (s, 1H), 7.13-7.38 (m, 10H), 7.48 (d, 1H, *J* = 7.3); Anal. $C_{32}H_{38}N_4O_7 \cdot 0.75H_2O$: C, H, N.

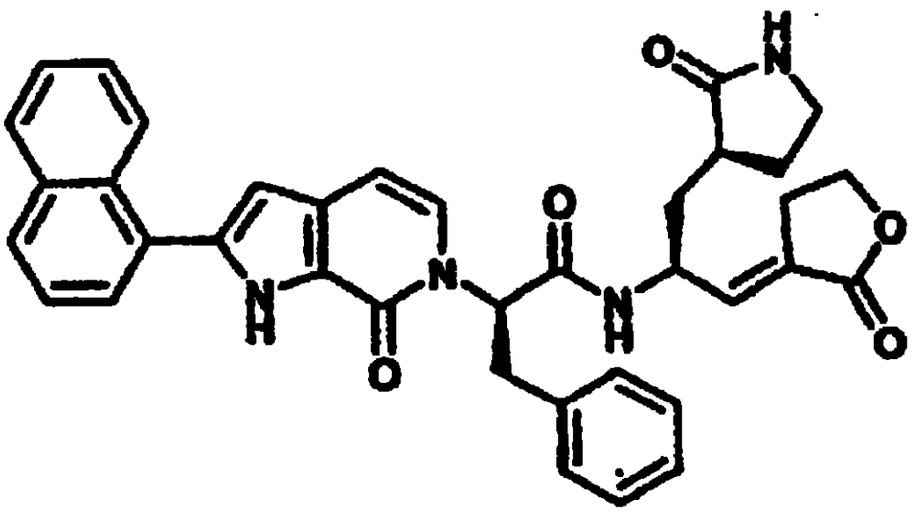
EJEMPLO 13

Preparación de 1:1 mezcla del Compuesto 13: trans-(2S,2''S,3S)-2-(2'-Naftalen-1'-il-7'-oxo-1',7'-dihidropirrolo[2',3'-c]piridin-6'-il)-N-

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[2''-(2'''-oxodihidrofurán-3'''-lideno)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]-3-fenilpropionamida y Compuesto 14: trans-(2R,2''S,3S)-2-(2'-Naftalen-1'-il-7'-oxo-1',7'-dihidropirrolo[2',3'-c]piridin-6'-il)-N-[2''-(2'''-oxodihidrofurán-3'''- lideno)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]-3-fenilpropionamida





Preparación del Intermediario Pirrol-2-Ester de Metilo de Ácido carboxílico

Pirrol-2-ácido carboxílico (10.0 g, 90.0 mmol) en éter de dietilo (200 mL) fue tratado con diazometano (270 mmol, generado

de N-nitroso-N-metil úrea), entonces la parte trasera tritada con ácido acético hasta cuando el color amarillo se disipó. La solución fue lavada con bicarbonato de sodio acuoso (3 x 20 mL), seguido por salmuera (3 x 20 mL) entonces fue evaporado para obtener 10 g (88%) de producto. ^{1}H NMR (CDCls) δ 3.86 (s, 3H), 6.26-6.29 (m, 1H), 6.91-6.94 (m, 1H), 6.65-6.98 (m, 1H), 9.14 (s, 1H).

Preparación del Intermediario 5-Bromo-1H-pirrol-2-Ester de Metilo de Ácido carboxílico

Una solución del intermediario precedente (10.0 g, 79.9 mmol, 1 equiv) en tetracloruro de carbono (300 mL) fue calentada a 70°C, entonces tratada gota a gota con una solución de bromuro (126.0 mL, 99.9 mmol, 1.25 equiv) en tetracloruro de carbóno (200 mL). La reacción fue iniciada por la adición de yodo (40 mg). Después que la adición estuvo completa, la reacción fue mantenida a 70°C durante 10 min, entonces enfriada a 23°C usando un baño de hielo. La mezcla fue lavada con 10% con carbonato de sodio acuoso (100 mL), seguida por agua (100 mL). Los volátiles fueron evaporados, y el residuo fue purificado por cromatografía de gel de sílice para obtener 4.5 g (27%) de producto: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.23 (dd, 1H, *J*= 3.8,2.6), 6.80 (dd, 1H, *J*= 3.9,2.7), 9.29 (s, 1H).

Preparación del Intermediario 5-Naftalen-1-il-1H-pirrol-2-Ester de Metilo de Ácido carboxílico

Gas de argón fue bombeado durante 15 min a través de una solución del intermediario precedente (2.04 g, 10.0 mmol, 1 equiv) en 2 M de carbonato de sodio acuoso (20 mL), y DMF (150 mL). La mezcla fue tratada con tris(dibencilidenacetona)dipaladio (0) (0.46 g, 0.50 mmol, 0.05 equiv), y trifenilarsina (0.61 g, 2.0 mmol, 0.20 equiv), entonces calentada a reflujo, bajo argón, durante 12 h. La mezcla fue tomada en acetato de etilo (500 mL) y agua (150 mL), entonces filtrada a través de celite. La capa orgánica fue lavada con salmuera (3 x 50 mL), entonces evaporada. La purificación del residuo por cromatografía de gel de sílice rindió 2.05 g (81%) del producto. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.22 (dd, 1H, *J*= 3.8.2.6),

7.50-7.59 (m, 4H), 7.88 (dd, 1H, *J*= 3.9,2.7), 7.89-8.16 (m, 2H), 8.17-8.22 (m, 1H), 9.37 (s. 1H). Este material fue tomado en 1:1 1,4-dioxano-agua (30 mL), y tratado con hidrato de hidroxido de litio (1.02 g, 24.4 mmol, 2.4 equiv), entonces calentada a reflujo durante 15 min. La solución fue acidificada con 20% ácido cítrico acuoso (30 mL), entonces extractada con acetato de etilo (75 mL). La capa orgánica fue lavada con salmuera (2 x 20 mL), entonces evaporada. El residuo fue tomado en CH_2Cl_2, (30 mL), y tratada con cloruro de oxalilo (2.10 mL, 24.0 mmol, 2.4 equiv), y DMF (una gota), entonces calentada a reflujo durante 30 min. La evaporación rindió 6-naftalen-1-il-1H-pirrol-2-cloruro de ácido carboxílico el cual fue usado en el procedimiento subsiguiente sin purificación adicional.

Preparación del Producto 13 y 14

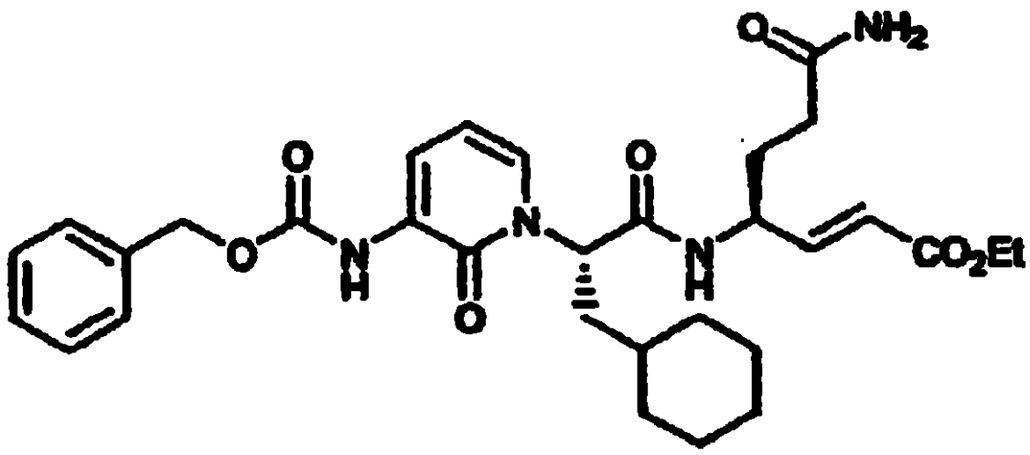
El intermediario precedente fue convertido a una inseparable mezcla de 1:1 de los compuestos del título por un proceso que fue análogo a aquel descrito en el Ejemplo 3 para la conversión de pirrol-2-cloruro de carbonilo a compuestos 3 y 4 y utilizando intermediario YI (Ejemplo 22) en lugar deY2 donde fuere apropiado. ^{1}H NMR ($CDCl_3$) δ 1.55-2.00 (m, 6H), 2.50-3.50 (m, 7H), 4.00-4.50 (m, 3H), 4.42-5.60 (m, 1H), 5.90-8.40 (m, 15H), 10.49 (s, 0.5H), 11.54 (s, 0.5H).

EXAMPLE 14

Preparación del Compuesto 15: trans-(2'S,4S)-4-[2'-(3''-Benciloxicarbonilamino-2''-oxo-2''H-piridin-1''-il)-3'- ciclohexilpropioniamino]-6-carbamoil-hex-2-Ester de Etilo de Ácido enóico

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Preparación del Intermediario (2R)-3-Ciclohexil-2-Ácido hidroxipropiónico

Boc-D-Ciclohexilalanina-OH (3.00 g, 11.1 mmol, 1 equiv) fue disuelto en 1,4-dioxano (10 mL), y una solución de HCl en 1,4-dioxano (4.0 M, 10 mL) fue agregada. La reacción fue agitada a 23 °C durante 5 h, entonces el solvente fue removido bajo presión reducida. El residuo fue disuelto en 1 M H_2SO_2 (22 mL), enfriado hasta O °C y 2 N $NaNO_2$ (22 mL) fue agregado vía tunel de adición bajo argón. La mezcla de reacción fue agitada a O °C durante 3 h y calentada a temperatura ambiente toda la noche. La mezcla resultante fue extractada con MTI (3 x 40 mL), secada sobre Na_2SO_4 y concentrada. El residuo fue triturado con éter de petróleo, filtrado y secado en el aire para proporcionar el intermediario del título (0.6 g, 31%) como un sólido casi blanco. ^1H NMR (DMSO-d_6) δ 3.09-3.24 (m, 2H), 4.20-4.24 (m, 1H), 7.13-7.18 (m, 1H), 7.38-7.47 (m, 2H), 8.49 (s, br. 1H).

Preparación del Compuesto 15

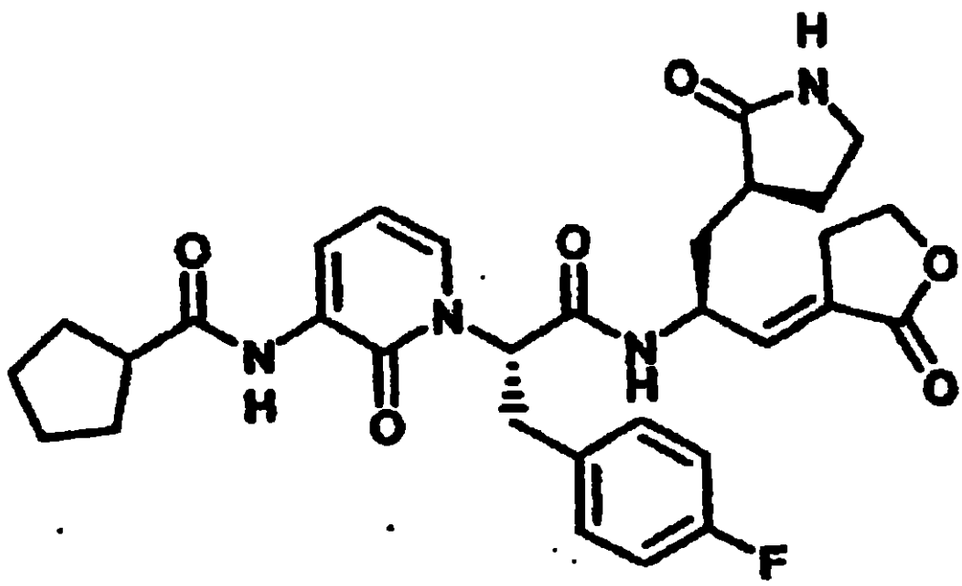
El intermediario C1 (Ejemplo 5) fue convertido a producto 15 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando (2R)-3-ciclohexil-2-ácido hidroxipropiónico (Ejemplo 14) donde fuere apropiado: mp = 64-66 ^oC; IR (cm^{-1}) 3302, 2925, 1721, 1651, 1197; ^1H NMR ($CDCl_3$)

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δ 0.93-1.05 (m,2H), 1.18-1.22 (m, 4H), 1.32 (t, 3H, *J*= 7.2), 1.66-1.75 (m, 4H), 1.82-1.91 (m, 2H), 1.94-2.06 (m, 2H), 2.10-2.17 (m, 2H), 2.90-2.92 (m, 2H), 4.23 (q, 2H, *J*= 7.2), 4.52-4.60 (m, 1H), 5.23 (s, 2H), 5.65 (t, 1H,J= 8.1), 5.82-5.86 (m, 1H), 5.62 (dd, 1H, *J*= 15.9,1.8), 6.01-6.05 (m, 1H), 6.37 (t, 1H,7= 7.2), 6.85 (dd, 1H,,*J*= 15.9, 5.7), 7.25-7.29 (m, 1H), 7.36-7.43 (m, 5H), 7.88 (s, br. 1H), 8.09 (d, 1H, J° 6.9); Anal. $C_{31}H_{40}N_4O_7 \cdot 1.0H_2O$: C, H, N.

EJEMPLO 16

Preparación del Compuesto 16: trans-(2'S,2'''S,3'''''S)-Ácido ciclopentanocarboxílico (l-{2'-(4"-fluorofenil)-1'-[2"-(2""-oxo-dihidrofurán-3""-ilideno)-1""-(2"""-oxopirrolidin-3"""-ilmetil) etilcarbamoil]etil}-2-oxo-l ,2-dihidropiridin-3-il)amida



Preparación del Intermediario de Ácido Ciclopentanocarboxílico (2-Hidroxipiridin-3-il)amida

Una muestra de 10% Pd sobre C (0.40 g) fue agregada a una solución de 2-hidroxi-3-nitropiridina (3.52 g, 25.0 mmol, 1 equiv) en EtOH. La mezcla de reacción fue agitada a temperatura ambiente

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bajo atmósfera de H_2 (aerostato) toda la noche y entonces fue filtrada a traves de Celita. El filtrado fue concentrado bajo presión reducida. EL residuo fue disuelto en CH_3CN (100 mL), enfriada hasta O ^oC, cloruro de ciclopentanocarbonilo (25 mmol, 3.04 mL, 1 equiv) y NMM (2.75 mL, 25 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla resultante fue agitada a O ^oC durante 20 min, entonces fue partida entre agua (400 mL) y 10% CH_3OH en CH_2Cl_2 (2 x 400 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4, concentrada, y el residuo resultante recristalizado de CH_2Cl_2/hexanos para proporcionar el intermediario del título como un sólido casi blanco (3.36 g, 65%); mp = 242-243 ^oC; IR (cm^{-1}) 3263, 644, 1605, 1521, 1199; ^1H NMR (DMSO-d_6) δ 1.51-1.57 (m,2H), 1.60-1.72(m, 4H), 1.79-1.88 (m, 2H), 2.98-3.08 (m, 1H), 6.20 (t, 1H, *J* = 6.9), 7.08 (d, 1H, *J*= 6.6), 8.23 (d, 1H, *J*= 7.5), 9.02 (s, br. 1H), 11.95 (s, br. 1H); $C_{11}H_{14}N_2O_2$: C, H, N.

Preparación del Compuesto 16

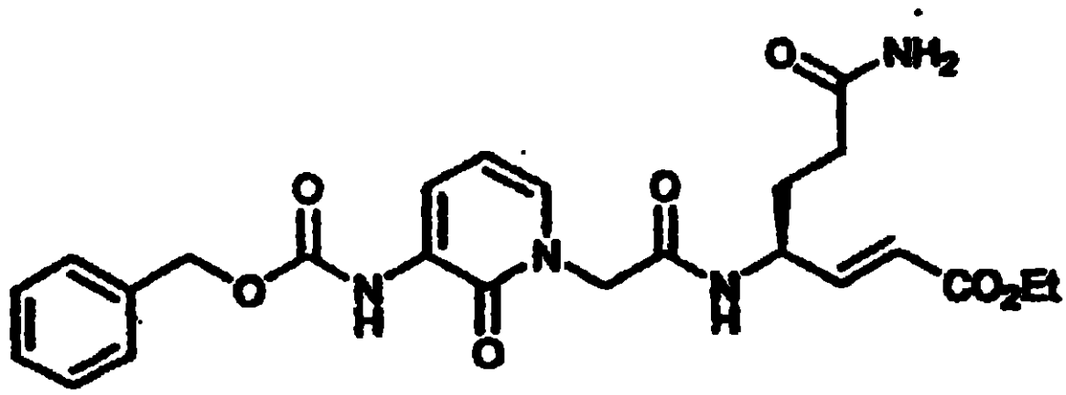
El intermediario precedente fue convertido a compuesto 16 por un proceso que fue análogo a aquel descrito en el Ejemplo 19 para la conversión de F2 a R1: mp =135-137 °C; IR (cm^{-1}) 3288, 2954, 1754, 1682, 1511, 1219; ^1H NMR ($CDCl_3$) δ 0.84-0.93 (m, 2H), 1.55-1.66 (m, 4H), 1.82-2.02 (m, 5H), 2.27-3.22 (m, 2H), 2.70-2.89 (m, 3H), 3.09-3.17 (m, 1H), 3.20-3.37 (m, 2H), 3.42-3.39 (m, 1H), 5.63 (t, 1H, *J*= 7.2), 6.03 (s, br. 1H), 6.25-6.35 (m, 2H), 6.94 (t, 2H, *J*= 8.7), 7.08-7.12 (m, 2H), 7.25 (d, 1H, J= 9.0), 8.30-8.36 (m, 2H), 8.44 (d, 1H, *J*= 6.0); Anal. $C_{31}H_{38}FN_4O_6 \cdot 1.0H_2O$: C, H, N.

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EJEMPLO 16

Preparación del Compuesto 17: trans-(4S)-4-[2'-(3"-Benciloxicarboniiamino-2"-oxo-2"H-piridin-1"-il)acetilamino]-6-cerbamoilhex-2-Ester de Etilo de Ácido enico

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Preparación del intermediario (3-benciloxicarboniiamino-2-oxo-2h-piridin-1-il)ester de tert-butilo de ácido acético

Hidruro de sodio (0.070 g de una suspensión 60% en aceite mienral, 1.75 mmol, 1.0 equiv) fue agregada a una solución de (2-hidroxipiridin-3-il)ester de bencilo de ácido carbámico (preparado tal como se describió en el Ejemplo 1) (0.415 g, 1.70 mmol, 1 equiv) en THF (20 mL) a O °C. La mezcla de reacción fue agitada durante 20 min a O °C, entonces bromoacetato de tert-butilo (0.275 mL, 1.86 mmol, 1.1 equiv) fue agregado. La reacción de mezcla fue calentada a 23 °C durante 45 min, entonces fue particionada entre 0.5 M HC1 (150 mL) and EtOAc (2 x 100 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4 y fueron concentradas. Purificación del residuo por comratografía de columna de destello (30% EtOAc en hexanos) proporciona el compuesto del título (0.485 g, 85%) como un sólido casi blanco: mp=88-90°C; IR (cm^{-1}) 3380, 1739, 1652, 1604; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 4.57 (s, 2H), 5.20 (s, 2H), 6.25 (t, 1H, *J*= 7.1), 6.87 (dd, 1H, *J*= 6.9,1.7), 7 27-7.41 (m, 5H), 7.86 (s, br, 1H), 8.05 (d, br, 1H J= 6.8); Anal. $C_{19}H_{22}N_2O_5$: C, H, N.

Preperación del intermediario (3-Benciloxicarboniiamino- 2-oxo-2H-piridin-1 -il)Ácido acético

(3-Benciloxicarboniiamino-2-oxo-2H-piridin-1-il) éster de tert-butilo de ácido acético (0,485 g, 1.35 mmol) fue agitada de una mezcla 1:1 de ácido trifluoroacético and CH_2Cl_2 a 23 °C durante 1

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h. Los volátiles entonces fueron removidos bajo presión reducida y el residuo fue triturado con Et_2O (40 mL). El sólido resultante fuefiltrado a través de una firtura media, lavada con Et_2O (20 mL) y secada al aire para dar el intermediario del titulo (0.315 g, 77%): mp =171-173 °C; ^1H NMR (DMSO-d_6) δ 4.67 (s, 2H), 5.15 (s, 2H), 6.28 (t, *IH*,*J*= 7.1), 7.29-7.43 (m, 7H), 7.85 (dd, 1H,J= 7.4,1.7), 8.47 (s, 1H).

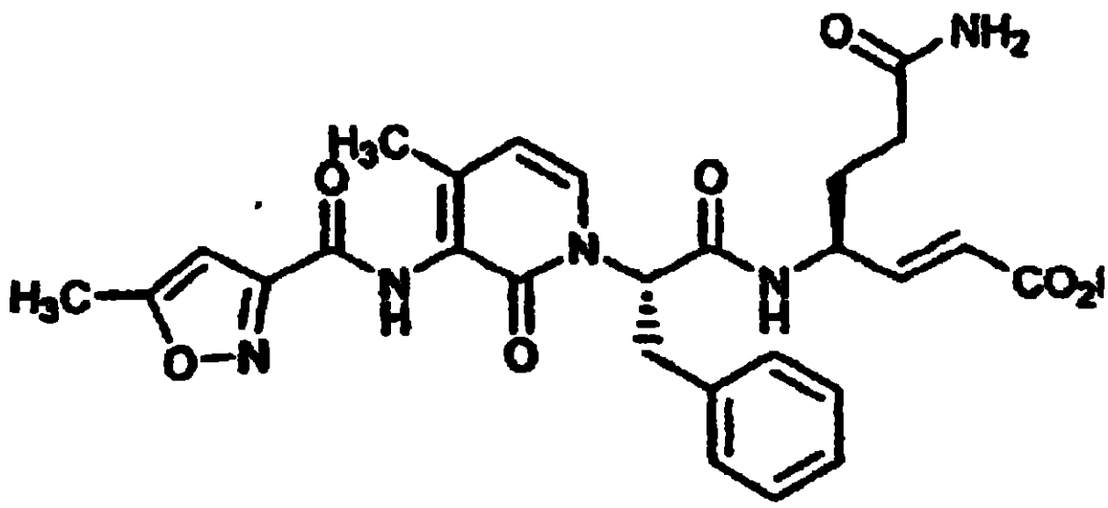
Preparation of Compound 17

El intermediario precedente fue convertido a compuesto 17 por un proceso análogo a aquel descrito en el Ejemplo 23 para la conversión de W2 a J2: mp = 169-174 °C; IR (cm^{-1}) 3273, 1719, 1649; ^1H NMR (DMSO-d_6) δ 1.19 (t,3H,J= 7.1), 1.64-1.85 (m,2H), 2.10(t, 2H,J=7.8),4.11 (q,2H,J=7.J), 4.38-4.41 (m, IH),4.60(d, 1H,^= 15.5), 4.67 (d, 1H, *J*=15.5),5.15 (s, 2H), 5.92 (dd, 1H, *J*=15.8,1.3), 6.26 (t, 1H,J= 7.1), 6.76-6.83 (m,2H), 7.09-7.42 (m, 7H), 7.84 (d, 1H, *J*=7.3), 8.41-8.44 (m, 2H); Anal. $C_{24}H_{28}N_4O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 17

Preparación del Compuesto 18: trans-(2'S,4S)-6-Carbamoil-4-(2'-{4"-metil-3"-[5"'-metilisoxazol-3""-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3'- fenilpropionilamino)hex-2-Ester de Etilo de Ácido enóico

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Preparación del Intermediario 5-Metilisoxazol-3-Ácido carboxílico (2' -hidroxi-4'-metilpiridin-3' -il)amide

Una muestra de 10% Pd sobre C (0.35g) fue agregada a una solución de 2-hidroxi-3-nitropiridina (2.03 g, 14.5 mmol, 1 equiv) en EtOH. La mezcla de reacción fue agitada a temperatura ambiente bajo atmósfera H_2 (aerostato) toda la noche y entonces fue filtrada a través de Celita. El filtrado fue concentrado bajo presion reducida. El residuo fue disuelto en CH_3CN (100 mL), enfriada a O °C, y 5-metilisoxazol-3-cloruro de carbonilo (2.11 g, 14.5 mmol, 1 equiv) y NMM (1.51 mL, 14.5 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla resultante fue agitada a O °C durante 20 min, y entonces fue partida por medio de agua (400 mL) y 10% CH_3OH en CH_2Cl_2 (2 x 400 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4, concentrada y el residuo resultante fue recristalizado de CH_2Cl_2/hexanos para proporcionar el intermediario del título como un sólido casi blanco (2.42 g, 76%): IR (cm^{-1}) 3330, 1650, 1536; ^1H NMR (DMSO-d_6) δ 3.34 (s, 3H). 6.31 (t, 1H, *J*=6.6), 6.73 (s, 1H), 7.21 (d, 1H, *J*= 7.2), 8.29 (s, 1H, *J*=7.2), 9.46 (s, br. 1H), 12.23 (s, br. 1H).

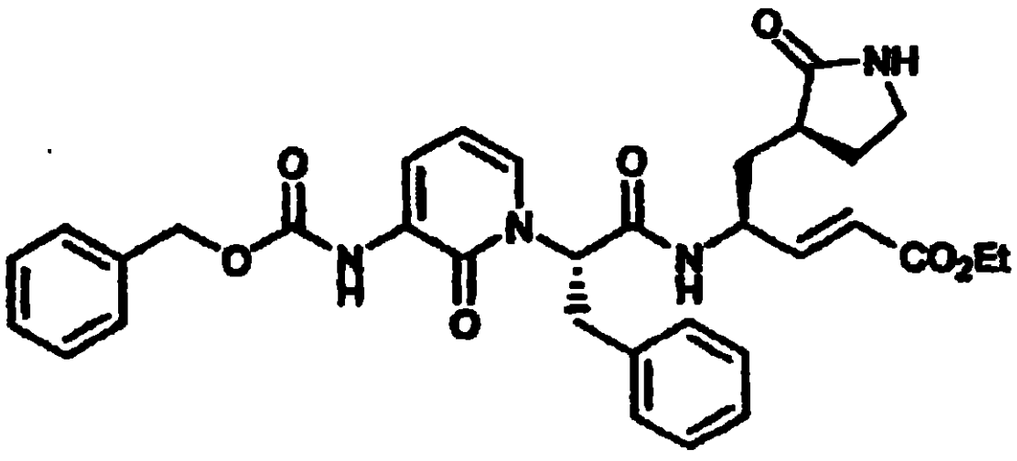
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Preparación del Compuesto 18

El intermediario precedente fue convertido a compuesto 18 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a Compuesto 7 utilizando (2R)-2-hidroxi-3-ácido fenilpropiónico donde fuere apropiado: mp = 138-141°C; IR (cm^{-1}) 3289, 1663, 1542, 1203; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, *J*=7.2), 1.62-1.89 (m, 2H), 1.99 (s, 3H), 2.02-2.07 (m, 1H), 2.47 (s, 3H), 3.03-3.39 (m, 5H), 4.12 (q, 2H,*J*= 7.2), 4.32-4.41 (m, 1H), 5.76 (dd, 1H, *J*=15.6,1.5), 5.80-5.83 (m, 1H), 6.13 (d, 1H, *J*=7.5), 6.60 (s, br. 1H), 6.75 (dd, 1H, *J*=15.6,5.4), 7.15-7.24 (m, 5H), 7.76 (d, 1H, *J*= 7.2), 8.65 (d, 1H, *J*=7.8), 9.59 (s, br. 1H); $C_{29}H_{33}N_5O_7$•1.5TFA: C, H, N.

EJEMPLO 19

Preparación del Compuesto 19: trans-(2'S,3'''S,4S)-4-[2'- (3''-Benciloxi- carboniiamino-2''-oxo-2''H-piridin-1'' -il)-3'-fenilpropioniiamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Ácido enóico



El compuesto del título fue preparado de K1 (Ejemplo 19) por un proceso análogo a aquel descrito en el Ejemplo 19 para la conversión de K1 a R1 utilizando el comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico, (2-hidroxipyridin-3-il)éster de bencilo de ácido carbámico (Ejemplo 2), y el comercialmente

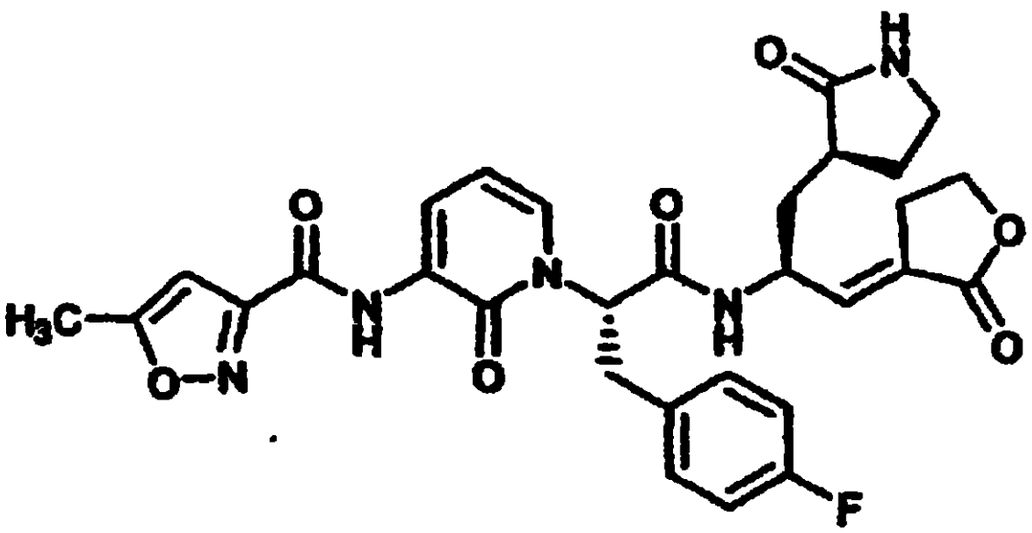
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disponible (carbetoximetileno)-trifenilfosforano donde fuere apropiado: IR (cm^{-1}) 3272, 1684 (br), 1590, 1514, 1273, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.42-1.55 (m, 1H), 1.59-1.75 (m, 1H), 2.00-2.27 (m, 3H), 3.07-3.28 (m, 3H), 3.43 (dd, 1H, *J*= 13.7,7.3), 4.19 (q, 2H, *J*= 7.1), 4.36-4.47 (m, 1H), 5.12-5.21 (m, 2H), 5.75 (dd, 1H, *J*= 15.6,1.2), 5.85-5.94 (m, 1H), 6.26 (t, 1H, *J*= 7.2), 6.58 (s, 1H), 6.70 (dd, 1H, *J*= 15.6, 5.7), 7.10-7.41 (m, 10H), 7.44-7.50 (m, 1H), 7.71 (s, 1H), 7.97 (d, 1H *J*= 6.2), 8.28 (d, 1H, *J*= 6.8); Anal. $C_{33}H_{38}N_4O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 19

Preparación del Compuesto 20: trans-(2''S,2''''S,3''''''S)-Metilisoxazol-3- Ácido carboxílico(1'-{2''-(4'''-fluorofenil)-1''-[2''''-(2''''''-oxodihidrofurán-3''''''-ilideno)-1''''-(2''''''-oxopirrolidin-3''''''-ilmetil)etilcarbamoil]etil}-2'-oxo-1',2'-dihidropiridin-3'-il)amida (R1)



Preparación del Intermediario (1S,3'S)-{2-(tert-Butildifenilsilaniloxi)-1-[1'-(2'',4''-dimetoxibencil-2'-oxopirrolidin-3'-ilmetil]etil} Ester de tert-Butilo de Ácido carbámico (L1)

El intermediario K1 (4.41 g, 10.8 mmol, 1 equiv) fue agitado en CH_2Cl_2 (50 mL) y la mezcla fue congelada a 0°C. Trietilamino

(7.52 mL, 54.0 mmol, 5 equiv), terl-butilclorodifenilsilano (5.53 mL, 21.6 mmol, 2 equiv) y 4-(dimetilamino)piridina (0.330 g, 2.70 mmol, 0.25 equiv) fueron agregados sucesivamente. La mezcla fue dejada calentar a 23 °C y fue agitado durante 2 h. Este fue entonces diluido con MTBE (400 mL), lavada con salmuera (2 x 100 mL), secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello para proporcionar el intermediario del título (3.51 g, 50%) como una espuma blanca: IR (cm^{-1}) 3319, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.42 (s, 9H), 1.44-1.65 (m, 2H), 2.05-2.17 (m, 1H), 2.23-2.35 (m, 1H), 2.44-2.56 (m, 1H), 3.14-3.21 (m, 2H), 3.55-3.68 (m, 2H), 3.69-3.81 (m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 4.42 (s, 2H), 4.77 (d, 1H, *J*=9.3), 6.41-6.46 (m, 2H), 7.09-7.13 (m, 1H), 7.34-7.46 (m, 6H), 7.61-7.67 (m. 4H); Anal. $C_{37}H_{50}N_2O_6Si$: C, H, N.

Preparación del Intermediario (1'S,2R,3''S)-N-{2'-(tert-Butildifenilsilanilioxi)-1'- [1''-(2''',4'''-dimetoxibencil)-2''-oxopirrolidin-3''-ilmetil]etil} -2-hidroxi-3-(4''''-fluorofenil)propionamida (M1)

El intermediario L1 de arriba (3.4 g, 5.26 mmol, 1 equiv) fue disuelto en 1,4-dioxano (20 mL) a 23°C. Una solución de HCl en el mismo solvente (4.0 M, 20 mL) fue agregada. Después de la agitación de 75 min, los volátiles fueron evaporados para proporcionar un residuo el cual fue disuelto en CH_3CN (25 mL) y enfriado a 0°C. (2R)-3-(4'-Fluorofenil)-2-ácido hidroxipropiónico (intermediario S1, ver abajo, 0.968 g, 5.26 mmol, 1 equiv), 4-metilmorfolina (1.91 mL, 17.4 mmol, 3.3 equiv) y HATU (2.20 g, 5.79 mmol, 1.1 equiv) fueron agregados sucesivamente y la mezcla de reacción fue dejado calentar a 23°C y agitada 2.5 h. Esta fue entonces diluida con EtOAc (500 mL) y lavada con una mezzcla de salmuera y 10% $KHSO_4$ (3:1,100 mL) y una mezcla de salmuera $NaHCO_3$ (1:1,100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (primero en 5% CH_3OH en CH_2Cl_2, entonces en 3%

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CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.90 g,51%) como una espuma blanca: IR (cm^{-1}) 3389, 3319, 1660, 1508; ^1H NMR ($CDCl_3$) δ 1.04(s, 9H), 1.52-1.66 (m, 2H), 2.02-2.13 (m, 2H), 2.20-2.39 (m, 2H), 2.77-2.86 (m, 1H), 3.07-3.23 (m, 3H), 3.47 (dd, 1H, *J*=9.9,5.9), 3.59 (dd, 1H, *J*=9.9,3.6), 3.77 (s, 3H), 3.78 (s, 3H), 3.99-4.11 (m, 1H), 4.22-4.29 (m, 1H), 4.31-4.41 (m, 2H), 6.36-6.45 (m, 2H), 6.81-6.89 (m, 2H), 7.05 (d, 1H, *J*= 8.0), 7.13-7.22 (m, 3H), 7.34-7.46 (m, 6H), 7.59-7.67 (m, 4H); Anal. $C_{41}H_{49}FN_2O_8Si \cdot 0.25H_2O$: C, H, N.

Preparación del Intermediario (1'S,2R,3"S)-Ácido de Metanosulfónico 1-*{*2'-*tert*- butildifenilsilaniloxi)-1'-[1"-(2"',4"'-dimetoxibencil)-2"-oxopirrolidin-3"- ilmetil]etilcarbamoil}-2-(4""-fluorofenil)Ester de etilo (N1)

El intermediario M1 de arriba (2.13 g, 2.99 mmol, 1 equiv) y iPr_2NEt (0.729 mL, 4.19 mmol, 1.4 equiv) fueron disueltos en CH_2C_2 (35 mL) y enfriados a -10°C. Cloruro de metanosulfónico (0.277 mL, 3.58 mmol, 1.2 equiv) fue agregado gota a gota, lentamente, con agitación vigorosa. Después de 30 min, la mezcla de reacción fue diluida con with MTBE (500 mL), lavada con una mezcla de salmuera y 10% $KHSO_4$ (2:1,100 mL) y salmuera (100 mL), secada sobre Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario 5-Metilisoxazol-3-Ácido carboxílico(2'-hidroxipiridin-3'-il)amida (F2)

Una suspensión de 10% paladio sobre carbono (0.45 g) y 2-hidroxi-3-nitropiridina (7.00 g, 50.0 mmol, 1 equiv) en EtOH (210 mL) fue sometido a una atmósfera de hidrógeno durante 16 horas. Después de la purgación la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-3-aminopiridina el cual fue usado sin más purificación. Este material crudo fue suspendido en CH_3CN

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(170 mL) y enfriada a O°C. 5-Metilisoxazol-3-cloruro de carbonilo (8.00 g, 55.0 mmol, 1 equiv) fue agregada en una parte. Después de 25 min a O°C, la mezcla de reacción fue dejada calentar a 23 °C y agitada durante unos 75 min adicionales. La mezcla espesa fue entonces vertida dentro de dilución HCl (0.02 M, 150 mL) y mezclada vigorosamente. El sólido sin indiluir fue recogido por filtración y lavado con H_2O (2 x 20 mL) entonces secado bajo vacio toda la noche para proporcionar el intermediario del título (7.1 g, 65%): ^{1}H NMR (DMSO-d_6) δ 6 2.48 (s, 3H), 6.29 (dd, 1H, *J*= 7.2, 6.6), 6.69 (s, 1H), 7.19 (dd, 1H, *J*= 6.6, 1.8), 8.26 (dd, IH.*J*= 7.2, 1.8), 9.43 (s, 1H), 12.20 (s, 1H).

Preparación del Intermediario (1'''S,2''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-{2'''-(tert-butildifenilsilaniloxi)-1'''-[1''''-(2''''',4''''')-dimetoxibencil)-2''''-oxopirrolidin-3''''-ilmetil]etilcarbamoil}-2''-(4'''''-fluorofenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (01)

El intermediario F2 de arriba (1.11 g, 5.06 mmol, 1.7 equiv) fue agitada en THF (14 mL). Hidruro de sodio (60% de dispersión de aceite mineral, 0.173 g, 4.32 mmol, 1.45 equiv) fue agregado. Despues de la agitación de 30 min, una solución del intermediario N1 de arriba (1 equiv basada sobre M1) en THF (11 mL) fue agregada. La mezcla resultante fue calentada a reflujo toda la noche, entonces diluida con EtOAc (500 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (3:1,100 mL) y salmuera y $NaHCO_3$ (3:1,100 mL). La fase orgánica fue secada bajo Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH en CH_2Cl_2) para proporcionar el intermediario deseado O1 como una espuma blanca (2.58 g, 95%): IR (cm^{-1}) 3331, 3284, 1666, 1596, 1531, 1455; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.45-1.71 (m, 2H), 1.94-2.32 (m, 3H), 2.52 (s, 3H), 3.07-3.19 (m, 3H), 3.42-3.52 (m, 2H), 3.67-3.74 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.99-4.10 (m, 1H), 430 (d, 1H, *J*= 14.6), 4.39 (d, 1H, *J*=14.6), 5.54-5.63 (m, 1H), 6.25 (t, 1H, *J*=7.3), 6.42-6.50 (m, 3H), 6.81-6.88 (m, 2H), 7.04-7.13 (m, 3H), 7.20-7.26

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(m, 1H), 7.36-7.48 (m, 7H), 7.60-7.68 (m, 4H), 8.40 (dd, 1H, *J*= 7.3, 1.6), 9.60 (s, 1H); Anal. $C_{51}H_{58}FN_5O_8Si$: C, H, N.

Preparation of Intermediate (2''S,2'''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-{1'''-[1''''-(2'''',4''''-dimetoxibencil)-2''''-oxopirrolidin-3''''-ilmetil]-2'''-hidroxietilcarbamoil}-2''-(4'''''-fluorofenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (P1)

El intermediario O1 de arriba (2.51 g, 2.75 mmol, 1 equiv) fue disuelto en una mezcla de CH_3CN (30 mL) y H_2O (1 mL) en un tubo plástico. Ácido hidrofluórico (48%, 5 mL) fue agregado gota a gota. Después de 1 h y 1.5 h, más ácido hidrofluórico (2.5 mL y 2 mL respectivamente) fue agregado. Después de 3.5 h total, la mezcla de reacción fue vertida dentro de $NaHCO_3$ (250 mL) acuoso saturado, extractado con CH_2Cl_2 (3 x 400 mL), secado bajo Na_2SO_4 y evaporado. El residuo fue purificado por cromatografía de columna de destello (5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (1.84 g, 99%) como una espuma blanca: IR (cm^{-1}) 3401 (br), 3331, 1655, 1590, 1531, 1508, 1455, 1208; ^1H NMR ($CDCl_3$) δ 1.47-1.63 (m, 2H), 1.87-1.99 (m, 1H), 2.07-2.18 (m, 1H), 2.33-2.44 (m, 1H), 2.49 (s, 3H), 3.10-3.24 (m, 3H), 3.46-3.56 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.84-3.89 (m, 1H), 3.92-4.03 (m, 1H), 4.19 (d, 1H, *J*= 14.5), 4.39 (d, 1H, *J*= 14.5), 5.54-5.61 (m, 1H), 6.22 (t. 1H, *J*= 7.2), 6.38-6.46 (m, 3H), 6.85-6.93 (m, 2H), 6.99-7.04 (m, 1H), 7.06-7.13 (m, 2H), 7.24 (dd, 1H. .7= 7.2,1.7), 8.33 (d, 1H, .7= 7.3), 8.38 (dd, 1H, *J*=7.2,1.7), 9.54 (s, 1H); Anal. $C_{35}H_{38}FN_5O_8 \cdot 0.5H_2O$: C, H, N.

Preparación del Intermediario trans-(2''S,2'''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-[1'''-[1''''-(2'''',4''''-dimetoxibencil)-2''''-oxopirrolidin-3''''-ilmetil]-2'''-(2-oxociclopentilideno)etilcarbamoil]-2''-(4'''''-fluorofenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (Q1)

El intermediario P1 de arriba (1.76 g, 2.60 mmol, 1 equiv) y comercialmente disponible de Dess-Martin periodinane (1.11 g, 2.60

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mmol, 1 equiv) fueron combinados en CH_2Cl_2 (20 mL) a 23 °C y agitados 2 h. Los volátiles fueron evaporados. El residuo fue suspendido en tolueno y concentrados secos (2 x 25 mL). El residuo resultante fue disuelto en una mezcla de éter de dimetil deglicol de etileno y DMF (5:1,24 mL). 3-(trifenil-λ^5-fosfanilideno)-dihidrofurán-2-ona (preparado en una manera análoga a aquel descrito en Baldwin y otros, *J. Org. Chem.* 1971, vol. 36,1441) (0.902 g, 2.60 mmol, 1 equiv) fue agregado y la mezcla de reacción dejada enfriar, diluida con EtOAc (500 mL), lavada con salmuera (200 mL, 100 mL), secada bajo $MgSO_4$ y evaporada. El residuo fue cromatografiado (elución de gradiente, 2→3% CH_3OH en CH_2Cl_2) entonces recromatografiado (50% EtOAc in CH_2Cl_2) para dar el intermediario del título (1.46 g) contenido con óxido de trifenilfosfina (aproximadamente 35% por peso): ^{1}H NMR ($CDCl_3$) δ 1.47-1.62 (m, 2H), 1.87-1.98 (m, 1H), 2.21-2.31 (m, 1H), 2.38-2.52 (m, 1H), 2.50 (s, 3H), 2.81-2.93 (m, 1H), 3.10-3.33 (m, 4H), 3.50 (dd, 1H, *J*= 14.1, 7.0), 3.76 (s, 3H), 3.77 (s, 3H), 4.19 (d, 1H, *J*= 14.3), 4.29-4.52 (m, 3H), 4.38 (d, 1H, *J*= 14.3), 5.42-5.49 (m, 1H), 6.23 (t, 1H, *J*=- 7.2), 6.27-6.33 (m, 1H), 6.40-6.48 (m, 3H), 10 6.90-6.97 (m, 2H), 7.00-7.12 (m, 3H), 7.15 (dd, 1H, *J*= 7.2,1.6), 8.39 (dd, 1H, *J*= 7.2,1.6), 8.83 (d, 1H, *J*= 5.7), 9.56 (s, 1H).

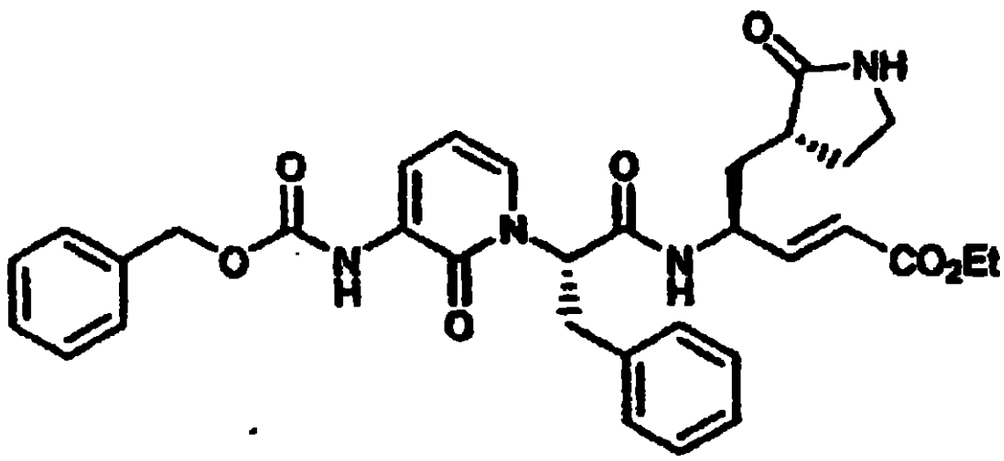
Preparación del Producto R1 (Compound 20)

El intermediario Q1, preparado arriba, fue disuelto en una mezcla de $CHCl_3$ (30 mL) y 15 H_2O (3 mL). DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue agregado y la mezcla de reacción fue calentada en solución de aceite a 60 °C durante 1.5 h. Más DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue agregado y la vasija de reacción fue conservado en una solución de aceite a 60 °C durante 1.5 h más. DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue nuevamente agregado. Despues de la agitación 2 h más, la mezcla de reacción fue dejada enfriar, diluida con CH_2Cl_2 (250 mL), y lavada secuencialmente con una mezcla de salmuera y 20 1 N HCl (2:1,80 mL), una mezcla de salmuera y $NaHCO_3$ (2:1,80 mL) y salmuera

(80 mL). La fase orgánica fue secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (2.5% CH_3OH in CH_2Cl_2) para proporcionar el producto deseado (0.530 g, 73%) como un sólido amorfo casi blanco: IR (cm^{-1}) 3336, 1750, 1682, 1530; ^1H NMR ($CDCl_3$) δ 1.39-1.49 (m, 1H), 1.63-1.80 (m, 1H), 2.09-2.37 (m, 3H), 2.49 (s, 3H), 2.74-2.86 (m, 1H), 25 3.11 (dd, 1H, *J*=13.8,8.5), 3.14-3.38 (m, 3H), 3.39 (dd, 1H, *J*= 13.8, 7.5), 4.30-4.46 (m, 3H), 5.72-5.79 (m, 1H), 6.29 (t, 1H, *J*=7.2), 6.30-6.36 (m, 1H), 6.44-6.47 (m, 1H), 6.77 (s, 1H), 6.88-6.97 (m, 2H), 7.04-7.11 (m, 2H), 7.44-7.50 (m. 1H), 8.37 (dd, 1H, *J*=7.2, 1.6), 8.66 (d, 1H, *J*=6.2), 9.47 (s, 1H); Anal. $C_{30}H_{30}FN_5O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 20

Preparación del Compuesto 21: *trans*-(2'S,3'''R,4S)-4-[2'-(3''-Benciloxicarbonilamino-2''-oxo-2''H-piridin-1''-il)-3'-fenilpropionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Ácido enóico

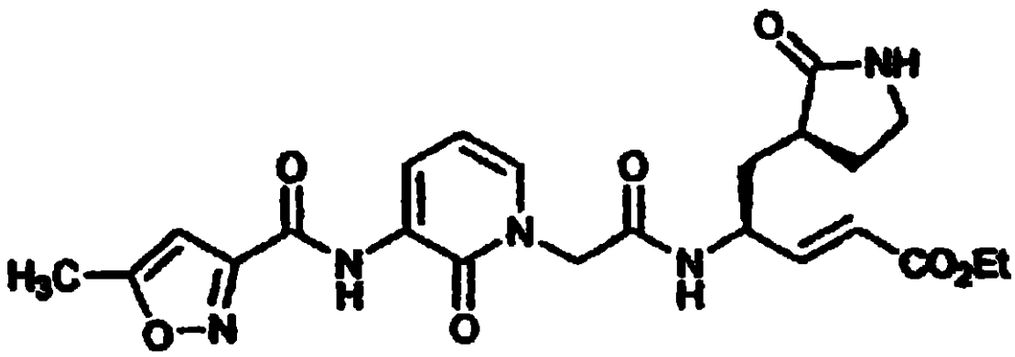


El compuesto del título fue preparado de (2S,3'R)-{1-[1'-(2'',4''-dimetoxibencil)-2'-oxopirrolidin-3'-ilmetil]-2-hidroxietil}éster de terl-butilo de ácido carbámico (preparado tal como se describio en Dragovich, et al. *J. Med. Chem.* 1999, *42*, 1213) por un proceso análogo a aquel descrito en el Ejemplo 19 para la conversión de K1 a R1 utilizando el comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico, (2-hidroxipiridin-

3-il)éster de bencilo de ácido carbámico (Ejemplo 2), y el comercialmente disponible (trifenil-λ^5-fosfanilideno)éster de etilo de ácido acético donde fuere apropiado: IR (cm^{-1}) 3483, 3272, 1684 (br), 1514, 1267, 1196; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*=7.1), 1.48-1.79 (m, 2H), 2.02-2.24 (m, 2H), 2.27-2.39 (m, 1H), 3.12 (dd, 1H, *J*= 13.7, 8.2), 3.19-3.34 (m, 2H), 3.48 (dd, 1H, *J*=13.7, 7.8), 4.19 (q, 2H, *J*=7.1), 4.43-4.53 (m, 1H), 5.17 (s, 2H), 5.73 (dd, 1H, *J*=15.6, 1.3), 5.90-5.98 (m, 1H), 6.27 (t, 1H, *J*=7.1), 6.63 (dd, 1H, *J*=15.6, 6.0), 6.65-6.71 (m, 1H), 7.13-7.27 (m, 6H), 7.31-7.40 (m, 4H), 7.50 (dd, 1H, *J*=7.1, 1.6), 7.75 (s, 1H), 7.97 (d, 1H,J= 6.6), 8.69 (d, 1H, *J*=7.0); Anal. $C_{33}H_{36}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 21

Preparación del Compuesto 22: trans-(4S,3''''S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}acetilamino)-5-(2''''-oxopirrilidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico



Preparación del Intermediario {3-[(5'-Metilisoxazol-3'-carbonil)amino]- 2-oxo-2H-piridin-1-il}Ester de tert-butilo de Ácido acético

Para una solución de 5-metilisoxazol-3-ácido carboxílico (2'-hidroxi-4'-metilpiridin-3'-il)amida (F2, Ejemplo 19) (0.520 g, 2.37 mmol, 1 equiv) en THF (20 mL) a 0 °C fue agregado NaH (0.095 g, 2.37 mmol, 1.0 equiv). La mezcla resultante fue agitada a 0 °C

durante 20 min, y entonces bromoacetato de t-butilo (0.385 mL, 2.61 mmol, 1.1 equiv) fue agregado. La mezcla de reacción fue agitada y calentada a temperatura ambiente durante 30 min, entonces fue partida por medio de 0.5 N HCl (100 mL) y EtOAc (2 x 100 mL). Las capas orgánicas combinadas fueron secadas bajo Na_2SO_4 y fueron concentradas. La purificación del residuo por cormatografía de columna de destello (30% EtOAc en hexanos) proporcionando el intermediario del título (0.628 g, 79%) como un sólido blanco: IR (cm^{-1}) 3343, 1743, 1651, 1581, 1156; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.53 (s, 3H), 4.65 (s, 2H), 6.32 (t, 1H, *J*= 7.2), 6.51 (s, 1H), 7.01 (dd, 1H, *J*=6.9,1.8), 8.50 (dd, IH, *J*=7.5,1.8), 9.63 (s, br. IH); Anal. $C_{16}H_{19}N_3O_5$: C, H, N.

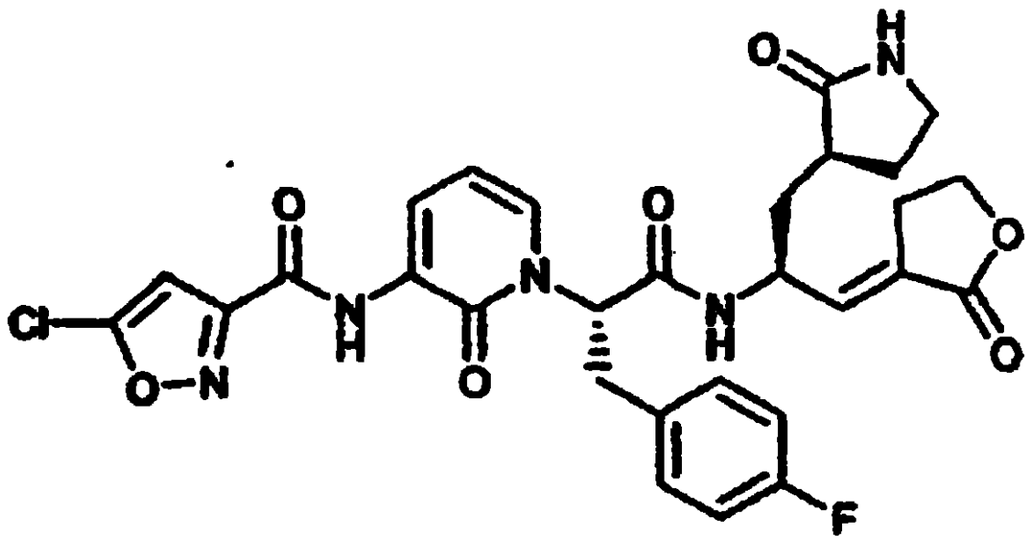
Preparación del Compuesto 22

El intermediario precedente fue transformado en Compuesto 22 por un proceso que fue análogo a aquel descrito en el Ejemplo 25 por la transformación de V3 a producto R3: mp = 102-106°C; IR (cm^{-1}) 3336, 1684, 1534, 1457; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*=7.2), 1.67-1.75 (m, 1H). 1.98-2.09 (m, 1H), 2.37-2.49 (m, 1H), 2.53 (s, 3H), 2.55-2.61 (m, 1H), 3.34-3.46 (m, 2H), 3.51-3.62 (m, IH), 4.17 (q, 2H, *J*=7.2), 4.61-4.78 (m, 3H). 5.98 (dd, 1H, *J*=15.6, 1.5), 6.20 (s, br. 1H), 6.35 (t, 1H, *J*= 7.8), 6.51 (s, IH), 6.85 (dd, 1H, *J*= 15.6, 5.1), 7.17 (d, 1H, *J*= 7.2), 8.33 (d, 1H, *J*= 7.2), 8.49 (d, 1H, *J*= 7.5), 9.57 (s, br. 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 22

Preparación del Compuesto 23: trans-(2''S,2''''S,3''''''S)-5-Cloroisoxazol- 3-Ácido carboxílico (1'-{2''-(4'''-fluorofenil)-1''-[2'''''-oxodihidrofurán-3'''''-ilideno)-1''''-(2''''''-oxopirrolidin-3''''''-ilmetil)etilcarbamoil]etil}-2'-oxo-1',2'-dihidropiridin-3'-il)amida (R2)

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Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ácido hidroxipropiónico (S1)

Este intermediario fue preparado de acuerdo a el método revelado en la solicitud co-pendiente, Solicitud de Patentes Provisional de los E.U. No. 60/150,365, presentada en Agosto 24 de 1999.

Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ester de Metilo de Ácido hidroxipropiónico (T1)

Este intermediario fue preparado tal como se describió en la Solicitud de Patente Provisional co-pendiente de los E.U. No. 60/150,365, presentada en Agosto 24 de 1999.

Preparación del Intermediario (2R)-3-(4-Fluorofenil)-2-trifluorometano- Ester de Metilo de Ácido sulfoniloxipropiónico (U1)

El intermediario T1 de arriba (0.198 g, 1.00 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (6 mL) y enfriada en una solución helada. 2,6-Lutidino (0.198 mL, 1.70 mmol, 1.7 equiv) y anhídrido de trifluorometanosulfónico (0.269 mL, 1.60 mmol, 1.6 equiv) fueron agregados y la mezcla de reacción fue agitada 30 min. Esta fue entonces diluida con MTBE (200 mL), lavada con una mezcla de salmuera y 1 N HCl (2:1, 75 mL) y salmuera (75 mL), secada bajo

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Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación .

Preparación del Intermediario 5-Cloroisoxazol-3-Ester de Etilo de Ácido caroxílico

A una solución de clorooximidoacetato (11.0 g, 72.6 mmol, 1 equiv) en 1,1-dicloroetileno (350 mL) fue agregado Et_3N (25.3 mL, 181 mmol, 2.5 equiv) en 1,1-dicloroetileno (100 mL) vía de tunel de adición sobre 30 min. La mezcla de reacción fue agitado a temperatura ambiente durante 23 h, entonces fue partida por medio de agua (150 mL) y CH_2Cl_2 (2x150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas. El residuo fue purificado por cromatografía de columna de destello (10% EtOAc en hexanos) para dar el intermediario del título (4.49 g, 35%) como un aceite amarillo pálido: IR (cm^{-1}) 1735, 1436, 1253; ^1H NMR ($CDCl_3$) δ 1.45 (t,3H, J=7.2), 4.49 (q, 2H, J=7.2), 7.29 (s, 1H).

Preparación del Intermediario 5-Cloroisoxazol-3-Ácido carboxílico

Una solución acuosa de LiOH (2.0 M, 22.5 mL, 45.0 mmol, 2.0 equiv) fue agregada a una solución del intermediario precendente (3.95 g, 22.5 mmol, 1 equiv) en EtOH (80 mL) a 23 °C. La mezcla resultante fue agitada a temperatura ambiente durante 45 min, entonces los volátiles fueron removidos bajo presión reducida. El residuo humeante obtenido fue partido por medio de 1.0 N HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas para dar el intermediario del título (crudo) (2.84 g, 86%) como un sólido casi blanco el cual fue usado sin más purificación: ^1H NMR (DMSO-d_6) δ 7.15 (s, 1H).

Preparación del Intermediario 5-Cloroisoxazol-3-Cloruro de carbonilo

Una solución 5-cloroisoxazol-3-ácido carboxílico (0.760 g, 4.32 mmol, 1 equiv) y cloruro de tionilo (9.0 mL, 120 mmol, 28 equiv) en CH_2Cl_2 (21 mL) fue calentado a reflujo durante 28 h. Los volátiles fueron evaporados para proporcionar un residuo el cual fue disuelto en benceno (40 mL), el cual fue subsiguientemente evaporado para dar el intermediario del título como un aciete amarillo el cual fue usado sin más purificación.

Preparación del Intermediario 5-Cloroisoxazol-3-Ácido carboxílico (2'-hidroxipiridin-3'-il)amida (F3)

Una suspensión de 10% paladio sobre carbono (0.15 g) y 2-hidroxi-3-nitropiridina (1.70 g, 12.1 mmol, 2.8 equiv) en EtOH (60 mL) fue sometido a una atmósfera de hidrógeno durante 16 horas. Después del purgamiento la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-3-aminopiridina (1.33 g, 99%) el cual fue usado sin más purificación. Una parte de este material (0.524 g, 4.76 mmoL 1.1 equiv) fue combinado con el 5-cloroisoxazol-3-cloruro de carbonilo preparado arriba (4.32 mmol, 1 equiv basado sobre rendimiento teórico) en THF (50 mL) y agitada 60 min. Los volátiles fueron evaporados y el residuo fue agitado en saturación media $NaHCO_3$ (20 mL) durante 30 min. El sólido sin diluir fue recogido por filtración, lavada con H_20 (3 x 5 mL) y secado bajo vacio toda la noche para proporcionar el intermediario del título (0.900 g, 87%) como un sólido tostado el cual fue usado sin más purificación. ^1H NMR (DMSO-d_6) δ 6.30 (t, 1H, J=6.9), 7.22 (dd, 1H, J=6.9, 1.7), 7.25 (s, 1H), 8.24 (dd, 1H, J=6.9, 1.7), 9.47 (s, 1H), 12.22 (s, 1H).

Preparación del Intermediario (2R)-2-{3'-[(5''-Cloroisoxazol-3''-carbonyl)amino]-2'-oxo-2'H-piridin-1'-il}-3-(4'''-fluorofenil) Ester de Metilo de Ácido propiónico (VI)

El intermediario F3 de arriba (0.280 g, 1.17 mmol, 1.17 equiv) fue suspendido en THF (7 mL). Hidruro de sodio (60% de dispersión en aceite mineral, 0.044 g, 1.1 mmol, 1.1 equiv) fue

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agregada en una parte. Después de la agitación 30 min, una solución del intermediario U1 de arriba (1.00 mmol, 1 equiv, basado sobre T1) en THF (10 mL) fue agregado gota a gota. La mezcla resultante fue agitada 16 horas, entonces diluida con MTBE (250 mL) y lavada con salmuera (2 x 80 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado cromatografía de columna de destello (33% EtOAc in hexanos) para proporcionar el intermediario del título (0.316 g, 75%) tal como una espuma blanca: IR (cm^{-1}) 3331 1743, 1690, 1643, 602, 1531,1437; ^1H NMR ($CDCl_3$) δ 3.33 (dd, 1H, *J*=14.5, 10.3), 3.53 (dd, 1H, *J*=14.5, 5.5), 3.78 (s, 3H), 5.36 (dd, 1H, *J*= 10.3, 5.5), 6.18 (t, 1H, *J*=7.2), 6.67 (s, 1H), 6.82 (dd, 1H, *J*= 7.2, 1.7). 6.89-6.97 (m, 2H), 7.01-7.07 (m, 2H), 8.38 (dd, 1H, *J*=7.2, 1.7), 9.52 (s, 1H); Anal. $C_{19}H_{15}ClFN_3O_5$: C, H, N.

Preparation of Intermediate (2R)-2-{3'-[(5''-Cloroisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}-3-(4'''-fluorofenil)Ácido propiónico (W1)

El intermediario V1 de arriba (0.445 g, 1.06 mmol, 1 equiv) fue disuelto en CH_3OH (10 mL). Una solución acuosa de NaOH (1.0 M, 4.2 mL, 4.2 mmol, 4 equiv) fue agregado gota a gota. La mezcla de reacción fue agitada 2 h, entonces vertido dentro de una mezcla de salmuera y 10% $KHSO_4$ (1:1, 50 mL) y extractada con CH_2Cl_2 (3 x 100 mL). Las fases orgánicas combinadas fueron secadas sobre $MgSO_4$ y evaporada para proporcionar el intermediario del título como una espuma amarilla el cual fue usado sin más purificación.

Preparation of Intermediate trans-(2'S,3''S)-3-[2'-Amino-3'-(2''-oxodihidrofurán-3' '-ilideno)propil]pirrolidin-2-ona (Y1)

El intermediario X1 (preparada en una manera análogo a aquel descrito en Baldwin y otros, J *Org. Chem.* 1971, *36*, 1441) (0.413 g, 1.27 mmol, 1.2 equiv) fue agitado deurante 45 min en una

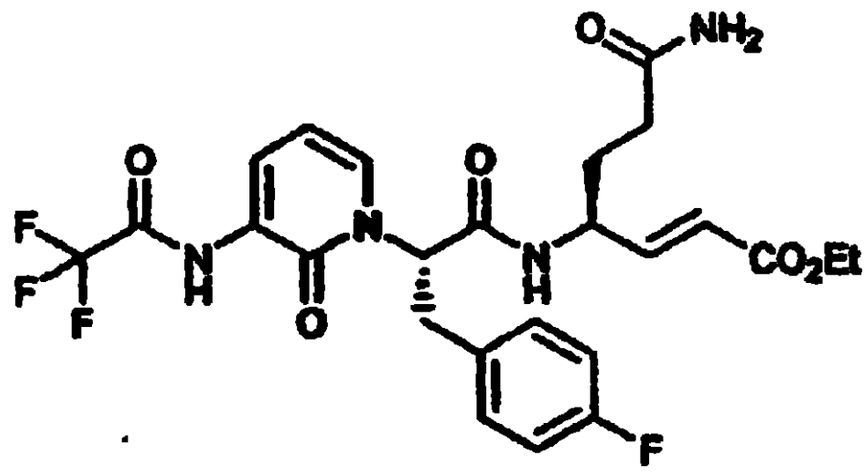
mezcla de TFA (5 mL) en CH_2Cl_2 (10 mL). Entonces los volátiles fueron evaporados para porporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Producto R2 (Compuesto 23)

Los intermediario W1 (1.06 mmol, 1 equiv based on VI) y Y1 (1.27 mmol, 1.2 equiv basada sobre X1) fueron combinados en CH_3CN (14 mL) y enfriada en un baño de hielo. 4-Metilmorfolina (0.583 mL, 5.30 mmol, 5 equiv) y HATU (0.403 g. 1.06 mmol, 1 equiv) fueron agregados y la mezcla de reacción fue dejada calentar a 23 °C y agitada a 1.5 h. Este fue entonces diluido con EtOAc (500 mL) y lavado con una mezcla de salmuera y 10% $KHSO_4$ (3:1, 80 mL), una mezcla de salmuera y $NaHCO_3$ (3:1, 80 mL) y salmuera (80 mL). La fase orgánica fue secada sobre Na_2SO_4 y evaporada. El residuo fue cromatografiado (5% CH_3OH in CH_2Cl_2) entonces recromatografiado (2.5% CH_3OH en CH_2Cl_2) para proporcionar el residuo deseado R2 (0.418 g, 64%) contaminado con un diastereomero (aproximadamente 30%, presumiblemente 2"R epimero): ^1H NMR ($CDCl_3$) (mezcla de isómeros) δ 1.33-1.51 (m), 1.62-1.88 (m), 2.06-2.39 (m), 2.73-2.88 (m), 2.98-3.45 (m), 4.27-4.44 (m), 5.71-5.88 (m), 6.27-6.43 (m), 6.66 (s), 6.68 (s), 6.81 (s), 6.88-6.98 (m), 7.03-7.24 (m), 7.48 (d, *J*= 7.3), 7.55-7.62 (m), 8.34-8.42 (m), 8.65 (d, J= 6.2), 8.77 (d, J= 7.0), 9.41-9.48 (m).

EJEMPLO 23

Preparación del Compuesto 24: trans-(2'S,4S)-6-Carbamoil-4-{3'-(4"-fluorofenil)-2'-[2"'-oxo-3"'-(2"",2"",2""-trifluoroacetilamino)-2"'H-piridin-1"'-il]propioniiamino}hex-2-Ester de Etilo de Ácido enóico (J2)



Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ester de Bencilo de Ácido hidroxipropiónico (T2)

El intermediario S1 (1.00 g, 5.43 mmol, 1 equiv) fue disuelto en CH_3CN (8 mL). 1,8-Diazabiciclo[5.4.0]undec-7-eno (0.812 mL, 5.43 mmol, 1 equiv) y bromuro de bencilo (0.646 mL, 5.43 mmol, 1 equiv) fueron agregados sucesivamente. La solución resultante fue agitada 40 h, entonces diluida con MTBE (250 mL) y lavada con 5% $KHSO_4$ y salmuera (75 mL cada una). La fase orgánica fue secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (1.25 g, 84%) como un aceite sin color el cual se solidifica sobre varios días: IR (cm^{-1}) 3450, 1954, 1890, 1725, 1602; ^1H NMR ($CDCl_3$) δ 2.76-2.81 (m. 1H), 2.94 (dd, 1H, *J*= 14.1,6.2), 3.08 (dd, 1H. *J*=14.1, 4.6), 4.42-4.49 (m, 1H), 5.14 (d, 1H, *J*= 12.1), 5.21 (d, 1H, *J*= 12.1), 6.86-6.94 (m, 2H), 7.03-7.11 (m, 2H), 7.28-7.42 (m, 5H); Anal. $C_{18}H_{15}FO_3$: C, H.

Preparación del Intermediario (2R)-3-(4-Fluorofenil)-2-trifluorometano- Ester de Bencilo de Ácido sulfoniloxipropiónico (U2)

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El intermediario T2 de arriba (0.134 g, 0.489 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (5 mL) y enfriada en un baño helado. 2,6-Lutidina (0.114 mL, 0.979 mmol, 2 equiv) y anhidrido de trifluorometanosulfónico (0.156 mL, 0.927 mmol, 1.9 equiv) fueron agregados y la mezcla de reacción fue agitada 30 min. Este fue entonces diluido con MTBE (150 mL), lavado con una mezcla de salmuera y 1 N HCl (2:1,75 mL) y salmuera (50 mL), secada sobre Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario 2,2,2-Trifluoro-N- (2'-hidroxipiridin-3' -il)acetamida (F4)

TFA (4 mL) fue agregado a una solución de intermediario F1 (0.700 g, 3.33 mmol, 1 equiv) en CH_2Cl_2 (6 mL). Después de la agitación de 30 min, los volátiles fueron evaporados. El residuo fue suspendido en tolueno y concentrado menos seco para proporcionar crudo 2-hidroxi-3-aminopiridina el cual fue (sin más purificación) suspendido en CH_2Cl_2 (14 mL) y enfriado en un baño helado. 4-Metilmorfolina (1.10 mL, 10.0 mmol, 3 equiv) y anhidrido trifluoroacético (0.471 mL, 3.33 mmol, 1 equiv) fueron agregados sucesivamente. Después 30 min, más 4-metilmorfolina (0.550 mL, 5 mmol, 1.5 equiv) fue agregado. La mezcla de reacción fue agitada un adicional 1.5 h, entonces diluida con EtOAc (250 mL) y lavada con salmuera, H20 y salmuera (25 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.173 g, 25%) tal como un sólido amorfo blanco: ^{1}H NMR (DMSO-d_6) δ 6.27 (t, 1H, J= 6.9), 7.32 (dd, 1H, J=6.9, 1.8), 7.94 (dd, 1H, J=6.9, 1.8), 10.16 (s, 1H), 12.20 (s, 1H); Anal. $C_7H_5F_3N_2O_2$: C, H, N.

Preparación del intermediario (2S)-3-(4'-Fluorofenil)-2-[2''-oxo-3''-(2''',2''',2'''- trifluoroacetilamino)-2''H-piridin-1''-il]Ester de Bencilo de Ácido propiónico (V2)

El intermediario F4 de arriba (0.111 g, 0.539 mmol, 1.1 equiv) fue suspendido en THF (3 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.020 g, 0.50 mmol, 1 equiv) fue agregado en una parte. Después de la agitación 30 min, una solución del intermediario U2 (0.489 mmol, 1 equiv, basado sobre T2) en THF (5 mL) fue agregado gota a gota. La mezcla resultante fue agitada 2 horas, entonces diluida con MTBE (150 mL) y lavada con salmuera (2 x 50 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (0.190 g. 84%) como un aceite delgado: IR (cm^{-1}) 3343, 1743, 1727, 1655, 1602, 1296, 1214, 1161; ^1H NMR ($CDCl_3$) δ 3.31 (dd, 1H, *J*=14.4, 10.0). 3.52 (dd, 1H, *J*=14.4, 5.4), 5.21 (s, 2H), 5.39 (dd, 1H, *J*=10.0, 5.4), 6.18 (t, 1H, *J*=7.3), 6.85 (dd, 1H, *J*=7.3, 1.7), 6.87-7-04 (m, 4H), 7.25-7.38 (m, 5H), 8.31 (dd, 1H, *J*=7.3, 1.7), 9.03 (s, 1H); Anal. $C_{23}H_{18}F_4N_2O_4$: C, H, N.

Preparación del Intermediario (2S)-3-(4'-Fluorofenil)-2-[2''-oxo-3''-(2''',2''',2'''-trifluoroacetilamino)-2''H-piridin-1''-il]Ácido propiónico (W2)

Una suspensión de 10% paladio sobre carbono (0.030 g) e intermediario V2 de arriba (0.151 g, 0.327 mmol, 1 equiv) en EtOH (5 mL) fue sometido para una atmósfera de hidrógeno durante 16 horas. Después del purgamiento la vasija de reacción con argón, la mezcla fue filtrado a través del papel Whatman #3 y el filtrado fue evaporado para dar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(4S)-4-Amino-6-(tritilcarbamoil)hex-2-Ester de Etilo de Ácido enóico (AA1)

El intermediario Z1 (preparado de acuerdo a Dragovich, y otros, *J. Med Chem.* 1998, *41*, 2806) (0.177 g, 0.326 mmol, 1 equiv) fue agitado durante 2 h en una solución de HCl en 1,4-dioxano (2.0 M, 8 mL). Entonces los volátiles fueron evaporados para

proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(2'S,4S)-4-{3'-(4''-Fluorofenil)-2'-[2'''-oxo-3'''-(2'''',2'''',2''''-trifluoroacetilamino)-2'''H-piridin-1'''-il]propioniiamino}-6-(tritilcarbamoil)hex-2-Ester de Etilo de Ácido enóico (I3)

Los intermediarios W2 y AA1 (preparado tal como arriba) fueron combinado en CH_2Cl_2 (5 mL) y enfriado en un baño helado. HOBt (0.049 g, 0.36 mmol, 1.1 equiv), iPr_2NEt (0.171 mL, 0.982 mmol, 3 equiv) y EDC (0.063 g, 0.33 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejado calentar a 23 °C toda la noche, entonces diluida con EtOAc (200 mL) y lavado con 5% $KHSO_4$ y salmuera (50 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (44% EtOAc en hexanos) para proporcionar el intermediario del título (0.138 g, 53%) como un sólido blanco amorfo: ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H, *J*=7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.26-2.34 (m, 2H), 3.01-3.10 (m, 1H), 3.31-3.40 (m, 1H), 4.19 (q, 2H, *J*=7.1), 4.46-4.56 (m, 1H), 5.42-5.49 (m, 1H), 5.63 (dd, 1H, *J*=15.7, 1.6), 6.18 (t, 1H, *J*=7.1), 6.62-6.71 (m, 2H), 6.88-6.96 (m, 2H), 7.00-7.06 (m, 2H), 7.10-7.34 (m, 17H), 8.25 (dd, 1H, *J*=7.3, 1.6), 9.02 (s, 1H); Anal. $C_{44}H_{40}F_4N_4O_6$: C, H, N..

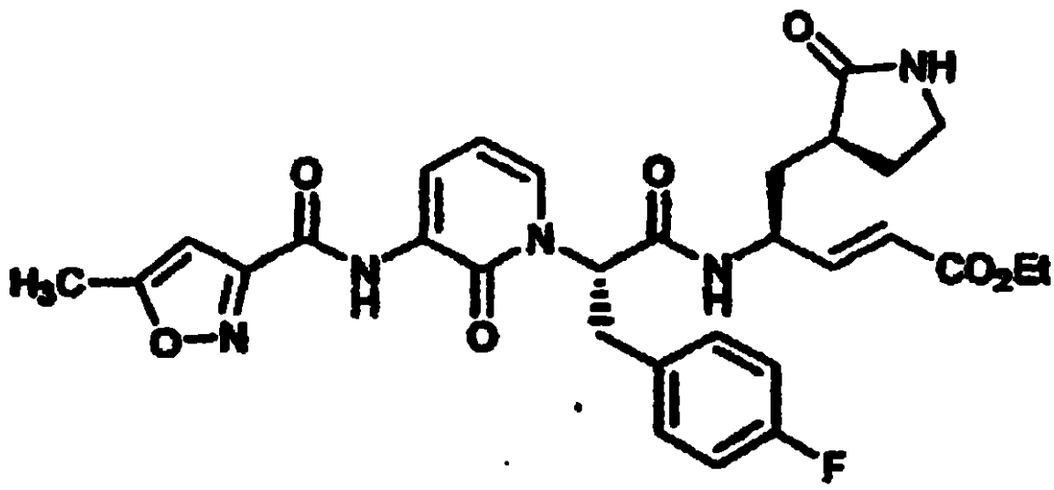
Preparación del Producto J2 (Compuesto 24)

El intermediario I3 de arriba (0.112 g, 0.141 mmol, 1 equiv) y triisopropilsilano (0.086 mL, 0.420 mmol, 3 equiv) fueron combinados en CH_2Cl_2 (4 mL). TFA (2 mL) fue agregado. Después de la agitación 30 min, CCl_4 (4 mL) fue agregado y los volátiles fueron evaporados. El residuo fue purificado por cromatografía de columna de destello (5% CH30H in CH_2Cl_2) para proporcionar el producto deseado (0.078 g, 100%) como un polvo amorfo tostado: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*=7.1), 1.75-1.96 (m, 2H), 2.13-2.30 (m, 2H), 3.12 (dd, 1H, *J*=13.7, 7.5), 3.46 (dd, 1H, *J*=13.7, 8.5), 4.20

(d, 2H, *J*=7.1), 4.45-4.55 (m, 1H), 5.83 (dd, 1H, *J*=15.7, 1.6), 5.66-5.74 (m, 1H), 5.92 (s, 1H), 6.28 (s, 1H), 6.37 (t, 1H, *J*=7.3), 6.67 (dd, 1H, *J*=15.7, 5.7), 6.92-7.00 (m, 2H), 7.09-7.17 (m, 2H), 7.54 (dd, 1H, *J*=7.3, 1.6), 7.60 (d, 1H, *J*=7.5), 8.34 (dd, 1H, *J*=7.3, 1.6), 9.04 (s, 1H); Anal. $C_{25}H_{28}F_4N_4O_6 \cdot 1.25H_2O$: C, H, N.

EJEMPLO 24

Preparación del Compuesto 25: trans-(2'S,3''''S,4S)-4-(3'-(4''-Fluorofenil)-2'- {3'''-[(5''''-metilisoxazol-3''''-carbonil)amino]-2'''-oxo-2'''H-piridin-1'''-il}propioniamino)-5-(2'''''-oxopirrolidin-3'''''-il)pent-2-Ester de Etilo de Ácido enóico

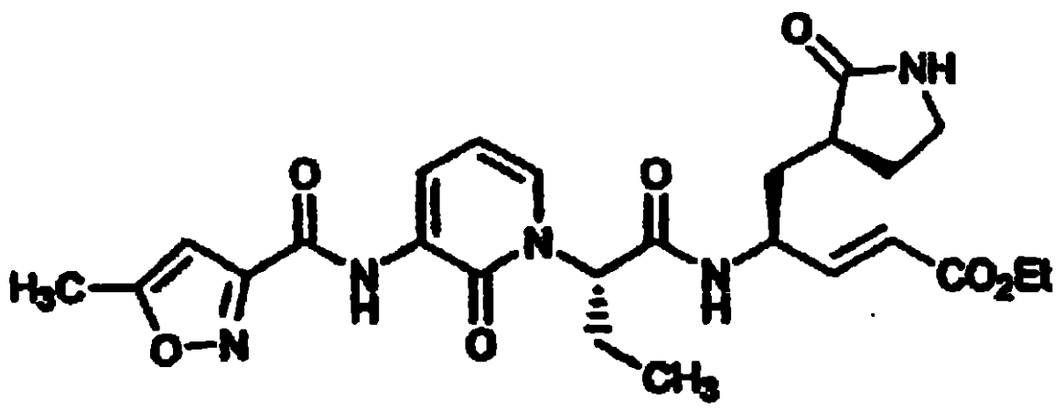


El compuesto del título fue preparado de F2 (Ejemplo 19) en una manera análoga a aquella descrita para la conversión de U2 a I3 en el Ejemplo 23 utilizando intermediario Y2 (Ejemplo 25) donde fuere apropiado: IR(cm^{-1}) 3331, 1690, 1590, 1531, 1455; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.0), 1.45-1.55 (m, 1H), 1.64-1.75 (m, 1H), 2.03-2.31 (m, 3H), 2.49 (s, 3H), 3.10 (dd, 1H, *J*=13.7, 7.9), 3.20-3.46 (m, 3H), 4.20 (q, 2H, *J*=7.0), 4.36-4.47 (m, 1H), 5.67 (dd, 1H, *J*=15.7, 1.4), 5.85-5.92 (m, 1H), 6.29 (t, 1H, *J*=7.2), 6.45 (s, 1H), 6.70 (dd, 1H, *J*=15.7,5.7), 6.86 (s, 1H), 6.90-6.97 (m, 2H), 7.10-7.16 (m, 2H), 7.60 (dd, 1H, *J*=7.2, 1.6), 8.37 (dd, 1H, *J*=7.2, 1.6), 8.51 (d, 1H, *J*=6.6), 9.47 (s, 1H).

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EJEMPLO 26

Preparación del Compuesto 26: *trans*-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metil-isoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}butirilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico (R3)



Preparación del intermediario (2R)-2-Trifluorometanosulfonil-ester de tert-butilo de ácido oxibutírico (U3)

Comercialmente disponible T3 (0.575 g, 3.59 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (25 mL) y enfriada en un baño helado. 2,6-Lutidina (0.836 mL, 7.18 mmol, 2 equiv) anhídrido trifluorometanosulfónico (1.15 mL, 6.84 mmol, 1.9 equiv) fue agregados y la mezcla de reacción fue agitada 30 min. Esta entonces fue diluida con MTBE (400 mL), lavada con una mezcla de salmuera y 1 N HCl (2:1,100 mL) y salmuera (100 mL), secado sobre Na_2SO_4 y evaporado para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario (2S)-2-{3'-[(5''-Metilisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ester de tert-Butilo de Ácido butírico (V3)

El intermediario F2 de arriba (0.200 g, 0-912 mmol, 1.1 equiv) fue suspendido en THF (6 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.0332 g, 0.830 mmol, 1 equiv) fue agregado en una parte. Después de la agitación 30 min, una

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solución del intermediario U3 (0.830 mmol, 1 equiv, basado en T3) en THF (7 mL) fue agregado gota a gota. La mezcla resultante fue agitada 2 horas, entonces diluida con EtOAc (200 mL) y lavada con salmuera (2 x 50 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (0.178 g, 59%) como un aceite: R_f=0.30 (25% EtOAc en hexanos); IR (cm^{-1}) 3331, 1731, 1690, 1649, 1602, 1531; ^1H NMR ($CDCl_3$) δ 50.93 (t, 3H, *J*=7.3), 1.45 (s, 9H), 1.83-2.01 (m, 1H), 2.17-2.31 (m, 1H), 2.50 (s,3H), 5.44-5.51 (m, 1H), 6.32(t, 1H, *J*=7.2), 6.48 (s, 1H), 7.10 (dd, 1H, *J*=7.2, 1.8), 8.45 (dd, 1H, *J*=7.2, 1.8), 9.64 (s, 1H); Anal. $C_{18}H_{23}N_3O_5$: C, H, N.

Preparación del Intermediario (2R)-2-{3'-[(5"-Metilisoxazol-3"-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ácido butírico (W3)

El intermediario V3 de arriba (0.143 g, 0.397 mmol, 1 equiv) fue agitado durante 1 h en una solución TFA (2 mL) en CH_2Cl_2 (3 mL). Los volátiles fueron evaporados. El residuo fue suspendido en tolueno (10 mL) y concentrado menos seco, proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(3'S,4S)-4-Amino-5-(2'-oxopirrolidin-3'-il)pent-2-Ester de Etilo de Ácido enóico (Y2)

El intermediario X2, preparado de acuerdo a el método revelado en la solicitud copendiente, Solicitud de Patente Provisional de los E.U. No. 60/150,358, presentada en Agosto 24 de 1999 (0.130 g, 0.398 mmol, 1 equiv), fue agitado durante 30 min en una solución de TFA (2 mL) en CH_2Cl_2 (3 mL). Los volátiles fueron evaporados. El residuo fue suspendido en tolueno (10 mL) y concentrado menos seco, proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del Compuesto R3 (Compuesto 26)

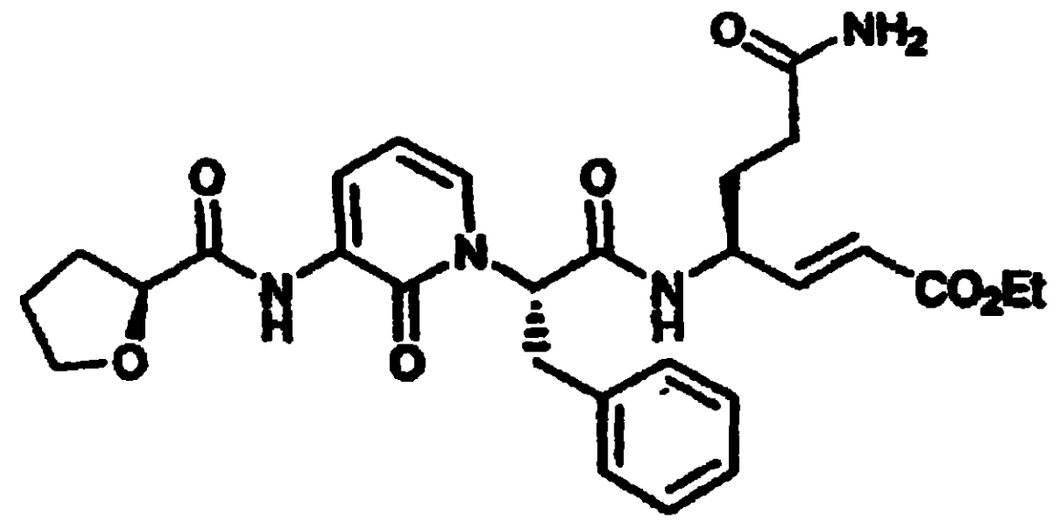
Los intermediarios W3 y Y2 (como preparados arriba) fueron combinados en CH_2Cl_2 (7 mL) y enfriada en un baño helado. HOBt (0.064 g, 0.47 mmol, 1.2 equiv), iPr_2NEt (0.484 mL, 2.78 mmol, 7 equiv) y EDC (0.084 g, 0.44 mmol, 1.1 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejada calentar a 23 °C toda la noche, entonces diluida con EtOAc (500 mL) y lavada con 5% $KHSO_4$, saturado por medio de $NaHCO_3$, y salmuera (100 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evpaorada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.118 g, 58%) como una espuma blanca: IR (cm^{-1}) 3331. 1684, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.3), 1.29 (t, 3H, *J* = 7.1), 1.47-1.58 (m, 1H), 1.62-1.77 (m, 1H), 1.85-2.00 (m, 1H), 2.08-2.33 (m, 4H), 2.49 (s, 3H), 3.25-3.42 (m, 2H), 4.19 (q, 2H, *J* = 7.1), 4.39-4.50 (m, 1H), 5.73 (dd, 1H, *J* = 8.8,6.8), 5.97 (dd, 1H, *J* = 15.7,1.4), 6.34 (t, 1H, *J*= 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J* = 15.7,5.9). 7.18 (s, 1H), 7.59 (dd, 1H, *J* = 7.2,1.8), 8.42 (dd, 1H, *J* = 7.2,1.8), 8.58-8.62 (m, 1H), 9.56 (s, 1); Anal. $C_{25}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

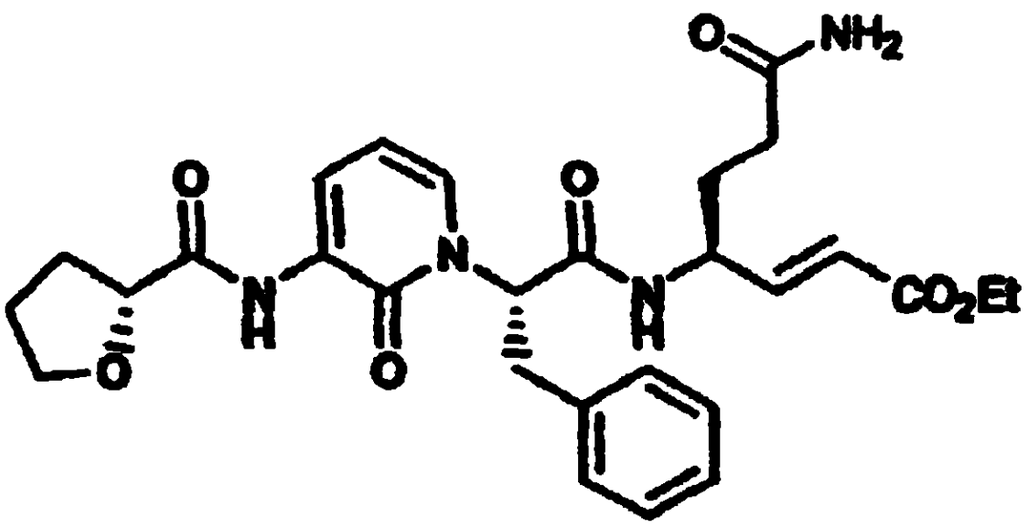
EJEMPLO 26

Preparación de una 1:1 Mezcla del Compuesto 27: trans-(2'S,2'''S,4S)-6-Carbamoil-4-(2'-{2''-oxo-3''-[(tetrahidrofurán-2'''-carbonil)amino]-2''H-piridin-1''-il}-3'-fenilpropioniliamino)hex-2-Ester de Etilo de Ácido enóico y Compuesto 28: trans-(2'S,2'''R,4S)-6-Carbamoil-4-(2'-{2''-oxo-3''-[(tetrahidrofurán-2'''-carbonil)amino]-2''H-piridin-1''-il}-3'-fenilpropioniliamino)hex-2-Ester de Etilo de Ácido enóico

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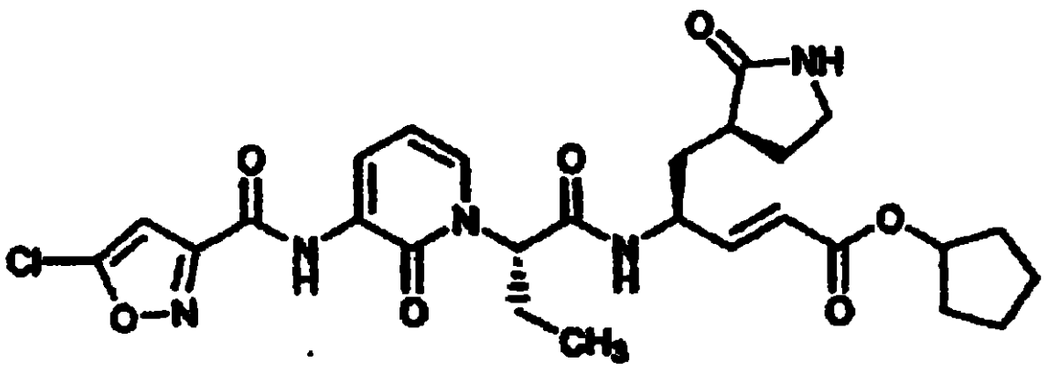
Los compuestos del título fueron preparados de I1 (Ejemplo 5) por un proceso análogo a aquel descrtio en el Ejemplo 5 para la conversiónn de I1 a J1 utilizando el intermediario tetrahidrofurán-2-cloruro de carbonilo (racemic, Aldrich) donde fuere apropiado: IR (cm^{-1}) 3344, 1646, 1519, 1178; ^1H NMR ($CDCl_3$) δ 1.34(t, 3H, *J*=7.2), 1.72-1.82 (m, 1H), 1.95-2.04 (m, 2H), 2.16-2.23 (m, 2H), 2.32-2.43 (m, 1H), 3.18-3.27 (m, 1H), 3.51-3.60 (m, 5H), 3.93-4.00 (m, 1H), 4.05-4.12 (m, 1H), 4.22 (q, 2H,J= 7.20, 4.46-4.55 (m, 2H), 5.54-5.69 (m, 2H), 6.34-6.41 (m, 2H), 6.68 (dd, 1H,J= 15.6,5.4), 6.86-6.93 (m, 1H), 7.17-7.41 (m, 5H), 8.42-8.45 (m, 1H), 9.37 (d, 1H,7= 10.2); Anal. $C_{28}H_{34}N_4O_7 \cdot 1.5TFA$: C, H, N.

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EJEMPLO 27

Preparación del Compuesto 29:

trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Cloroisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il} butirilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Ciclopentilo de Ácido enóico (R4)



Preparación del Intermediario (2S)-2-{3'-[(5''-Cloroisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ester de tert-Butilo de Ácido butírico (V4)

El intermediario F3 de arriba (0.781 g, 3.26 mmol, 1.1 equiv) fue suspendido en THF (10 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.119 g, 2.98 mmol, 1 equiv) fue agregado en una parte. Despues de agitación 30 min, una solución del intermediario U3 (2.96 mmol, 1 equiv, basado sobre T3) en THF (15 mL) fue por jeringa. La mezcla resultante fue agitada 2 horas, entonces diluida con EtOAc (500 mL) y lavada con salmuera (2 x 100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporado. El residuo fue purificado por cromatografía de columna de destello (20% EtOAc en hexanos) para proporcionar el intermediario del título (0.834 g, 74%): R*f* = 0.33 (20% EtOAc en hexanos); IR (cm^{-1}) 3334, 1732, 1694, 1650, 1603, 1537; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J*=7.4), 1.46 (s, 9H), 1.85-2.00 (m, 1H), 2.17-2.32 (m, 1H), 5.44-5.50 (m, 1H), 6.33 (t, 1H, *J*=7.3), 6.68 (s, 1H), 7.12 (dd, 1H, *J*=73,1.7), 8.43 (dd, 1H, *J*=7.3, 1.7), 9.61 (s, 1H); Anal. $C_{17}H_{20}ClN_3O_5$: C, H, N.

Preparación del Intermediario (2S)-2-{3'-[(''-Cloroisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ácido butírico (W4)

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El intermediario V4 de arriba (0.544 g, 1.42 mmol, 1 equiv) fue agitado durante 1 h en una mezcla de TFA (9 mL) y CH_2Cl_2 (9 mL). Los volátiles fueron evaporados. El residuo fue suspendido en CCU y concentrado menos seco (2 x 10 mL), proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(3'S,4S)-4-tert-Butoxicarbonilamino-5-[1'-(2",4"-dimetoxibencil)-2'-oxopirrolidin-3'-il]pent-2-Ester de Ciclopentilo de Ácido enóico (X3)

El intermediario K1 (preparado de acuerdo a Dragovich, y otros, J. *Med. Chem.* 1999, *42*, 1213) (2.00 g, 4.90 mmoL 1 equiv) y el comercialmente disponible Dess-Martin "periodinane" (2.30 g, 5.38 mmol, 1.1 equiv) fueron combinados CH_2Cl_2 (50 mL) y agitada 2 h. El solvente fue evaporado y el residuo fue suspendido en y entonces evaporado de tolueno (2 x 25 mL). El residuo resultante fue sidueito en (100 mL). (Trifenil-P-fosfanilideno)éster de ciclopentil de ácido acético (preparado en una manera análoga a aquella descrita en Baldwin, y otros *J. Org. Chem.* 1971, *36*, 1441) (2.28 g, 5.87 mmol, 1.2 equiv) fue agregado. La mezcla de reacción fue calentado a reflujo durante 100 min, dejada enfriar, diluida con EtOAc (300 mL) y lavada con una mezcla de salmuera y $NaHCO_3$ (1:1, 100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 44→50% EtOAc en hexanos) para proporcionar el intermediario del título (1.58 g, 62%) como una espuma: IR (cm^{-1}) 3307, 1708, 1678,1508; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.50-1.93 (m, 10H), 1.97-2.08 (m, 1H), 2.21-2.33 (m, 1H), 2.48-2.60 (m, 1H), 3.17-3.23 (m, 2H), 3.80 (s, 6H), 4.26-4.40 (m, 1H). 4.41 (s, 2H), 5.18-5.24 (m, 1H), 5.26-5.33 (m, 1H), 5.92 (dd, 1H, *J*=15.6, 1.6), 6.41-6.47 (m, 2H), 6.82 (dd, 1H, *J*=15.6, 5.2), 7.08-7.13 (m, 1H); Anal. $C_{26}H_{40}N_2O_7 \cdot 0.75H_2O$: C, H, N.

Preparación del Intermediario trans-(3'S,4S)-4-tert-Butoxicarbonilamino-5-(2'-oxopirrolidin-3'-il)pent-2-Ester de Cilcopentilo de Ácido enócio (X4)

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El intermediario X3 de arriba (1.54 g, 2.98 mmol, 1 equiv) fue disuelto en una mezcla de H_2O (5 mL) y $CHCl_3$ (50 mL). DDQ (0.947 g, 4.17 mmol, 1.4 equiv) fue agregado y la mezcla de reacción fue calentada en un baño de aceite a 60 °C durante 1.5 h. Más DDQ (0.90 g, 3.96 mmol, 1.3 equiv) fue agregado y calentado a 60 °C fue continuada durante 2 h más. Después del agitamiento a 23 °C, la mezcla de reacción fue diluida con CH_2Cl_2 (600 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (1:1,150 mL) y una mezcla de salmuera y $NaHCO_3$ (2 x 200 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.850 g, 78%) como una espuma color canela: IR (cm^{-1}) 3305, 1698, 1522, 1279, 1165; ^1H.NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.52-2.05 (m, 1H), 2.38-2.54 (m, 2H), 3.29-3.40 (m, 2H), 4.29-4.41 (m, 1H), 5.17-5.27 (m, 2H), 5.93 (dd, 1H, J=15.7, 1.6), 5.96-6.40 (m, 1H), 6.82 (dd, 1H, J=15.7, 5.3); Anal. $C_{19}H_{30}N_2O_5 \cdot 0.30H_2O$: C, H, N.

Preparación del Intermediario trans-(3'S,4S)-4-Amino-5-(2'-oxo-pirrolidin-3'-il)pent-2-Ester de Ciclopentilo de ácido enólico (Y3)

El intermediario X4 (0.522 g, 1.42 mmol, 1 equiv) fue agitado durante 40 min en una solución de TFA (7 mL) in CH_2Cl_2 (10 mL). Los volátiles fueron evaporados. El residuo fue suspendido en CCU y concentrado menos seco (2 x 20 mL), proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del Producto R4 (Compuesto 29)

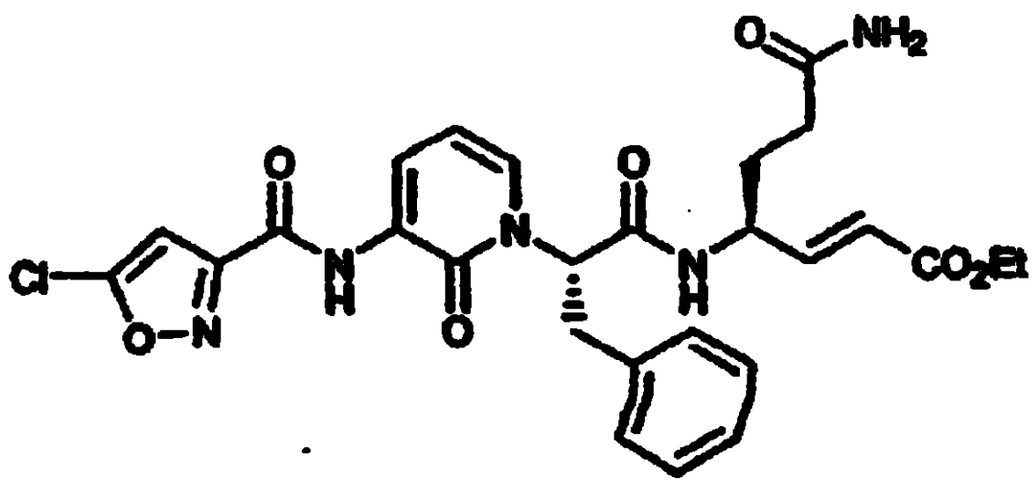
Los intermediarios W4 y Y3 (como preparado arriba) fueron combinados en CH_2Cl_2 (25 mL) y enfriado en una baño helado. HOBt (0.269 g, 1.99 mmol, 1.4 equiv), iPr2NEt (1.74 mL, 9.99 mmol, 7 equiv) y EDC (0.341 g, 0.1.78 mmol, 1.25 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejada calentar a 23 °C durante el fin de semana. Esta fue entonces diluida con EtOAc (500 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (1:1,100 mL) y salmuera (100 mL). La fase orgánica fue secada

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sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (2% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.590 g, 72%) como una espuma blanca: IR (cm^{-1}) 3295, 1690, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.3), 1.50-2.02 (m, 10H), 2.11-2.37 (m, 4H), 3.25.3.44 (m, 2H), 3.64-3.74 (m, 1H), 4.41-4.52 (m, 1H), 5.18-5.24 (m, 1H), 5.69 (dd, 1H, J = 9.0,6.6), 6.94 (dd, 1H, J = 15.6, 1.4), 6.36 (t, 1H, J = 7.3), 6.67 (s, 1H), 6.82 (dd, 1H, J = 15.6,5.9), 7.15 (s, 1H). 7.58 (dd, 1H, J = 7.3,1.7), 8.42 (dd, 1H, J = 7.3, 1.7). 8.49 (m, 1H), 9.52 (s, 1H); Anal. $C_{27}H_{32}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 28

Preparación del Compuesto 30: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3"-[(5"'-cloroisoxazol-3"' -carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3'-fenilpropioniiamino)hex-2- Ester de Etilo de Ácido enóico



Preparación del Intermediario (1'S,4"S)-5-Cloroisoxazol-3-Ácido carboxílico {1'-[1"-Bencil-4"-(tert-butildimetilsilaniloximetil)-2"-oxo-6'-(tritilcarbamoil)hexil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida

A una solución de 5-cloroisoxazol-3-ácido carboxílico (Ejemplo 22, 0.253 g, 1.71 mmol, 2.0 equiv) en $CHCl_3$ (21 mL) fue agregada $SOCl_2$ (9 mL). La mezcla de reacción fue calentada a reflujo durnate 26 h. Los volátiles fueron removidos bajo presión reducida para dar 5-cloroisoxazol-3-cloruro de carbonilo crudo.

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Una muestra de 10% Pd sobre C (0.070 g) fue agregada a una solución de (1'S,4"S)-5-cloroisoxazol-3-ácido carboxílico {1'-[1"-Bencil-4-(terl-butildimetilsilaniloxi-metil)-2"-oxo-6"-(tritilcarbamoil) hexil]-2'-oxo-1',2'-dihidropiridín-3'-il}amida (Ejemplo 1, 0.74 g, 0.855 mmol, 1 equiv) en EtOAc (15 mL). La mezcla de reacción fue agitada a temeprature ambiente bajo atmósfera H2 (aeróstato) durante 4 h, y entonces fue filtrada a través de Celita. El filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en THF (15 mL), enfriada a O °C, y 5-cloroisoxazol-3-cloruro de carbonilo (1.71 mmol, 2.0 equiv) y NMM (0.188 mL, 1.71 mmol, 2.0 equiv) fueron agregados secuencialmente. La mezcla de reacción fue agitada a O °C durante 1 h, entonces fue partida por medio de agua (100 mL) y EtOAc (2 x 100 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4 y concentradas. El residuo fue purificado por cromatografía de columna de destello (35% EtOAc en hexanos) para proporcionar el intermediario del título (0.666 g, 90%): IR (cm^{-1}) 3332, 1684, 1531; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.60-1,71 (m, 1H), 1.80-1.83 (m, 1H), 2.12-2.16 (m, 2H), 3.16-3.23 (m, 1H), 3.36-3.41 (m, 1H), 3.47-3.55 (m, 2H), 3.81-3.90 (m, 1H), 5.64-5.70 (m, 1H), 6.26 (t, 1H, *J*= 7.2), 6.47 (d, 1H, *J*= 8.7), 6.70 (s, 1H), 7.02 (s, br. 1 H), 7.17-7.33 (m, 20H), 7.37 (d, 1H, *J*= 7.2), 8.40 (d, *J*= 7.8), 9.56 (s, br. 1H).

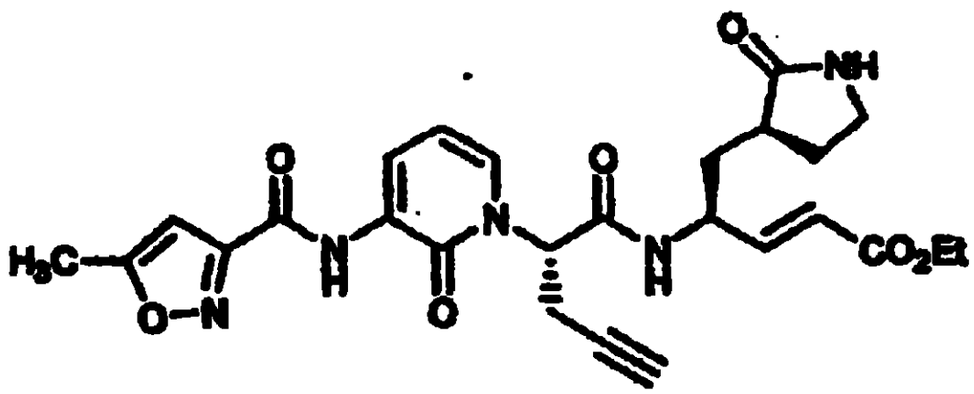
Preparación del Compuesto 30

El intermediario precedente fue convertido en compuesto 30 por un proceso que fue análogo a aquel descrito en el Ejemplo 7 para la conversión del intermediario C1 a compuesto 7: mp = 163-165 °C; IR (cm^{-1}) 3335, 1648, 1533, 1179; ^1H NMR ($CDCl_3$) δ 0.34 (t, 3H, *J*=7.2), 1.76-1.86 (m, 1H), 1.94-2.00 (m, 1H), 2.23 (t, 2H, *J*= 6.9), 3.20-3.27 (m, 1H), 3.35-3.42 (m, 2H), 3.51-3.58 (m, 1H), 4.22 (q, 2H, *J*= 7.2), 4.52-4.57 (m, 1H), 5.69 (dd, 1H, *J*= 15.6, 1.5), 6.70 (s, br. 1H), 6.14 (s, br. 1H), 6.32 (s, br. 1H), 6.39 (t, 1H, J = 7.2), 6.69 (dd, 1H, *J*= 15.6, 5.4), 7.21-7.33 (m, 4H), 7.47 (d, 1H, *J*= 7.2), 8.44 (d, 1H, *J*= 7.5), 9.47 (s, br. 1H); Anal. $C_{27}H_{28}ClN_5O_7 \cdot 0.6H_2O$: C, H, N.

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EJEMPLO 29

Preparación del Compuesto 31: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}pent-4'-inoil-amino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico



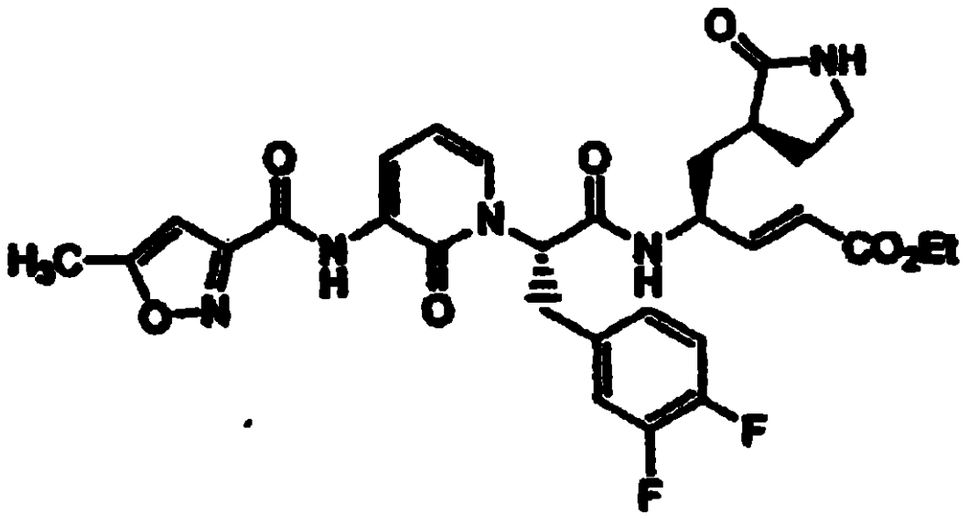
El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito en el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando el intermediario F2 y Y2 y una desprotección alternada del intermediario correspondiente a VI (LII en piridina) donde fuere apropiado: IR (cm^{-1}) 3295, 1684, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 0.95(s, 9H), 1.54-1.80 (m, 2H), 2.05 (t, 1H, *J*= 2.6), 2.10-2.39 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, *J*= 17.0, 8.2,2.6), 3.01 (ddd, 1H, *J*= 17.0, 6.8, 2.6), 3.22-3.38 (m, 2H), 3.82 (s, 2H), 4.45-4.56 (m, 1H), 5.72-5.79 (m, 1H), 6.06 (dd, 1H, *J*= 15.7, 1.5), 6.33 (t, 1 H, *J*= 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J*= 15.7,5.4), 6.93 (s, 1H), 7.51 (dd, 1H, *J*= 7.2,1.7), 8.41 (dd, 1H, *J*= 7-2,1.7), 8.69 (d, 1H, *J*= 6.6), 9.52 (s, 1H); Anal. $C_{29}H_{35}N_5O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 31

Preparación del Compuesto 33:

trans-(2'S,3''''''S,4S)-4-(3'-(3'',4''-Difluorofenil)-2'-{3'''-[(5''''-metilisoxazol-3''''-carbonil)amino]-2'''-oxo-2'''H-piridin-1'''-il}propionilamino)-5-(2''''''-oxopirrolidin-3''''''-il)pent-2-Ester de Etilo de Ácido enóico

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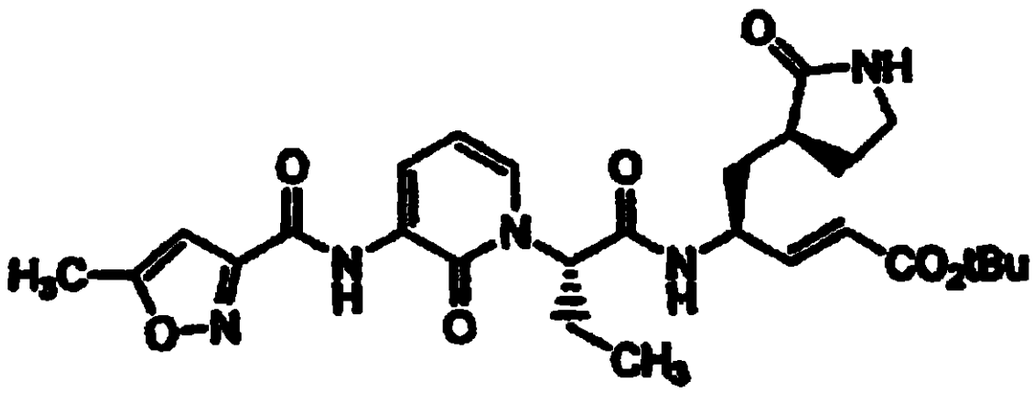
El compuesto del título fue preparado por un un método análogo a aquel descrito en el Ejemplo 19 para la preparación del intermediario específico R1 utilizando (2R)-3-(3',4'-difluorofenil)-2-ácido hidroxipropiónico (sintetizado de (2R)-2-tert-butoxicarbonilamino-3-(3',4'-difluorofenil)ácido propiónico en analogía a la preparación del intermediario S1 descrito en el Ejemplo 22) y trietilfosfonoacetato donde fuere apropiado: IR(cm^{-1}) 3331, 1690, 1649, 1596, 1531, 1455, 1278; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.44-1.54 (m, 1H), 1.63-1.78 (m, 1H), 2.08-2.9 (m, 3H), 2.49 (d, 3H, *J*= 0.9), 3.05 (dd, 1H, *J*= 13.6,7.5), 3.20-3.42 (m, 3H), 4.19 (dq, 2H, *J*= 7.1,1.7), 4.34-4.45 (m, 1H), 5.64 (dd, 1H, *J*= 15.7,1.4), 6.00 (t, 1H, *J*= 7.8), 6.32 (t, 1H, *J*= 7.3), 6.45 (s, 1H), 6.71 (dd, 1H, *J*= 15.7,5.6), 6.86-6.91 (m, 1H), 6.98-7.08 (m, 2H), 7.15 (s, 1H), 7.68 (dd, 1H, *J*=7.3, 1.7), 8.39 (dd, 1H, *J*= 7.3,1.7), 8.65 (d, 1H, .7= 6.8). 9.46 (s, 1H); Anal. $C_{30}H_{31}F_2N_5O_7$: C, H, N.

EJEMPLO 32

Preparación del Compuesto 34:

trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5''''-Metilisoxazol-3''''-carbonil) amino]-2''-oxo-2''H-piridin-1''-il}butirilamino)-6-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de tert-Butilo de Ácido enoico

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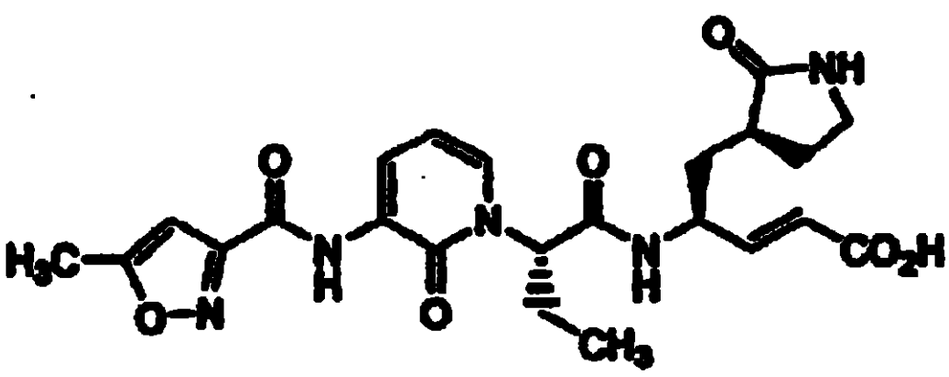


El compuesto del título fue preparado por un método análogo a aquel descrito para la síntesis del compuesto R3 en el Ejemplo 25: IR (cm^{-1}) 3331, 3295, 1690, 1649, 1590, 1531, 1455, 1155; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J*= 7.3), 1.40-1.60 (m, 1H), 1.49 (s, 9H), 1.62-1.78 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.36 (m, 4H), 2.50 (s, 3H), 3.26-3.43 (m, 2H), 4.39-4.50 (m, 1H), 5.78 (dd, 1H, .7= 8.9, 6.7), 5.89 (dd, 1H, *J*= 15.7, 1.3), 6.35 (t, 1H, *J*= 7.3), 6.47 (s, 1H), 6.76 (dd, 1H, *J*= 15.7,5.9), 7.33 (s, 1H), 7.64 (dd, 1H, *J*= 7.3, 1.8), 8.43 (dd, 1H, *J*= 7.3, 1.8), 8.59 (d, 1H, *J*= 6.8), 9.57 (s, 1H); Anal. $C_{27}H_{35}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 33

Preparación del Compuesto 35:

trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil) amino]-2''-oxo-2''H-piridin-1'' -il} butirilamino)-5-(2'''' -oxopirrolidin-3''''-il)pent-2-Ácido enóico

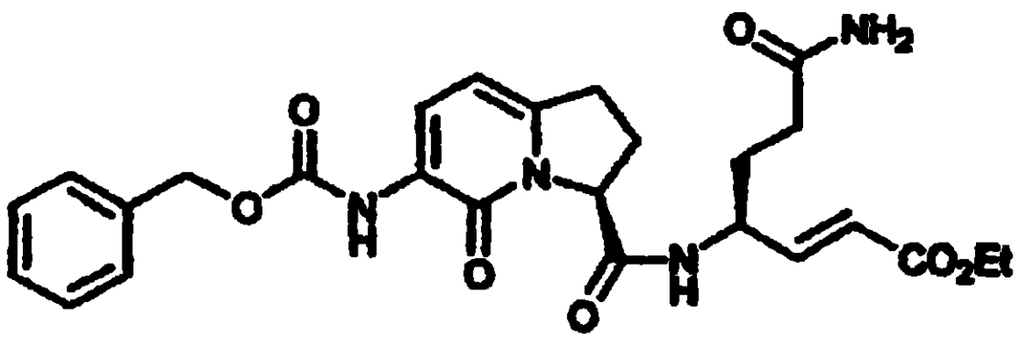


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El compuesto del título fue preparado del compuesto 34 por desprotección acídica de la mitad de éster de tert-butilo presente en aquel compuesto (procedimientos de literatura normales siguietnes): IR (cm^{-1}) 3319, 1678, 1643, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J*= 7.2), 1.61-1.99 (m, 3H), 2.08-2.32 (m, 3H), 2.40-2.54 (m, 1H), 2.49 (s, 3H), 3.25-3.41 (m, 2H), 4.58-4.69 (m, 1H), 5.56-5.64 (m, 1H), 5.98 (d, 1H, *J*= 15.6), 6.21 (br, 1H), 6.37 (t, 1H, *J*= 7.3), 6.47 (s, 1H), 6.96 (dd, 1H, *J*= 15.6, 6.6), 7.50 (dd, 1H, *J*= 7.3, 1.6), 7.52 (s, 1H), 8.26 (d, 1H, *J*= 7.7), 8.44 (dd, 1H, *J*= 7.3, 1.6), 8.62 (s, 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 34

Preparación del Compuesto 36: trans-(3'S,4S)-4-[(6'-Benciloxicarboniiamino-5'-oxo-1',2',3',5'-tetrahidroindolizina-3'-carbonil)amino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico



Preparación del intermediario 6-But-3-enil-2-hidroxini cotinonitrilo (a1)

n-Butiilitio (100 mL de una solución de 1.6 M en hexanos, 160 mmol, 2.5 equiv) fue agregada vía cánula más de 10 min a una solución de diisopropiiamina (22.4 mL, 160 mmol, 2.5 equiv) en THF (600 mL) a -78 °C. La solución amarilla pálido resultante fue agitada a -78 °C durante 5 min, entonces fue calentada a O °C durante un adicional de 5 min. 2-Hidroxi-6-metiinicotinonitrilo (8) (8.56 g, 64.0 mmol, 1 equiv) fue agregado como un sólido en pequñas partes más de 15 min y la solución anaranjada intensa así obtenida fue agitada durante 1 h a O °C. Bromuro de alilo (8.31 mL,

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96.0 mmol, 1.5 equiv) fue entonces agregado y la mezcla de reacción fue calentada a 23 °C, mantenida a aquella temperatura durante for 30 min, y fue partida por medio de 1.0 M HC1 (300 mL) y EtOAc (2 x 250 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. El sólido naranja resultante fue triturado con cocción de EtzO (100 mL) y subsiguientemente enfriado a 23 °C, entonces fue filtrada a través de un derretimiento medio, lavado con Et_2O (2 x 50 mL) y secado al aire para dar a1 (6.42 g, 58%) como un sólido tostado: mp = 122-125 °C; IR (pildora KBr, cm^{-1}) 2223, 1654; ^1H NMR (DMSO-d_6) δ 2.32-2.37 (m, 2H), 2.62 (t, 2H, *J*= 7.6), 4.96-5.06 (m, 2H), 5.69-5.83 (m, 1H), 6.23 (d, 1H, *J*= 7.3), 8.03 (d, 1H, *J*= 7.3), 12.55 (s, br, 1H); Anal. $C_{10}H_{10}N_2O \cdot 0.10H_2O$: C, H, N.

Preparación del Intermediario 6-But-3-enil-2-hidroxinicotinamida (b1)

Peroxido de hidrógeno (30 wt. % solución en agua, 45 mL) fue agregada a una solución de a1 (12.13 g, 70.2 mmol) en una mezcla de EtOH (150 mL) y 10% NaOH acuoso (280 mL) a 23 °C. La mezcla resultante fue calentada a 50 °C for 18 h, entonces fue enfriada a 23 °C y los volátiles fueron removidos bajo presión reducida. El residuo fue acidificado con 12 M HCl a pH 2-3, y el precipitado resultante fue filtrado, lavado con agua (2 x 50 mL), y secado al aire para proporcionar b1 como un sólido amarillo (13.48 g, 100%): mp = 195-198 °C; IR (cm^{-1}) 3329, 3134, 1688, 1642; ^1H NMR (DMSO-d_6) δ 2.31-2.38 (m, 2H), 2.64 (t, 2H, *J*= 7.6), 4.96-5.05 (m; 2H), 5.71-5.84 (m, 1H), 6.29 (d, 1H, *J*= 7.3), 7.45 (s, br, 1H), 8.21 (d. 1H, *J*= 7.3), 9.00 (s, br, 1H), 12.37 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparación del Intermediario 6-But-3-enil-2-Ácido hidroxinicotínico (c1)

Una solución de b1 (12.38 g, 70.1 mmol) en 10% KOH acuoso (350 mL) fue calentado a reflujo durante 20 h y subsiguientemente enfriada a temperatura ambiente. La mezcla de reacción fue

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acidificada con 12 M HCl a pH 2-3, y el precipitado resultante fue filtrado, lavado con agua (2 x 50 mL), y secado bajo vacío para proporcionar c1 como un sólido amarillo (12.46 g, 92%): mp = 151-155 °C; IR (cm^{-1}) 2905 (br), 1736, 1652; ^1H NMR (DMSO-d_6) δ 2.34-2.29 (m, 2H), 2.73 (t, 2H, *J*= 7.6), 4.96-5.07 (m, 2H), 5.72-5.85 (m, 1H), 6.56 (d, 1H, J= 7.5), 8.28 (d, 1H, *J*= 7.5), 13.26 (s, br, 1H), 14.64 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparación del Intermendiario (6-But-3-enil-2-hidroxipiridin-3-il)Ester de Bencilo de Ácido carbámico (d1)

Trietilamino (13.9 mL, 99.7 mmol, 2.0 equiv) y ácido de difenilfosforilo (16.1 mL, 74.7 mmol, 1.5 equiv) fueron agregados secuencialmente a una supensión de c1 (9.63 g, 49.8 mmol, 1 equiv) en 1,4-dioxano (450 mL) a 23 °C. La solución resultante fue calentada a reflujo durante 7.5 h, entonces alcohol de bencilo (10.5 mL, 99.5 mmol, 2.0 equiv) fue agregado y el reflujo fue continuado durante un adicional de 16 h. La mezcla de reacción café obscura fue enfriada a 23 °C y los volátiles fueron removidos bajo presión reducida. El aceite café obscuro resultante fue partida por medio de agua (300 mL) y EtOAc (2 x 250 mL) y las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y conccentrada. El sólido así obtenido fue triturado con Et_2O (150 mL) y filtrado a través de derretimiento medio, lavado con Et_2O (2 x 50 mL)y secado al aire para dar d1 (7.34 g, 49%) como un polvo casi blanco: mp = 179-180 °C; IR (cm^{-1}) 3386, 1727, 1645; ^1H NMR ($CDCl_3$) δ 2.39-2.46 (m, 2H), 2.66 (t, 2H, *J*= 7.5), 4.97-5.07 (m, 2H), 5.21 (s, 2H), 5.73-5.87 (m, 1H), 6.10 (d, 1H, *J* = 7.5), 7.32-7.44 (m, 5H), 7.68 (s, br, 1H), 8.08 (s, br, 1H), 12.74 (s, br, 1H); $C_{17}H_{18}N_2O_3$: C, H, N.

Preparación del Intermendiario (6-But-3-enil-2-metoxipiridin-3-il)Ester de Bencilo de Ácido carbámico (e1)

Tetrafluoroborato de trimetiloxinio (2.0 g, 13.5 mmol, 1.2 equiv) y 2,6-di-tert-butilpiridina (1.52 mL, 6.76 mmol, 0.6 equiv) fueron agregados a una solución de d1 (3.36 g, 11.26 mmol, 1 equiv) en CH_2Cl_2 (80 mL) a 23 °C. La mezcla de reacción fue

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agitada a aquella temperatura durnate 65 h, entonces fue partida por medio de agua (2 x 50 mL) y CH_2Cl_2 (2 x 200 mL) y capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas. El residuo fue purificado por cromatografía de columna de destello (5% EtOAc en hexanos) para proporcionar e1 (3.19 g, 91%) como un aceite descolorido: IR (cm^{-1}) 3432, 1733; ^1H NMR ($CDCl_3$) δ 2.42-2.49 (m, 2H), 2.73 (t, 2H, *J*= 7.6), 3.96 (s, 3H), 4.94-5.07 (m, 2H), 5.20 (s, 2H), 5.80-5.94 (m, 1H), 6.71 (d, 1H, *J*= 7.9), 7.11 (s, br, 1H), 7.32-7.43 (m, 5H), 8.16 (s, br, 1H); Anal. $C_{18}H_{20}N_2O_3$: C, H, N.

Preparación del Intermediario (3'R)-[6-(3',4'-Dihidroxibutil)-2-metoxipiridin-3-il]Ester de Bencilo de Ácido carbámico (f1)

A una mezcla de 1:1 t-BuOH y agua (300 mL) a O °C fue agregado $(DHQD)_2AQN$ (0.148 g, 0.164 mmol, 0.01 equiv), $K_3Fe(CN)_8$ (16.2 g, 49.2 mmol, 3 equiv), K_2CO_3 (6.8 g, 49.2 mmol, 3 equiv), dihidrato de osmato de potasio (0.024 g, 0.066 mmol, 0.004 equiv), y entonces e1 en t-BuOH (25 mL), secuencialmente. La mezcla resultante fue agitada a O °C durante 20 h, entonces calentada a temperatura ambiente y Na_2SO_3 (30 g) fue agregado cuidadosamente. La mezcla fue agitada a temperatura ambiente durante 2 h, entonces los volátiles fueron removidos bajo presión reducida. El residuo fue partido por medio de agua (200 mL) y EtOAc (3 x 200 mL) y las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas. El residuo fue purificado por cromaografía de columna de destello (2% CH_3OH en CH_2Cl_2) pafra proporcionar f1 (5.57 g, 98%) como un aceite amarillo pálido: IR (cm^{-1}) 3427(br), 1731; ^1H NMR ($CDCl_3$) δ 1.76-1.87 (m, 2H), 2.07-2.11 (m, 1H), 2.80-2.89 (m, 2H), 3.46-3.53 (m, 1H), 3.60-3.67 (m, 1H), 3.71-3.77 (m, 1H), 3.96 (s, 3H), 4.64 (d, 1H, *J*= 3.2), 5.21 (s, 2H), 6.76 (d, 1H, *J*= 7.8), 7.12 (s, br, 1H), 7.34-7.43 (m, 5H), 8.22 (s, br, 1H); Anal. $C_{18}H_{22}N_2O_5$: C, H, N.

Preparación del Intermediario

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(3'R)-{6-[4'-(tert-Butil-dimetil-silaniloxi)-3'-hidroxibutil]-2-metoxipiridin-3-il}Ester de Bencilo de Ácido carbámico (g1)

Trietilamino (1.55 mL, 11.1 mmol, 2.5 equiv), cloruro de tert-butildimetilsililo (1.07 g, 7.10 mmol, 1.6 equiv), y 4-dimetilaminopiridina (0.025 g, 0.20 mmol, 0.045 equiv) fueron agregados secuencialmente a una solución de f1 (1.64 g, 4.45 mmol, 1 equiv) en CH_2Cl_2 (50 mL) a 23 °C. La mezcla de reacción fue agitada durante 19 h a 23 °C, entonces fue partida por medio de 0.5 M HCl (150 mL) y una mezcla 1:1 de EtOAc y hexanos (2 x 150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas. Purificación del residuo por cromatografía de columna de destello (20% EtOAc en hexanos) proporciona g1 (1.69 g, 82%) como un aceite descolorido: IR (cm^{-1}) 3436, 1734; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.72-1.94 (m, 2H), 2.72-2.88 m, 2H), 3.26 (d, 1H, *J*= 3.1), 3.50 (dd, 1H, *J*= 9.8,6.9), 3.58-3.63 (m, 1H), 3.65-3.70 (m, 1H), 3.95 (s, 3H), 5.20 (s. 2H), 6.75 (d, 1H, *J*= 8.1), 7.11 (s, br, 1H), 7.33-7.43 (m, 5H), 8.20 (s, br, 1H); Anal. $C_{24}H_{36}N_2O_5Si$: C, H, N.

Preparación del Intermediario (3S)-(3-Hidroximetil-5-oxo-1,2,3,5-tetrahidroindolizin-6-il)-Ester de Bencilo de Ácido Carbámico (h1)

2,6-Lutidina (2.43 mL, 20.84 mmol, 4.0 equiv) y anhídrido de trifluorometanesulfónico (1.31 mL, 7.82 mmol, 1.5 equiv) fueron agregados secuencialmente a una solución de g1 (2.4 g, 5.21 mmol, 1 equiv) en CH_2Cl_2 (100 mL) a -78 °C. La mezcla de reacción descolorida fue agitada a -78 °C durante 45 min, calentada a 23 °C durante un adicional de 15 min, entonces fue partida por medio de 0.5 M HCl (150 mL) y CH_2Cl_2 (2x150 mL). La capa orgánica fue secada sobre Na_2SO_4 y fue concentrada. El residuo así obtenido fue disuelto en THF (120 mL) a 23 °C fluoruro de tetrabutilamonio (15.63 mL a una solución 1:0 M en THF, 15.63 mmol, 3.0 equiv) fue agregado. La mezcla de reacción fue agitado a aquella temperatura durante 1 h, entonces fue partida por medio de 0.5 M HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas fueron secadas sobre

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Na_2SO_4 y concentradas. El residuo así obtenido fue purificado por cromatografía de columna de destello (80% EtOAc en hexanos) para dar h1 (0.953 g, 58%) como un aceite descolorido: IR (cm^{-1}) 3379 (br), 1727, 1649; ^1H NMR ($CDCl_3$) δ 1.86-1.97 (m, 1H), 2.29-2.41 (m, 1H), 2.90-3.15 (m, 2H), 3.80-3.93 (m, 2H), 4.78-4.86 (m, 1H), 5.11-5.15 (m, 1H), 5.20 (s, 2H), 6.20 (d, 1H, *J*= 7.5), 7.30-7.41 (m, 5H), 7.75 (s, br, 1H), 8.07 (d, IH,^ 7.5); Anal $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

Preparación del Intermediario (3S)-6-Benciloxicarbonilamino-5-oxo-l,2,3,5-tetrahidroindolizina-3-Ácido carboxílico (I1)

Dimetilsulfixido (0.522 mL, 7.36 mmol, 2.6 equiv) fue agregado gota a gota a una solución de cloruro de oxalilo (0.321 mL, 3.68 mmol, 1.3 equiv) en CH_2Cl_2 (80 mL) a -78 °C. La mezcla de reacción fue agitada durante 20 min a aquella temperatura, entonces una solución de h1 (0.890 g, 2.83 mmol, 1 equiv) en CH_2Cl_2 (20 mL) fue agregada vía cánula. Después de la agitación un adicional de 20 min a -78 °C, trietilamino (1.97 mL, 14.15 mmol, 5.0 equiv) fue agregado gota a gota. La mezcla de reacción fue mantenida a -78 °C durante 1.5 h, entonces ácido acético (15.57 mmol, 0.891 mL, 5.5 equiv) fue agregado. La mezcla de reacción fue calentada a O °C durante 5 min, entonces fue lavada con agua (50 mL), saturada $NaHCO_3$ (50 mL) y salmuera (50 mL). La capa orgánica fue secada sobre Na_2SO_4 y concentrada para proporcionar el producto de aldehído crudo como una espuma casi blanca. Este material fue utilizado sin más purificación.

Una solución de $NaClO_2$ (2.88 g, 25.47 mmol, 9.0 equiv) y NaH_2PO_4 (2.73 g, 19.81 mmol, 7.0 equiv) en agua (60 mL) fue agregada gota a gota para una solución del aldehído crudo precedente (2.83 mmol, 1 equiv) en una mezcla de tBuOH (60 mL) y 2-metil-2-buteno (10 mL) sobre 15 min a 23 °C. La mezcla resultante fue agitada a temperatura ambiente durante 1 h, entonces, los volátiles fueron removidos bajo presión reducida. El

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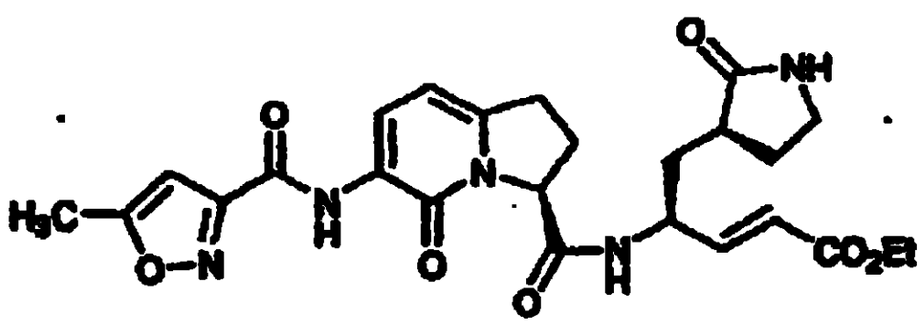
residuo así obtenido fue partido por medio de 0.5 M HCl (150 mL) y 10% CH_3OH en CH_2Cl_2 (2 x 150 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. El residuo resultante fue purificado por cromatografía de columna de destello (10% CH_3OH en CH_2Cl_2). Para dar I1 (0346 g, 37%) como un sólido casi blanco: mp = 204-206 °C; IR (cm^{-1}) 3298, 1722, 1564, 1208; ^1H NMR (DMSO-d_6) δ 2.17-2.55 (m, 2H), 2.45-2.59 (m, 2H), 4.98 (dd, 1H, *J*= 9.6,2.7), 5.16 (s, 2H), 6.23 (d, 1H, *J*= 7.5), 7.34-7.45 (m, 5H), 7.83 (d, 1H, *J*= 7.5), 8.34 (s, 1H); Anal. $C_{17}H_{16}N_2O_5$: C, H, N..

Preparación del Producto k1 (Compuesto 36)

El intermediario I1 fue transformado en compuesto 36 (vía acoplamiento con el intermediario AA1) por un proceso que fue análogo a aquel en el Ejemplo 23 para la transformación de W2 a producto J2: ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, *J*= 7.1), 1.64-1.84 (m,2H), 2.01-2.16 (m,2H), 2.41-2.60 (m, 1H), 3.01-3.06 (m,2H), 4.11 (q, 2H, *J*= 7.1), 4.41 (m, br, 1H), 5.01 (dd, 1H, *J*= 9.2, 2.7), 5.14 (s,2H), 5.87 (dd, 1H, *J*= 1.4), 6.20 (d, 1H, *J*= 7.6), 6.75 (s, br, 1H), 6.82 (dd, 1H, *J*= 15.8,5.0), 7.09-7.42 (m, 7H), 7.81 (d, 1H, *J*= 7.6), 8.38 (s, 1H), 8.55 (d, 1H, *J*= 8.4).

EJEMPLO 36

Preparación del Compuesto 37: trans-(3'S,3'''S,4S)-4-({6'-[(5''-Metilisoxazol-3''-carbonil)amino]-5'-oxo-1',2',3',5'-tetrahidroindolizina-3'-carbonil}amino-5-(2'''-oxopirrolidin-3'''-il)-pent-2-Ester de Etilo Ácido de enóico



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Sg4

Preparación del intermediario (3"R)-(5-Metilisoxazol-3-Ácido carboxílico-{6'-[4"-(tert-butildimetilsilaniloxi)-3"-hidroxibutilo] 2'-metoxipiridin-3'-il}amida (g2)

Una suspensión del intermediario g1 (preparada como se describió en el Ejemplo 34) (4.21 g, 9.14 mmol, 1 equiv) y Pd en C (10%, 0.375 g) en EtOAc (120 mL) fue agitado bajo una atmósfera H_2 (aerostato) a 23°C durante 1 h. La mezcla de reacción fue filtrada a través de Celite y el filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en CH_3CN (120 mL), enfriada a 0 °C, y NMM (1.00 mL, 9.10 mmol, 1.0 equiv) y 5-metilisoxazol-3-cloruro de carbonilo (1.33 g, 9.14 mmol, 1.0 equiv) fue agregado secuencialmente. La mezcla de reacción fue agitada a 0 °C durante 1 h, entonces fue partida por medio de 0.5 M HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. La trituración del residuo con una mezcla de 1:3 de Et_2O y hexanos (130 mL) proporciona un sólido blanco el cual fue recogido por filtración, lavado con hexanos (25 mL), y secado al aire (2.61 g, 66%): mp = 100-102°C; IR (cm^{-1}) 3390, 1696, 1593, 1536; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.78-1.95 (m, 2H), 2.52 (s, 3H), 2.78-2.90 (m, 2H), 3.45-3.53 (m, 2H), 3.60-3.74 (m, 2H), 4.03 (s, 3H), 6.51 (s, 1H), 6.79 (d, 1H, *J*= 7.9), 8.55 (d, 1H, *J*= 7.9), 8.95 (s, 1H); Anal. $C_{21}H_{33}N_3O_5Si$: C, H, N.

Preparación de los intermediarios (3S)-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5'-oxo-1,2,3,5-tetrahidro indolizina-3-Ácido carboxílico (I2) y (3S)-8-Cloro-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5'-oxo-1,2,3,5-tetrahidroindolizina-3-Ácido carboxílico (I3)

El intermediario precedente (g2) fue transformado en una mezcla 1:4 de los intermediarios I2 y I3 por un proceso que fue análogo a aquel descrito en el Ejemplo 34 por la transformación de g1 a I1: (I2) IR (cm^{-1}) 3343, 2977 (br), 1741, 1688, 1648; ^1H NMR ($CDCl_3$) δ 2.28-2.74 (m, 2H), 2.50 (s, 3H), 3.04-3.32 (m, 2H), 5.31 (d, 1H, *J*= 7.9), 6.36 (d, 1H, *J*= 7.7), 6.48 (s, 1H), 8.58 (d, 1H, *J*= 7.7), 9.40 (s, 1H); (I3) IR (cm^{-1}) 2240, 1652, 1532, 1260; ^1H NMR

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(DMSO-d_6) δ 1.53-1.63 (m, 2H), 3.11-3.20 (m, 2H), 5.14 (dd, 1H, *J* = 6.9, 2.7), 6.75 (s, 1H), 8.32 (s, 1H), 9.41 (s, br. 1H).

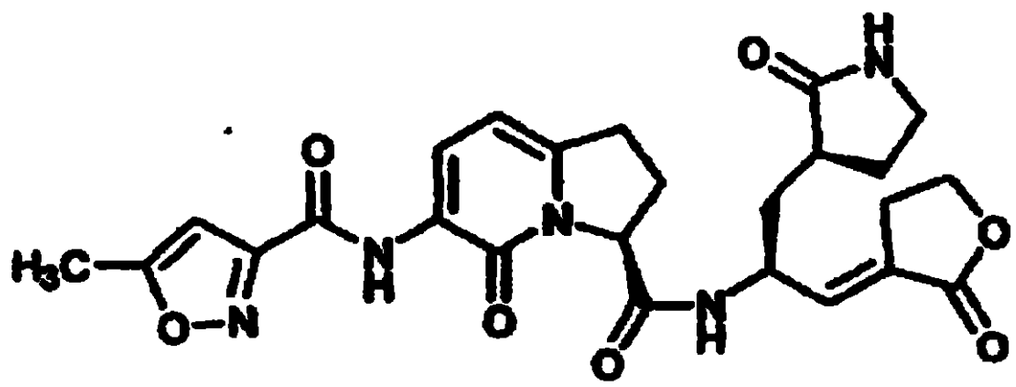
Preparación del Producto I1 (Compuesto 37)

El intermediario I2 fue transformado en compuesto 37 (vía acoplamiento con el intermediario Y2) por un proceso que fue análogo a aquel descrito en el Ejemplo 25 para la transformación de W3 a producto R3: IR (cm^{-1}) 3336, 1684, 1651, 1596, 1536; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.63-1.89 (m, 2H), 2.04-2.15 (m, 1H), 2.38-2.64 (m, 3H), 2.50 (s, 3H), 2.98-3.06 (m, 1H), 3.26-3.42 (m, 4H), 4.19 (q, 2H, *J*= 7.1), 4.63-4.65 (m, 1H), 5.15 (dd, 1H, *J*= 8.3,2.7), 5.97-6.05 (m, 2H), 6.21 (d, 1H, *J*= 7.3), 6.48 (s, 1H), 6.89 (dd, 1H, J= 15.6, 5.5), 8.44-8.52 (m, 2H), 9.40 (s, 1H); Anal. $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 38

Preparación del Compuesto 38:

trans-(2''S,3S,3''''S)-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5-oxo-1,2,3,5-tetrahidroindolizina-3-Ácido carboxílico [2''-(2'''-oxodihidrofurán-3''-ilideno)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]amida



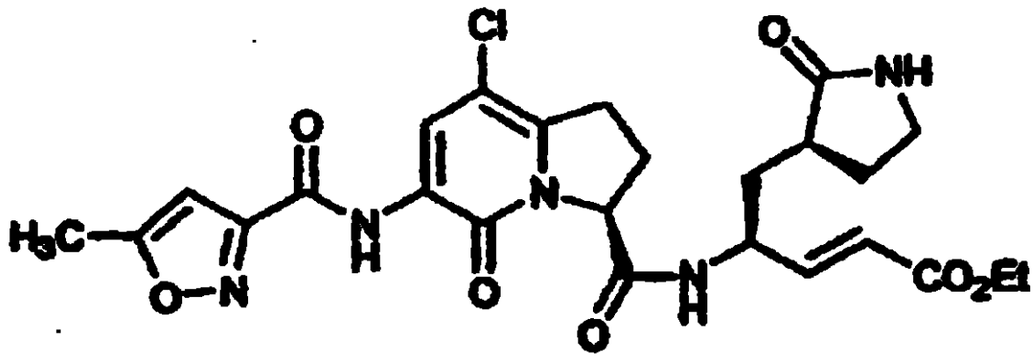
El compuesto del intermediario fue preparado del intermediario I2 (vía acoplamiento con intermediario Y1) por un proceso que fue análogo a aquel descrito en el Ejemplo 22 por la transformación de W1 a producto R2: IR (cm^{-1}) 3336, 1752, 1686, 1651, 1594, 1535; ^1H NMR ($CDCl_3$) δ 1.59-1.68 (m, 1H), 1.77-1.81 (m, 1H), 2.09-1.81 (m, 1H), 2.37-2.45 (m, 2H), 2.50 (s, 3H), 2.58-2.66 (m, 1H), 2.91-

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3.05 (m, 2H), 3.23-3.44 (m, 4H), 4.39 (t, 2H, *J*= 7.2), 4.60-4.67 (m, 1H), 5.10-5.13 (m, 1H), 6.09 (s, 1H), 6.21 (d, 1H, *J*= 7.9), 6.41-6.48 (m, 2H), 8.45-8.50 (m, 2H), 8.77 (d, 1H, *J*= 6.2), 9.39 (s, 1H).

EJEMPLO 37

Preparación del Compuesto 39: trans-(3'S,3'''S,4S)-({8'-Cloro-6'-[(5''-metilisoxazol-3''-carbonil)amino]-5'-oxo-1',2',3',5,-tetrahidroindolizina-3'-carbonil}amino)-5-(2'''-oxopirrolidin-3'''-il)-pent-2-Ester de Etilo de Ácido enóico



El compuesto del título fue preparado del intermediario I3 (vía acoplamiento con el intermediario Y2) por un proceso qu fue análogo a aquel descrito en el Ejemplo 25 para la transformación de W3 a producto R3: IR (ccm^{-1}) 3334, 1683, 1532; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*= 7.2), 1.66-1.89 (m, 4H), 233-2.50 (m, 1H), 2.53 (s, 3H), 2.67-2.72 (m, 1H), 3.04-3.20 (m, 2H), 3.27-3.48 (m, 2H), 4.21 (q, 2H, J= 7.2), 4.62-4.64 (m, 1H), 5.16-5.20 (m, 1H), 5.94 (s, br. 1H), 5.99 (dd, 1H,J= 15.6, 1.5), 6.51 (s, 1H), 6.89 (dd, 1H, *J*= 15.6, 5.7), 8.52 (s, 1H), 8.56 (s, br. 1H), 9.41 (s, br. 1H); Anal. $C_{25}H_{28}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

Los resultados de las pruebas dirigidas usando ejemplarmente compuestos de la invención están descritos abajo.

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EVALUACIÓN BIOLOGICA Y BIOQUIMICA

Inhibición de proteasa de Rinovirus 3C:

Las soluciones depositadas (50 mM, en DMSO) de varios compuestos fueron preparadas; las diluciones fueron en el mismo solvente. Las proteasas de rinovirus recombinantes de 3C proteasas (ver Birch y otros, "Purificación de rinovirus humano recombinante de proteasas 14 3C expresada en Esquerichia coli," *Protein Expr. Pur.* (1995), vol. 6(5), 609-618) de serotipos 14,16, y 2 fueron preparadas por los procedimientos cromatográficos normales siguientes: (1) intercambio de ión usando flujo rápido de seferosa Q de farmacia; (2) usando cromatografía de afinidad Affi-Gel Blue de Biorad.; y (3) calibrando el uso de Sefadex G-100 de farmacia. Cada muestra de ensayo contenía 2% DMSO, 50 mM de tris pH 7,6, 1 mM EDTA, un compuesto de prueba en la concentración indicada, aproximadamente 1 μM de sustrato, y 50-100 nM de proteasa. Los valores k_{obs}/I fueron obtenidos de reacciones iniciadas por adición de enzima distinta de sustrato. La actividad RVP fue medida en el ensayo de transferencia de energía de resonancia fluorecencia. El sustrato fue (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Fe-Gln-Gly-Pro-Val-Gly)-EDANS. En el peptida sin partir, la fluoerencia EDANS fue extinguida por la mitad próxima DABCYL. Cuando el peptida fue partido, la extinción fue revelada, y la actividad fue medida en un incremento en la señal fluorecencia. Los datos fueron analizados usando programas de ajuste no lineal normales (Enzfit), y están mostrados en la tabla de abajo. Los datos tabulados en la columna designada $k_{obs}/[I]$ fueron medidos de curvas de progreso en experimentos de inicio de enzima.

Ensayo de Célula Antirinoviral H1-HeLa

En este ensayo de protección de célula, la habilidad de los compuesto para la proteger de células con infección HRV fue media por el método de reducción de tinte XTT, el cual está descrito en Weislow y otros, J. Natl. Cancer Ints. (1989), vol. 81, 577-586. Las células H1-HeLa fueron infectadas con HRV-14 a una multiplicidad de infección (m.o.i.) de 0.13 (particulas de

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virus/células) o copia infectada con el medio solamente. Las células infectadas o copias infectadas fueron resuspendidas en células 8 x 10^5 por mL, e incubadas con concentraciones apropiadas de los compuestos a ser probados. Dos días más tarde, XTT/PMS fueron agregados a las placas de prueba y la cantidad de formazan producido fue cuantificada espectrofotométricamente a 450/650 nm. El valor EC_{50} fue calculado como la concentración de compuesto que incrementó el porcentaje de la producción formazan en compuesto tratado, células de virus infectadas a 50% de aquel producido por compuesto libre, células de copia infectadas. El 50% de dosis citotócica (CC_{50}) fue calculado como la concentración de compuesto que decreció el porcentaje de formazan producido en el compuesto tratado, células de copias infectadas a 50% de aquel producido por el compuesto libre, de células de copia infectada. El índice terapéutico (TI) fue calculado dividiendo el valor CC_{50} por el valor EC_{50}.

Todo lo referente a rinovirus humano (HRV) para uso en este ensayo fueron comprados de American Type Culture Collection (ATCC), excepto para serotipo-14 HRV (producido de la infección de clon cDNA construida por el Dr. Robert Rueckert, Instituto para Virología Molecular, Universidad de Wisconsin, Madison, Wisconsin). Los depósitos de HRV fueron propagados y ensayos virales fueron llevados a cabo en células H1-HeLa (ATCC). Las células crecieron en medio esencial mínimo con 10% de suero bobino fetal, disponibles de Life Technologies (Gaithersburg, MD). Los resultados de prueba para el ensayo HRV están mostrados en la tabla abajo.

Ensayo de Cultivo de Célula Anticoxsackieviral

Los tipos coxsackievirus A-21 (CAV-21) y B3 (CVB3) fueron comprados American Type Culture Collection (ATCC, Rockville, MD). Los depósitos de virus fueron propagados y ensayos antivirales fueron llevados a cabo en células H1-HeLa (ATCC). Las

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células crecieron en medio mínimo esencial con 10% de suero bobino fetal (Life Technologies, Gaithersburg, MD). La habilidad de los compuestos de esta invención para proteger células contra ya sea infección de CAV-21 o CVB3 fue medida por el método de reducción de tinte XTT. Este método está descrito en Weislow y otros, J. Natl. Cancer Inte. (1989), vol. 81, 577-586. Las células H1-HeLa fueron infectadas con CAV-21 o CVB3 en una multiplicidad de infección (m.o.i.) de 0.025 o 0.075, respectivamente, o copia infectada con el medio solamente. Las células H1-HeLa fueron plateadas a 4 x 10^4 células por fuente en una placa de 96-fuente e incubadas con concentraciones apropiadas del compuesto de prueba. Un día (CVB3) o dos días (CAV-21) más tarde, XTT/PMS fueron agregados a las placas de prueba y la cantidad de formazan producido fue cuantificada espectrofotométricamente a 450/650 nm. El EC_{50} fue calculado como la concentración de compuesto que incrementó la producción formazan en compuesto tratado, células de virus infectadas a 50% de aquella producido por el compuesto libre, células no infectadas. El 50% de dosis citotóxica (CC_{50}) fue calculado como la concentración de compuesto que decreció la producción de formazan en el compuesto tratado, las células no infectadas a 50% de aquella producida en el compuesto libre, células no infectada. El índice terapéutico (TI) fue calculado dividiendo el CC_{50} por el EC_{50}.

Ensayos de Cultivo de Célula Antienteroviral y Antiecoviral

El tipo Ecovirus 11 (ECHO 11) fue comprado de ATCC (Rockville, MD). Los depósitos de virus fueron propagados y ensayos antivirales fueron llevados a cabo en células MRC-5 (ATCC). Las células crecieron en medio mínimo esencial con 10% de suero bobino fetal (Life Technologies, Gaithersburg, MD). La habilidad de los compuestos de esta invención para proteger células contra infección ECHO 11 fue medida por el método de reducción de tinte XTT (Weislow y otros, J. Natl. Cancer Inte. (1989), vol. 81, 577-586). Las células MRC-5 fueron infectadas con

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ECHO 11 en un m.o.i. de 0.003 o 0.004, respectivamente, o copia infectada con medio solamente. Las células o no infectadas fueron agregadas a 1 x 10^4 células por fuente e incubadas con concentraciones apropiadas del compuesto. Cuatro días más tarde, XTT/PMS fueron agregados a las placas de prueba, y la cantidad de formazan producido fue cuantificado espectrofotométricamente a 450/650 nm. El EC_{50} fue calculado como la concentración de compuesto que incrementó la producción de formazan en compuesto tratado, células de virus infectadas a 50% de aquella producida por el compuesto libre, células no infectadas. El 50% de dosis citotóxica (CC_{50}) fue calculado como la concentración de compuesto que decreció la producción de formazan en el compuesto tratado, las células no infectadas a 50% de aquella producida en el compuesto libre, células no infectada. El índice terapéutico (TI) fue calculado dividiendo el CC_{50} por el EC_{50}. La actividad de los compuestos contra el tipo enterovirus 70 (EV70) puede ser medida por el mismo ensayo tal como se describió arriba en esta sección. El tipo de enterovirus 70 (EV70) puede ser obtenido de American Type Culture Collection ATCC (Rockville, MD).

Los resultados obtenidos para los compuestos de la invención pueden ser comparados con los resultados obtenidos de la misma manera para los compuestos de control WIN 51711, WIN 52084, y WIN 54954 (obtenidos de Sterling-Winthrop Pharmaceuticals), Pirodavir (obtenida de Janssen Pharmaceuticals), y Pleconaril (preparado de acuerdo al método descrito en Diana y otros, J. Med. Chem. (1995), vol. 38, 1355). Los datos antivirales obtenidos para los compuestos de prueba están mostrados en la tabla abajo. La designación "ND" indica que el valor no fue determinado para el compuesto, y la designación "NA" no es medio aplicable.

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TABLA

Compu.#	Estereotipo de Virus	$K_{obs}/[I]$ ($M^{-1}s^{-1}$)	EC_{50}(μM)	CC_{50} (μM)	II
1+2 (1:1)	HRV-14[a]	36,900	0.179	50.1	280
	HRV-1A	ND	0.825	74.1	90
	HRV-10	ND	0.145	60.3	416
1	HRV-14	114,000	0.033	50.1	1518
	CAV-21[c]	ND	1.48	>10	>7
	ECHO-11[d]	ND	0.16	>10	>63
	CVB3[e]	ND	0.539	>10	>19
	ENT-70[f]	ND	0.012	>10	>833
3	HRV-14	2,900	1.27	>10	>8
4	HRV-14	574	ND	ND	ND
5	HRV-14	329,000	0.016	>10	>625
	CAV-21	ND	1.39	>10	>7
	ECHO-11	ND	0.054	>10	>185
	CVB3	ND	0.577	>10	>17
	ENT-70	ND	0.018	>10	>556
6	HRV-14	37,400	0.034	>10	>294
	CAV-21	ND	4.68	>10	>2
	ECHO-11	ND	0.346	>10	>29
	CVB3	ND	2.50	>10	>4
	ENT-70	ND	0.061	>10	>164
7	HRV-14	81,000	0.014	>10	>714
8	HRV-14	7,660	0.888	>10	>11
9	HRV-14	5,040	0.518	>10	>19
10	HRV-14	113,600	0.104	>10	>96
	HRV-1A	ND	1.182	>10	>9
	HRV-10	ND	1.406	>10	>7
11	HRV-14	193,000	<0.0032	>10	>3125
12	HRV-14	25,800	0.075	>10	>133
13+14 (1:1)	HRV-14	31,000	ND	ND	ND
15	HRV-14	6,500	0.178	>10	>56
16	HRV-14	74,000	0.325	>10	>31
17	HRV-14	348	>10	>10	ND
18	HRV-14	116,000	0.125	>10	>80
19	HRV-14	380,000	0.003	>1	>333
20	HRV-14	600,000	0.015	>10	>667
21	HRV-14	6,340	0.469	>10	>21
22	HRV-14	18,500	1.0	>10	>10
23	HRV-14	385,000	0.064	>10	>156

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SAR

Compu.#	Estereotipo de Virus	$K_{obs}/[I]$ ($M^{-1}s^{-1}$)	EC_{50}(μM)	CC_{50} (μM)	TI
24	HRV-14	8,800	ND	ND	ND
25	HRV-14	1,250,000	0.002	>10	>5000
	HRV-1A	ND	0.015	>10	>667
	HRV-10	ND	0.004	>10	>2500
	HRV-2	ND	0.004	>10	>2500
	HRV-16	ND	0.005	>10	>2000
	HRV-3	ND	0.004	>10	>2500
	HRV-25	ND	0.022	>10	>454
	HRV-9	ND	0.01	>10	>1000
	HRV-39	ND	0.009	>10	>1111
	HRV-87	ND	0.008	>10	>1250
26	HRV-14	170,000	0.055	>10	>182
	HRV-1A	ND	0.014	>10	>714
	HRV-10	ND	0.027	>10	>370
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.050	>10	>200
	HRV-3	ND	0.029	>10	>344
	HRV-25	ND	0.102	>10	>98
	HRV-9	ND	0.045	>10	>222
	HRV-39	ND	0.047	>10	>212
	HRV-87	ND	0.021	>10	>476
27+28 (1:1)	HRV-14	3,750	1.78	>10	>7
29	HRV-14	148,000	0.079	>10	>126
	HRV-1A	ND	0.046	>10	>217
	HRV-10	ND	0.046	>10	>217
30	HRV-14	133,500	0.024	>10	>416
31	HRV-14	223,400	0.022	>10	>454
	HRV-1A	ND	0.036	>10	>277
	HRV-10	ND	0.048	>10	>208
	HRV-2	ND	0.013	>10	>769
	HRV-16	ND	0.038	>10	>263
	HRV-3	ND	0.021	>10	>476
	HRV-25	ND	0.087	>10	>114
	HRV-9	ND	0.044	>10	>227
	HRV-39	ND	0.043	>10	>232
	HRV-87	ND	0.021	>10	>476
32	HRV-14	127,500	0.126	>10	>79
	HRV-1A	ND	0.179	>10	>55
	HRV-10	ND	0.156	>10	>64
33	HRV-14	1,800,000	0.001	>10	>10000
34	HRV-14	45,100	ND	ND	ND

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Compu.#	Estereotipo de Virus	$K_{obs}/[I]$ ($M^{-1}s^{-1}$)	EC_{50}(μM)	CC_{50} (μM)	TI
35	HRV-14	220	ND	ND	ND
36	HRV-14	4,540	9.0	>100	>11
37	HRV-14	177,000	0.162	>10	>62
	HRV-1A	ND	0.108	>10	>93
	HRV-10	ND	0.041	>10	>244
	HRV-2	ND	0.037	>10	>270
	HRV-16	ND	0.072	>10	>138
	HRV-3	ND	0.043	>10	>232
	HRV-25	ND	0.162	>10	>61
	HRV-9	ND	0.121	>10	>82
	HRV-39	ND	0.016	>10	>625
	HRV-87	ND	0.058	>10	>172
38	HRV-14	0.089	16.8	>100	>6
39	HRV-14	200,000	0.040	>10	>250
	HRV-1A	ND	0.042	>10	>238
	HRV-10	ND	0.088	>10	>113
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.057	>10	>175
	HRV-3	ND	0.039	>10	>256
	HRV-25	ND	0.107	>10	>93
	HRV-9	ND	0.048	>10	>208
	HRV-39	ND	0.048	>10	>208
	HRV-87	ND	0.017	>10	>588
WIN 51711	HRV-14	ND	0.78	>60	>77
WIN 52084	HRV-14	ND	0.07	>10	>143
WIN 54954	HRV-14	ND	2.13	>63	>30
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
Pirodavir	HRV-14	ND	0.03	>10	>300
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
	EV-11	ND	3.7	>10	>3
	ENT-70	ND	0.06	>10	>167
Pleconaril	HRV-14	ND	0.01	>10	>1000
	CAV-21	ND	0.09	>10	>107
	CVB3	ND	>10	>10	NA
	EV-11	ND	0.16	>10	>62

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[a]HRV = rinovirus humano o serotipo designado.

[b]3C actividad de inhibición de proteasa.

[c]CAV-21 = coxsackievirus A21.

[d]ECHO-11 = ecovirus 11.

[e]CVB3 = coxsackievirus B3.

[f]ENT-70 = enterovirus 70.

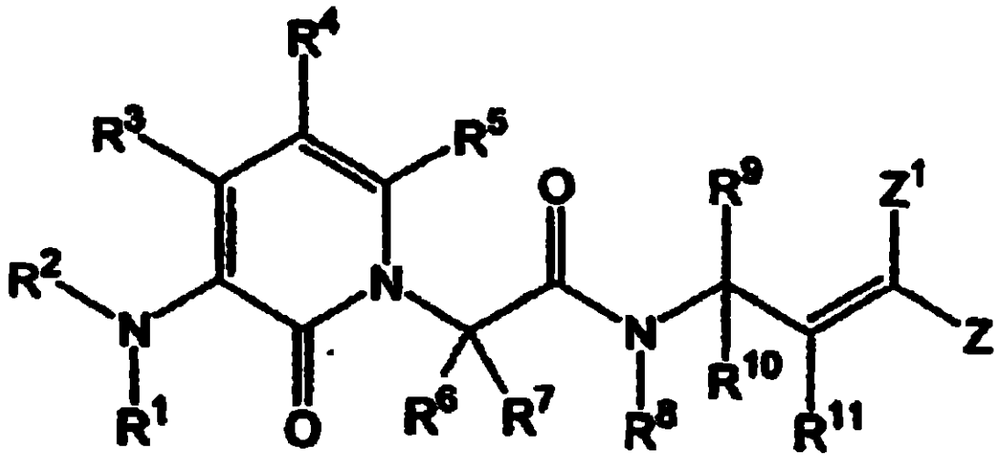
Valor [g]K_i, μM.

Aunque la invención ha sido descrita en términos de modalidades preferidas y ejemplos específicos, aquellos versados en el arte reconocerán que varios cambios y modificaciones pueden ser hechos sin apartarse del espíritu y alcance de la invención. Además, la invención debería entenderse como estando limitada por la descripción detallada anterior, pero como estando definida por las reivindicaciones adjuntas y sus equivalentes.

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REIVINDICAMOS:

1. Un compuesto que tiene la fórmula:



en la cual:

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuado;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, o un grupo alcoxicarbonilo, en los cuales cada una de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo en los grupos de arriba puede ser sustituida o no sustituida, o un grupo adecuado de protección de nitrógeno;

R^3 es un sustituyente adecuable; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o grupo heteroarilo, el cual puede ser opcionalmente sustituido;

R^4 es un sustituyente adecuable;

R^5 es un sustituyente adecuable; y

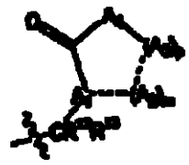
R^6 es un grupo alquilo sustituido o no sustituido; o

R^5 junto con R^6 forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido;

R^7 y R^{10} son independientemente H, halógeno o un grupo de alquilo más bajo sustituido o no sustituido;

R^8 es H o un grupo alquilo inferior sustituido o no sustituido;

R^{11} es H, halógeno, hidróxilo, un grupo sustituido o no sustituido de alquilo, alquiltio o alcoxi;

R^9 es un sustituyente que tiene la fórmula:  en la cual,

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, u O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cada A_3 presente es independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, u O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, u O; y cuando p es 0 (es decir, A_3 no está presente), A_4 es $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, y $O(R^{16})$, donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, cada R^{17} es H, alquilo, arilo, o acilo, y cada R^{18} es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada línea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2 está ausente (es decir, m=0); y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, -

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$C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados juntos con los átomo a los cuales ellos están unidos, forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido,

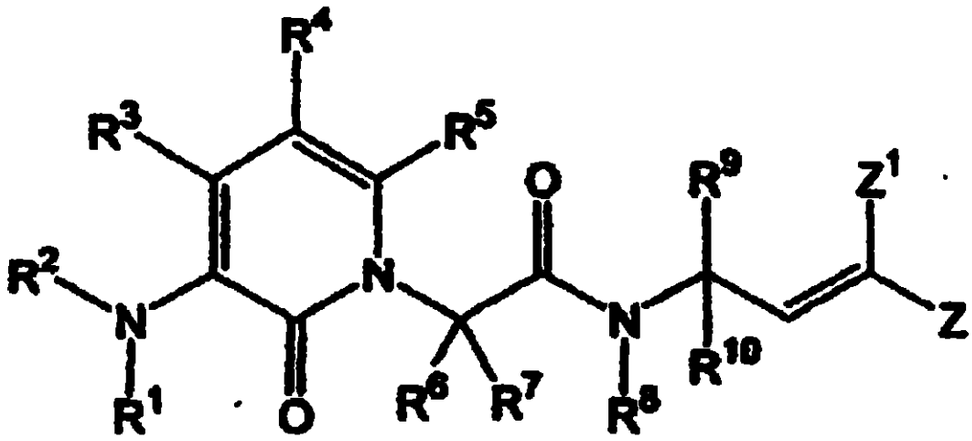
o una prodroga, sal farmacéuticamente aceptable metabolito farmacéuticamente activo o soluble farmacéuticamente aceptable de ésta.

2. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 1, en el cual R^1, R^2, R^3, y R^{10} son cada uno H.

3. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 1 en el cual R^4, R^5 y R^6 son sustituyentes adecuables, dichos sustituyentes adecuables son independientemente seleccionados de H, alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, hidróxilo, alcoxi, arilioxi, cicloalcoxi, heterocicloalcoxi, heteroarilioxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, arilioxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquiloxicarbonilo, carbóxilo, carbamoilo, formilo, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilamino carbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo,

dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarboniamino, cicloalquil carboniamino, arilcarboniamino, heterocicloalquilcarboniamino, heteroarilcarbonilo, alquiltiocarboniamino, cicloalquil tiocarboniamino, ariltiocarboniamino, heterocicloalquiltiocarboniamino, heteroariltiocarboniamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfoniamino, arilsulfoniamino, mercapto, alquiltio, ariltio, y heteroariltio, en el cual cualesquiera de los alquilo, arilo, cicloalquilo, heterocicloalquilo, mitades de heteroarilo presentes en los sustituyentes de arriba pueden ser además sustituido.

4. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 1 que tiene la fórmula:



en la cual

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo arilioxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de la mitades de los

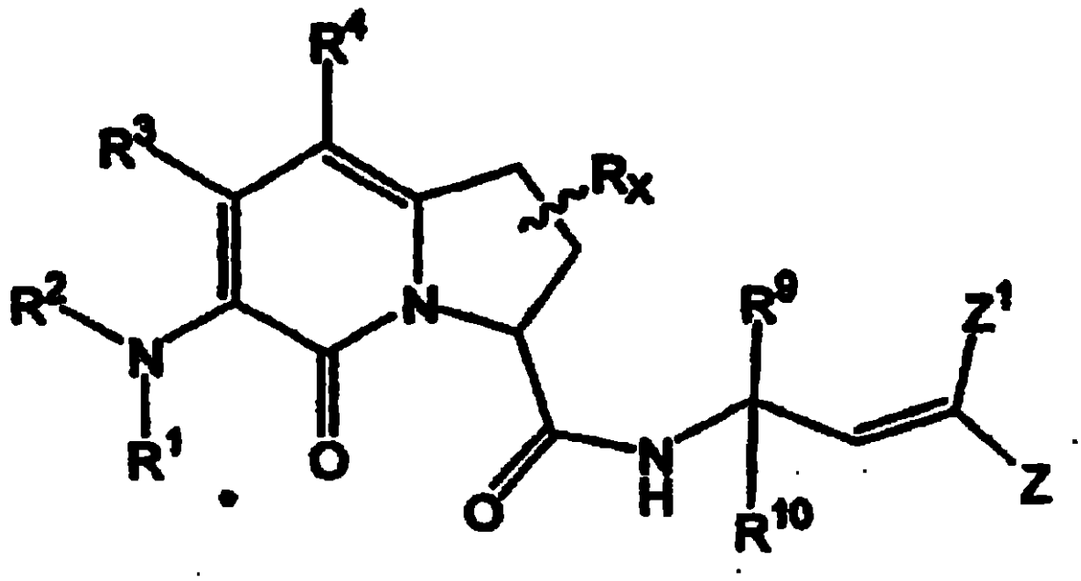
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alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidos o no sustituidos;

R^6 es un grupo sustituido o no sustituido;

y R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, Z y Z^1, son como sean definido en la reivindicación 1.

5. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 1 que tiene la fórmula:



en la cual:

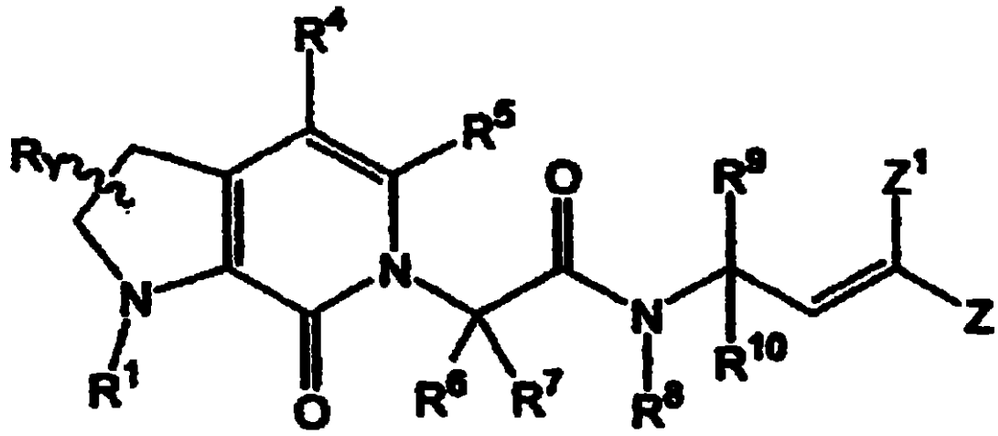
R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo arilioxicarbonilo o un grupo alquilioxicarbonilo, en los cuales cada una de las mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidas o no sustituidas;

R_x representa uno o más sustituyentes adecuables;

y R^1, R^3, R^4, R^9, R^{10}, Z y Z^1, son como sean definido en la reivindicación 1.

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6. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 1 que tiene la fórmula:



en la cual:

R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R^6 es un grupo alquilo sustituido o no sustituido;

R_y representa uno o más sustituyentes adecuables;

y R^1, R^4, R^5, R^9, Z y Z^1 son como se han definido en la reivindicación 1.

7. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con las reivindicaciones 1, 4 o 5 en la cual R^2 es un grupo heteroarilcarbonilo o arilcarbonilo, bencilioxicarbonilo sustituido o no sustituido.

8. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 7 en la cual R^2 es un grupo heteroarilcarbonilo, en el cual la mitad de heteroarilo es un heterocicio de 5-miembros que tiene desde uno hasta tres heteroátomos seleccionados de O, N, y S.

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9. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 8, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es un heterociclo de 5-miembros que tiene por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxigeno.

10. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 9, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es 1,2-oxazolilo sustituido o no sustituido, 1,3-oxazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo.

11. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 10, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es seleccionada de 1,2,4-oxadiazolilo de monometilo sustituido y no sustituido.

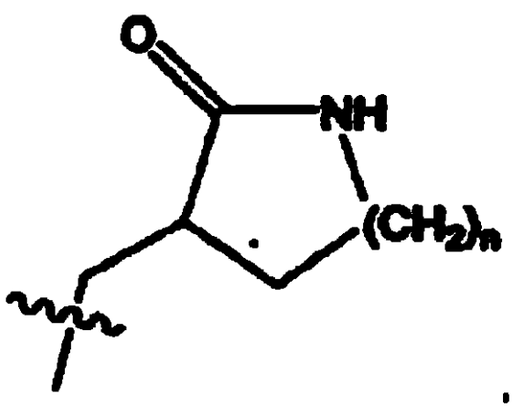
12. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 11, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es seleccionada de 3-isoxazolilo y 5-isoxazolilo, cada una sustituida o no sustituida con uno o dos sustituyentes seleccionados de los grupos metilo y halógenos.

13. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con las reivindicaciones 1, 4 o 6, en la cual R^5 es un heteroarilalquilo, arilalquilo, alquilo inferior sustituido o no sustituido, grupo cicloalquilo, una mitad de hidrocarburo saturado de cadena recta o una mitad de hidrocarburo no saturado.

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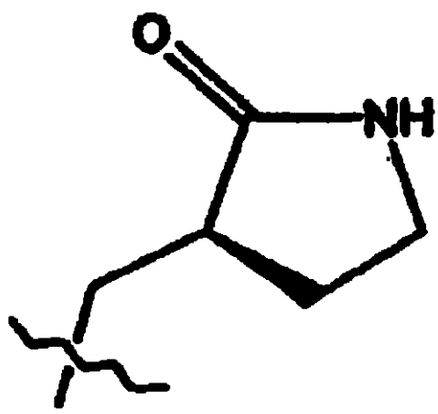
14. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 13, en la cual R^6 es etilo, 2-propin-1-ilo, metiloxiciohexilo, o bencilo sustiuido o no sustituido, en la cual la mitad de fenilo del bencilo sustituido comprende uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior y halógeno.

15. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con las reivindicaciones 1, 4, 5 o 6, en la cual R^9 es seleccionado de $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alquilo; $-CH_2NHC(O)CH_3$; y

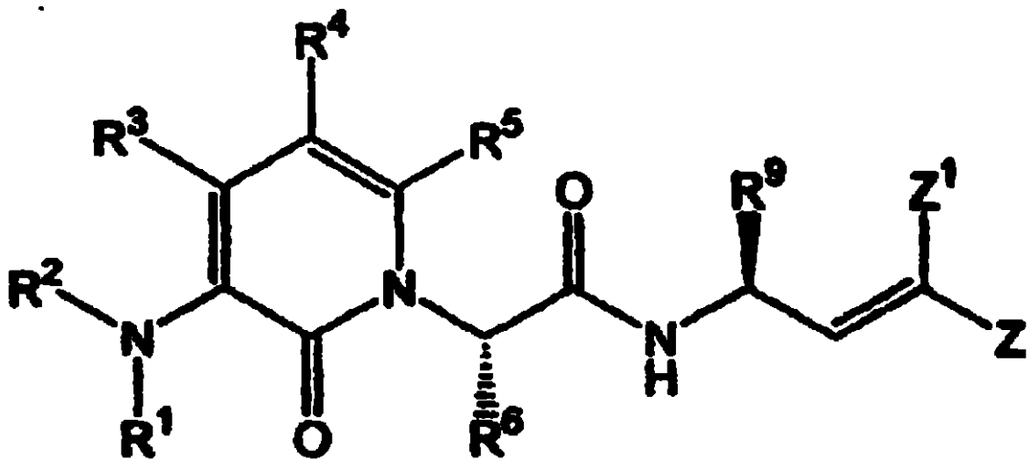


, donde n es 1 o 2.

16. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 15, en la cual R^9 es



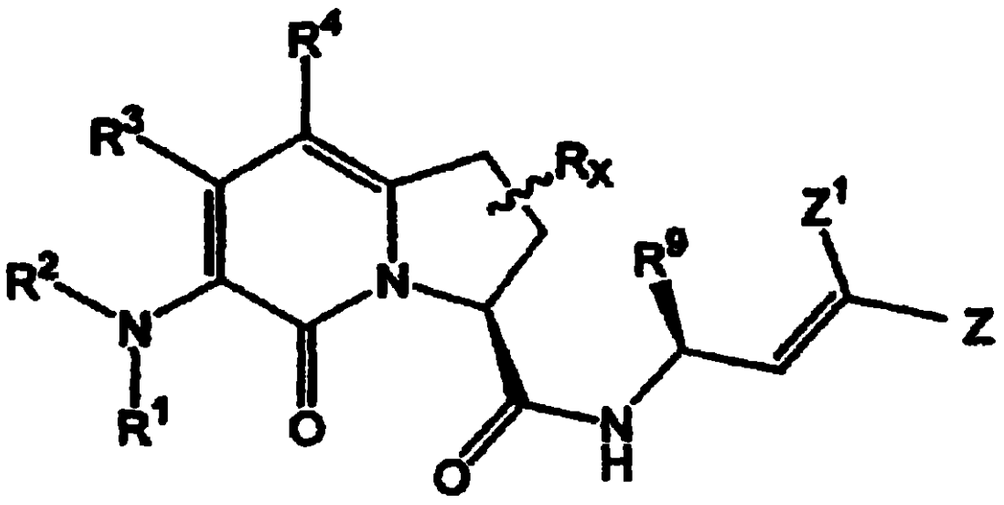
17. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:



en la cual R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z y Z^1 son tal como se definieron previamente.

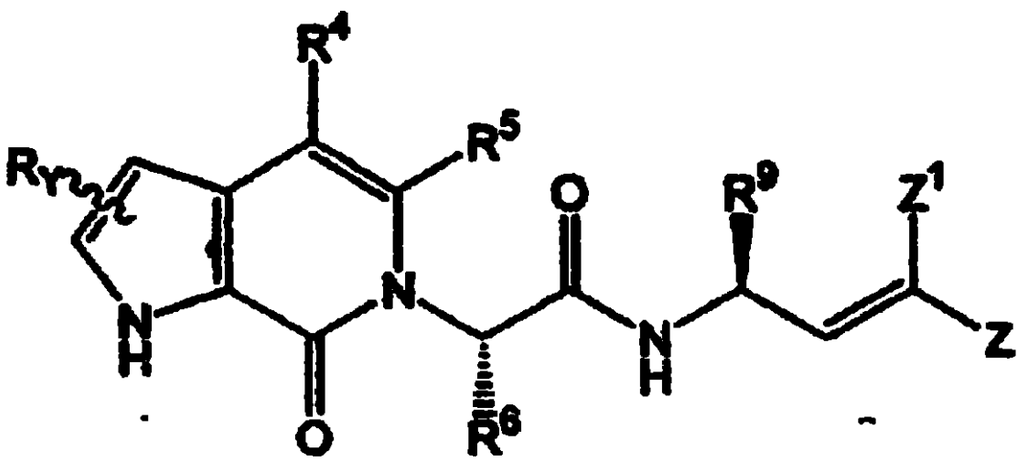
18. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 5, que tiene la fórmula:

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en la cual R^1, R^2, R^3, R^4, R^9, R_x, Z y Z^1 son tal como se definieron previamente.

19. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 6 qu tiene la fórmula:



en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son previamente definidos.

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20. Un compuesto de acuerdo con la reivindicación 1 que tiene actividad antipicornaviral correspondiente con un EC_{50} de menos de o igual a 100 μM en un ensayo de cultivo de célula H1-HeLa.

21 Una composición farmacéutica comprende:
(a) una cantidad terapéuticamente efectiva de por lo menos un agente antipicornaviral seleccionado de compuestos, prodrogas, sales farmacéuticamente aceptables, metabolitos farmacéuticamente activos, y solubles farmacéuticamente aceptables definidos en la reivindicación 1; y

un portador farmacéuticamente aceptable, diluyente, vehículo, o excipiente.

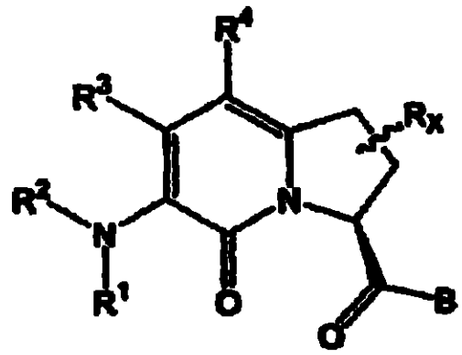
22. Un método de tratar una condición de enfermedad de mamífero mediada por actividad de proteasa picornaviral, comprende administrar a un mamífero en necesidad de ésta una cantidad terapéuticamente efectiva de por lo menos un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmacéuticamente aceptable definido en la reivindicación 1.

23. Un método de inhibir la actividad de una proteasa picornaviral 3C, comprende contactar la proteasa picornaviral 3C con una cantidad efectiva de por lo menos un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmacéuticamente aceptable definido en la reivindicación 1.

24. Un método tal como está definido en la reivindicación 23, en el cual la proteasa picornaviral 3C es una proteasa rinoviral.

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25. Un compuesto que tiene la fórmula:



en la cual:

R^3 y R^4 son independientemente sustituyentes adecuables.;

R_x representa uno o más sustituyentes adecuables.;

B es H, $-OR^{24}$, donde R^{24} es un grupo protector adecuable para una mitad de carbóxilo; y

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuable;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de las mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidas o no sustituidas, o un grupo de protección de nitrógeno sustituido o no sustituido; o

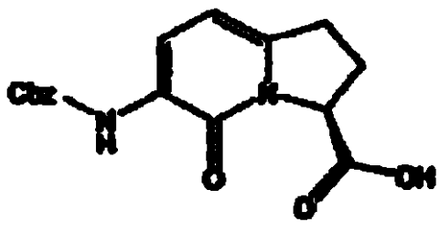
R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable;

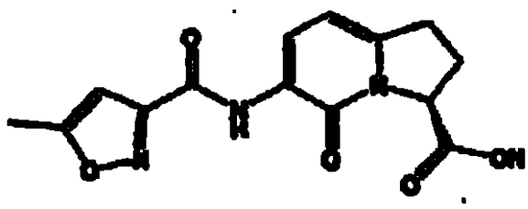
o una sal farmacéuticamente aceptable de ésta.

26. Un compuesto de acuerdo con la reivindicación 25 que tiene la fórmula:

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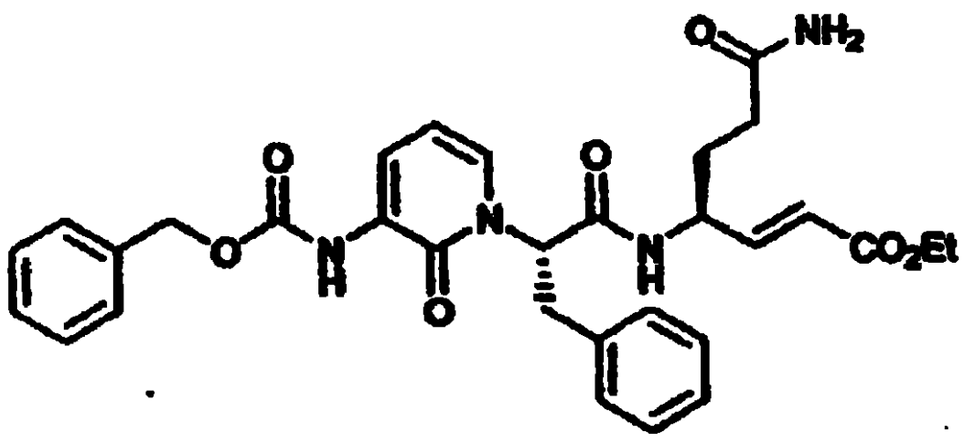




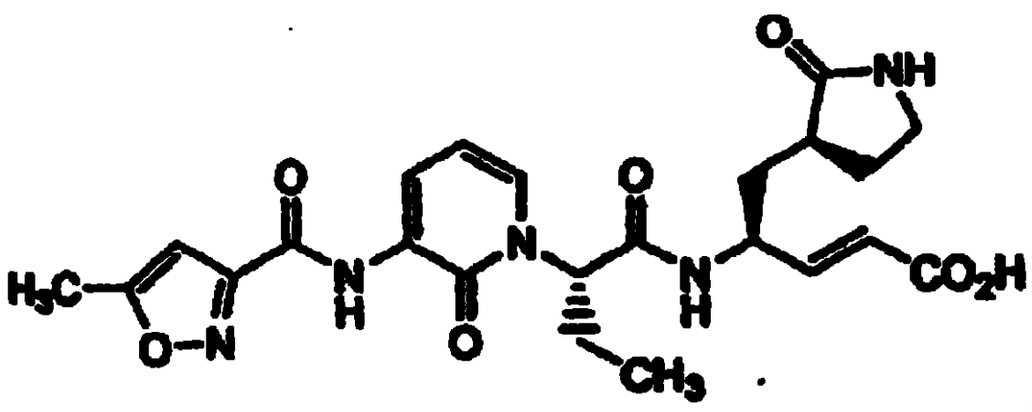
o

o una sal farmacéuticamente aceptable de ésta.

27. Un compuesto seleccionado de:

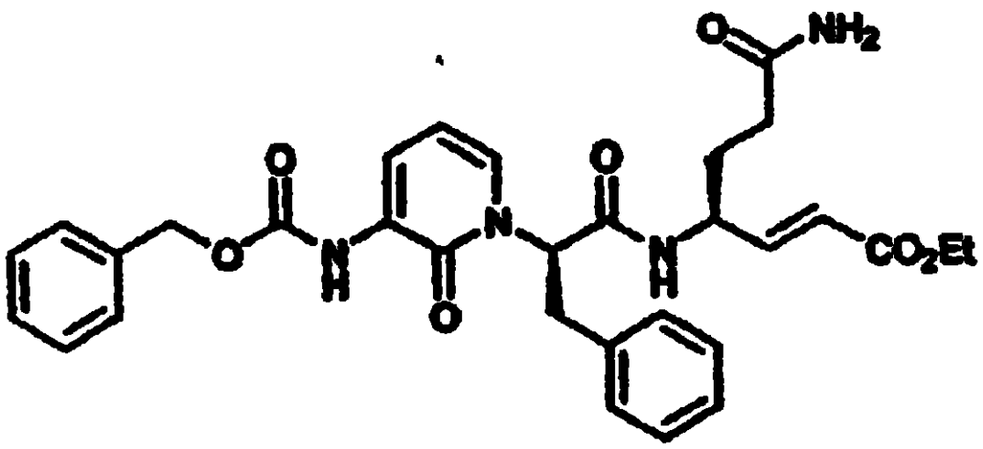


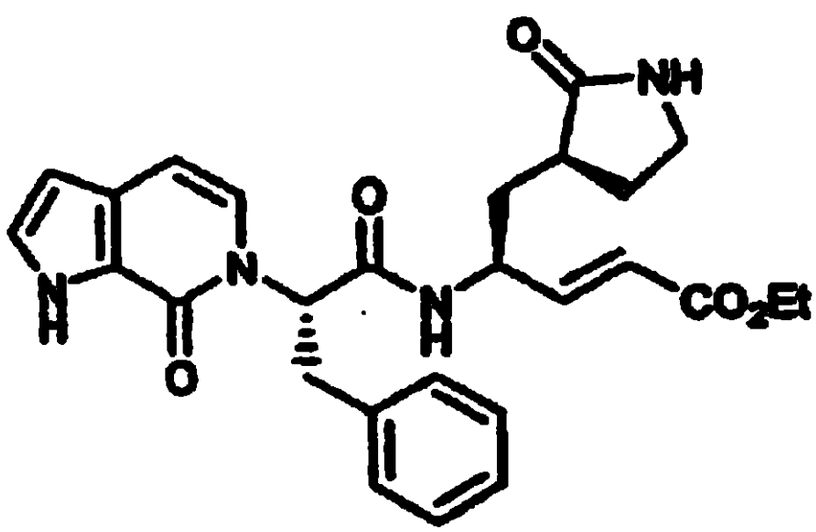
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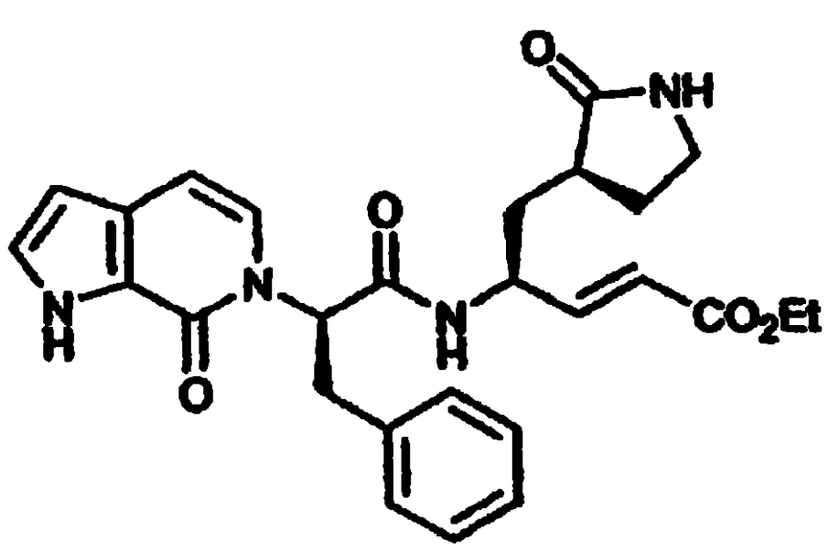


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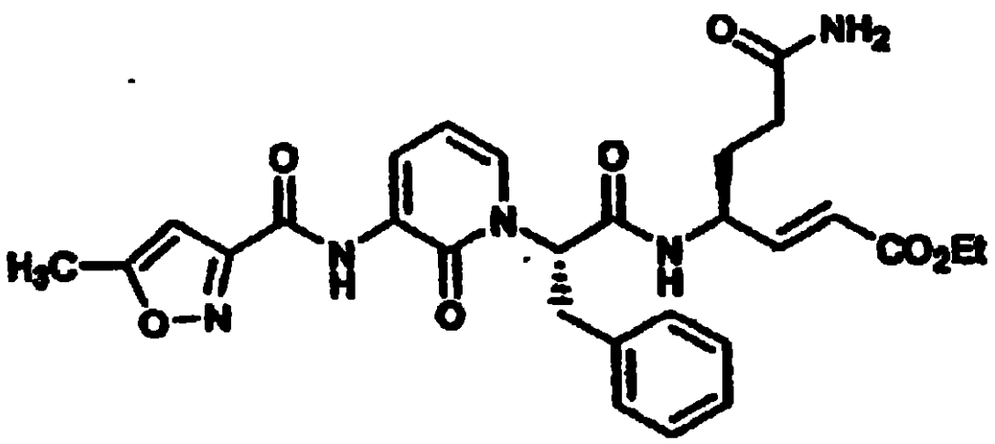
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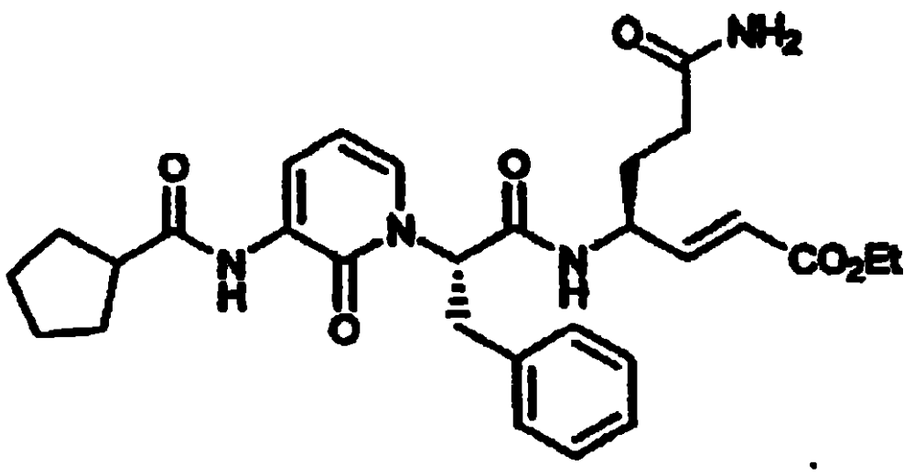


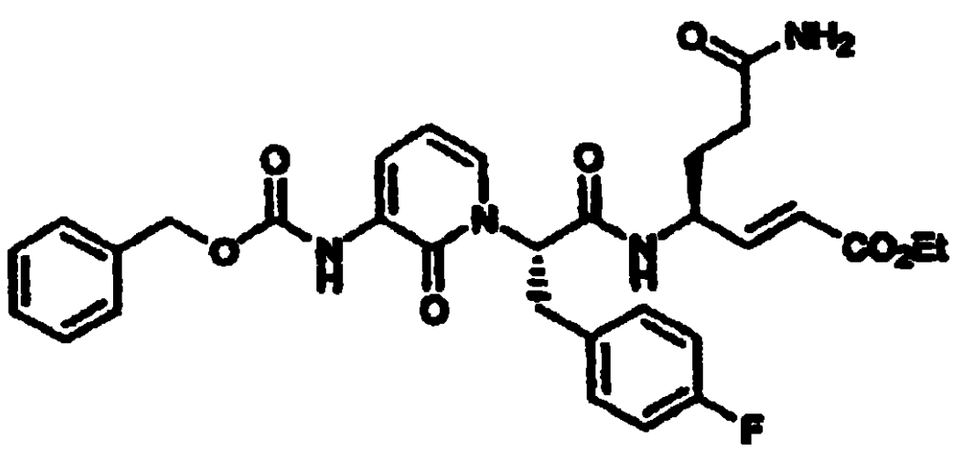




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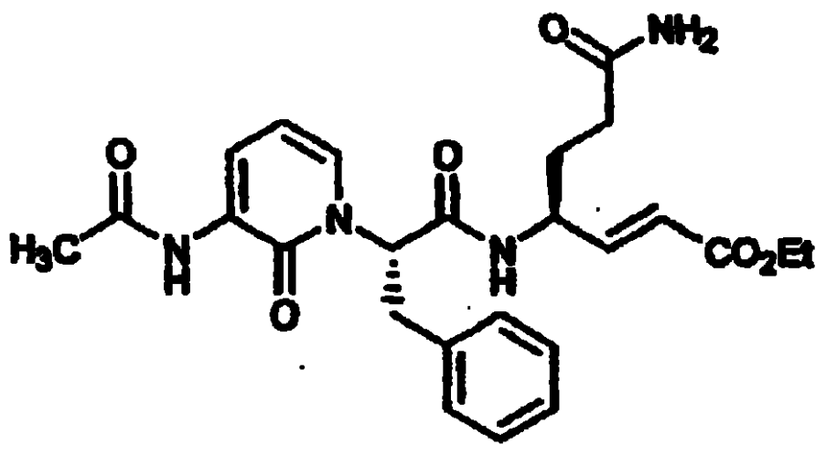


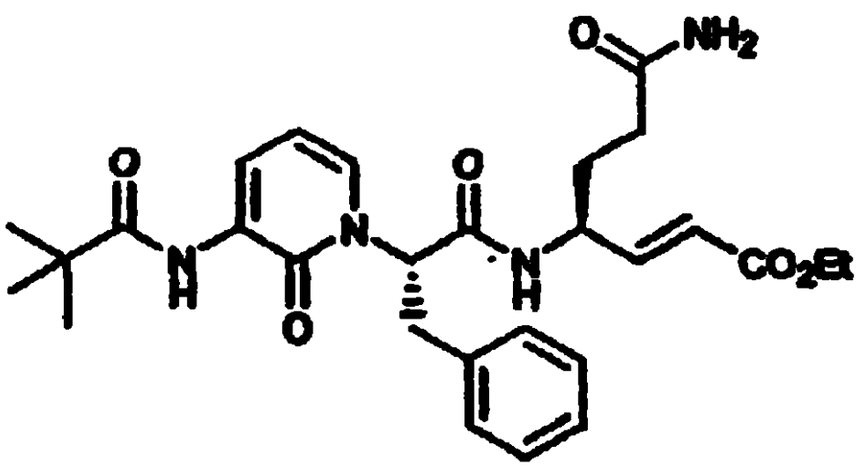


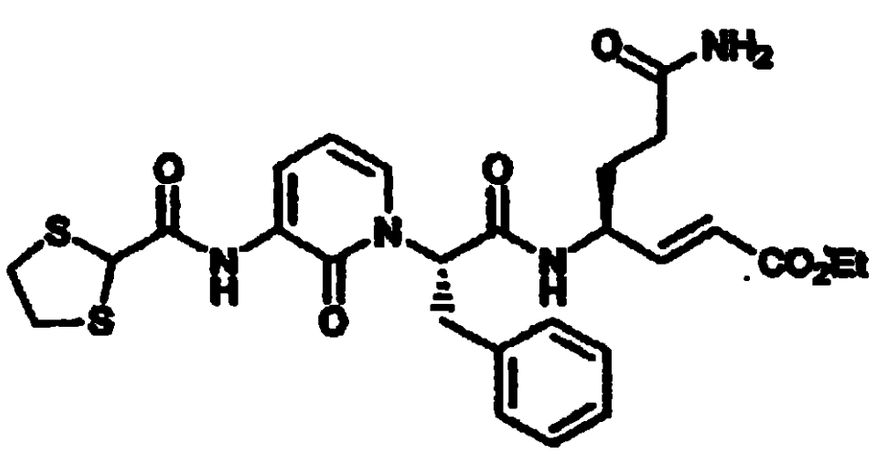


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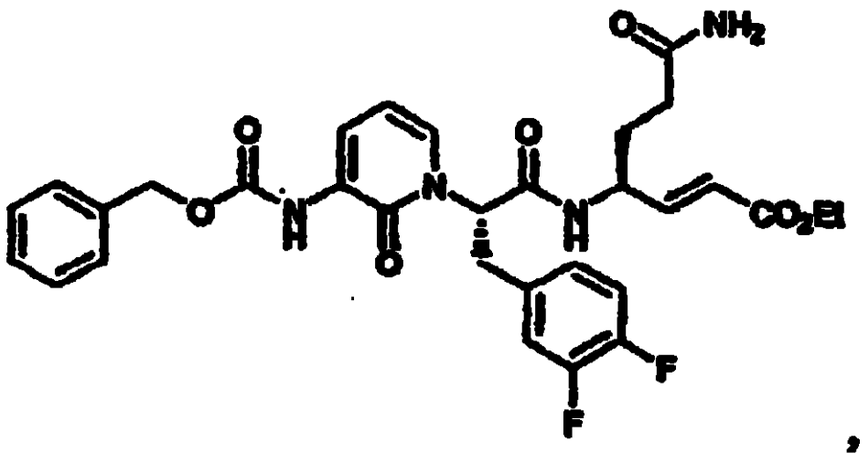


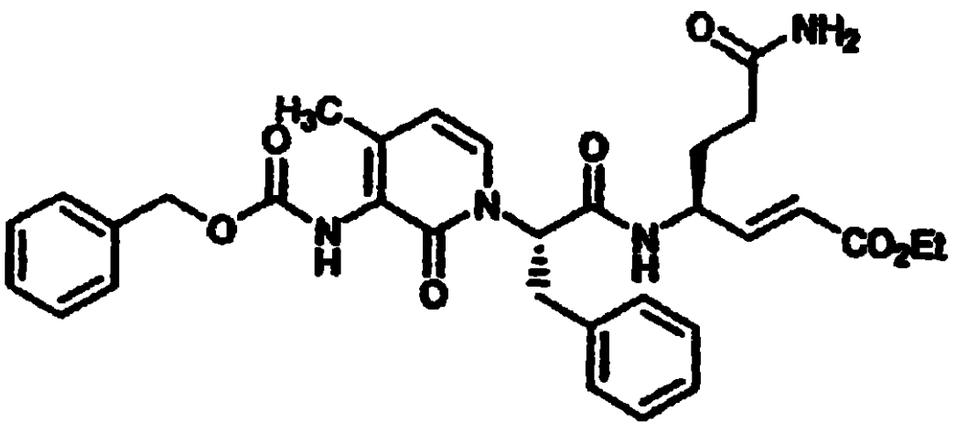


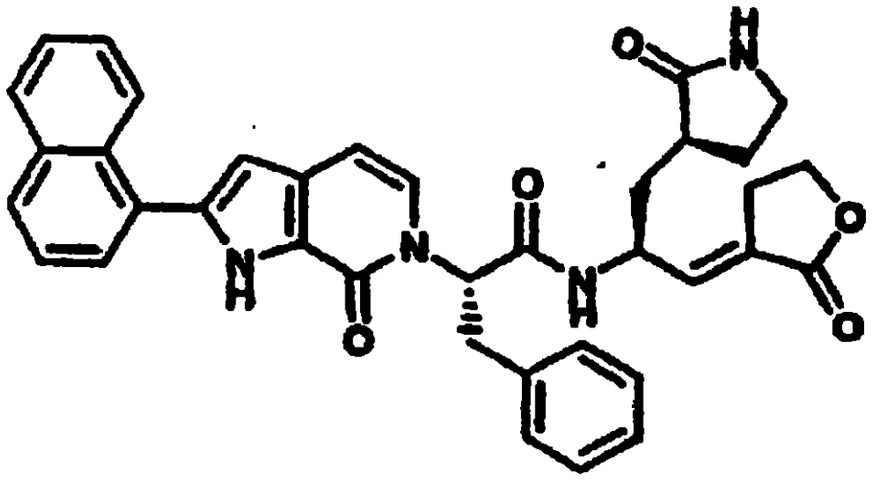


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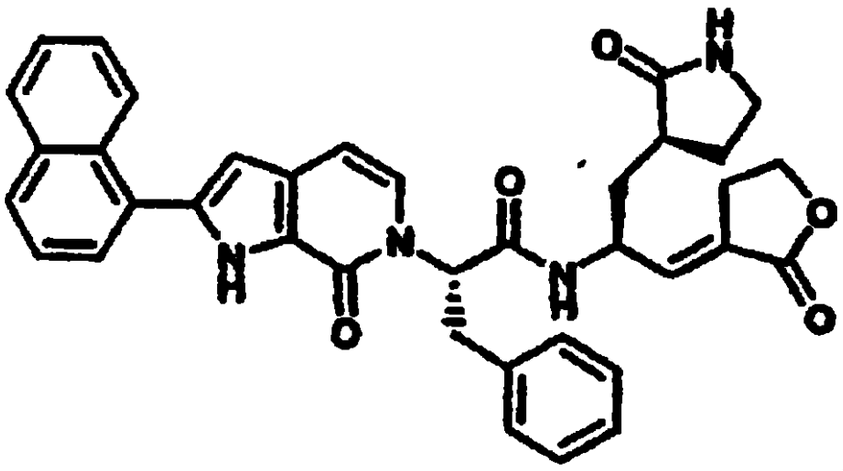
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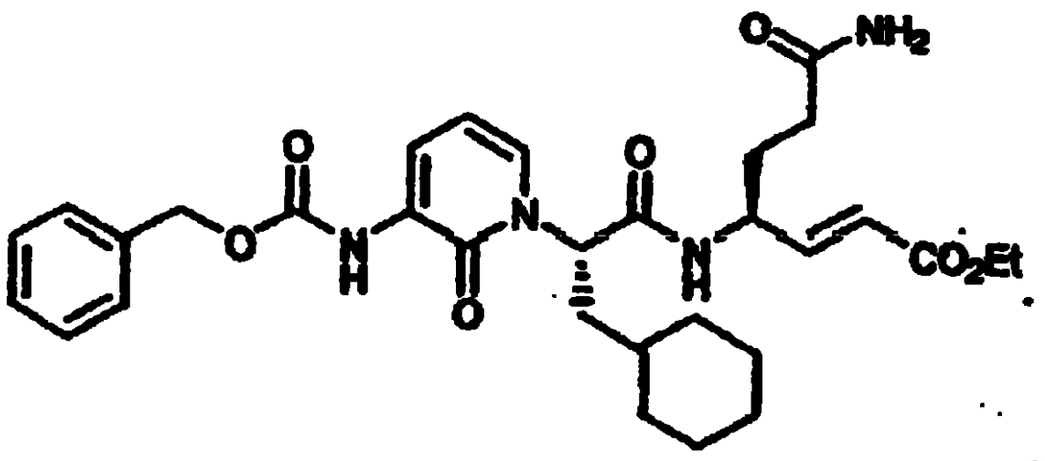


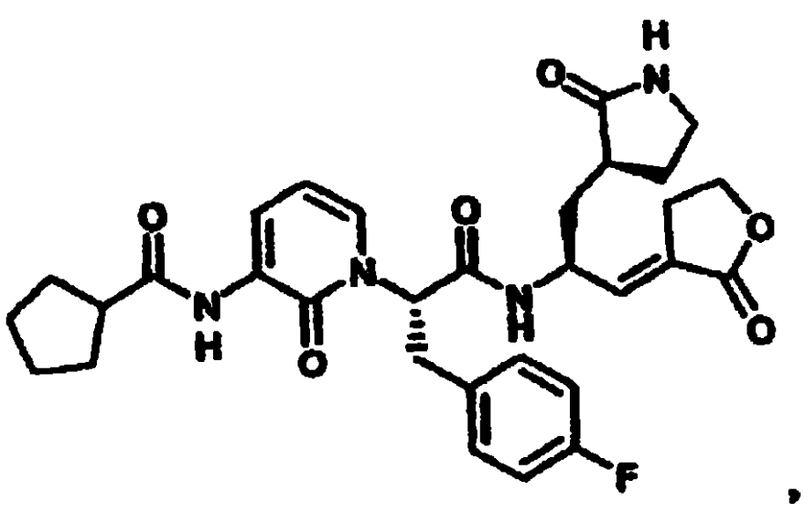




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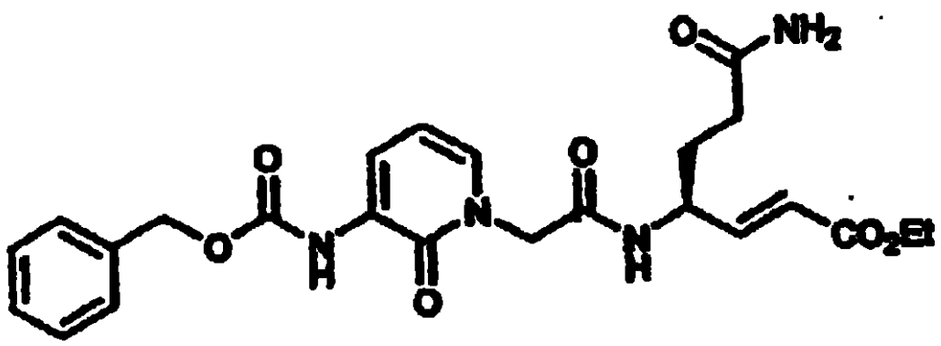


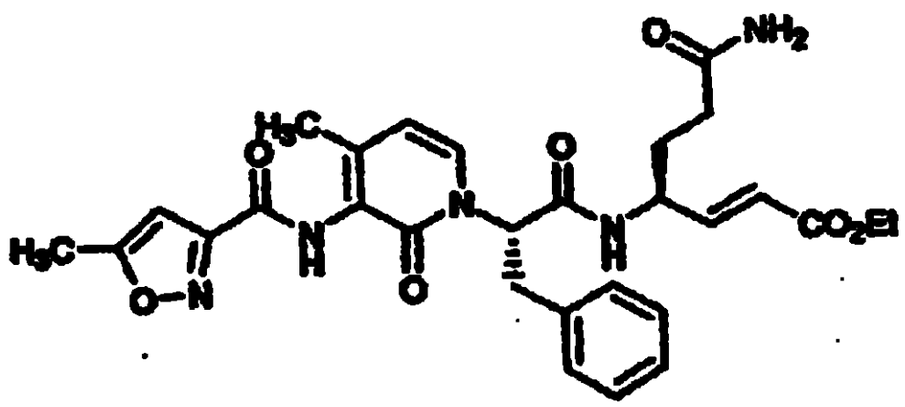


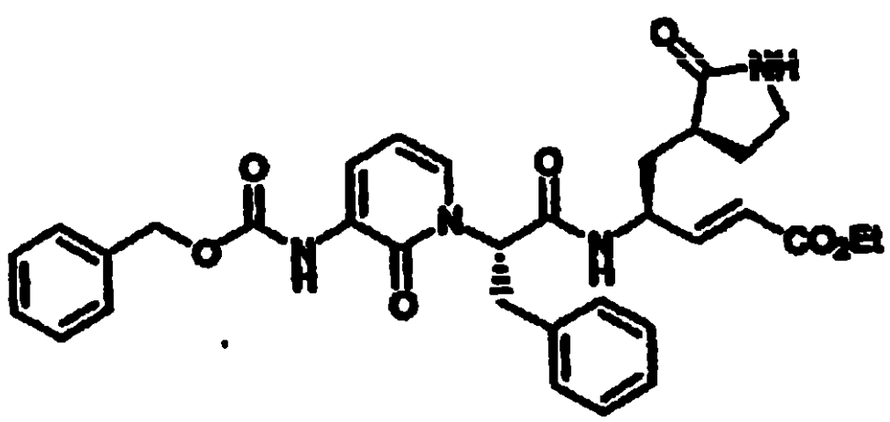


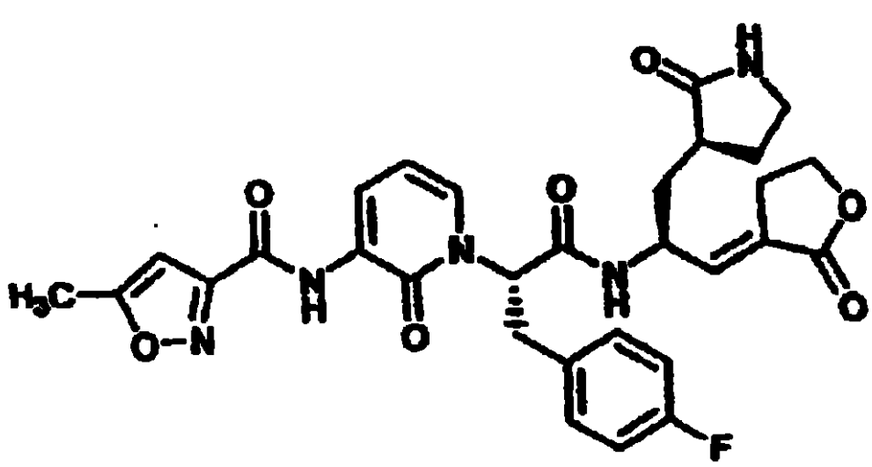
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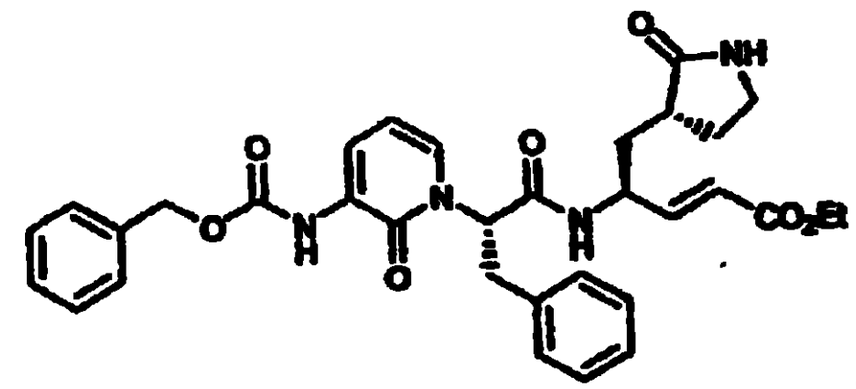




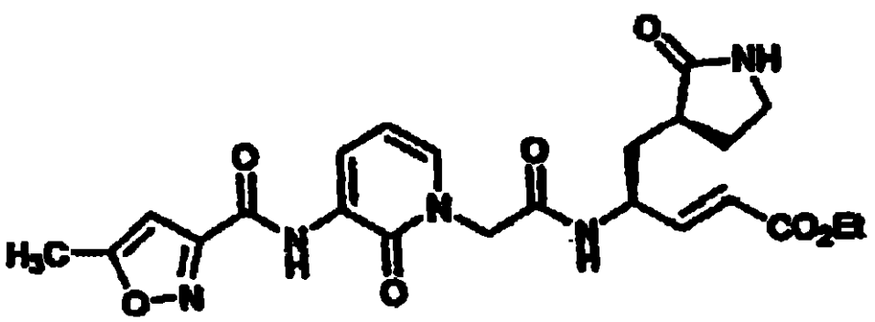


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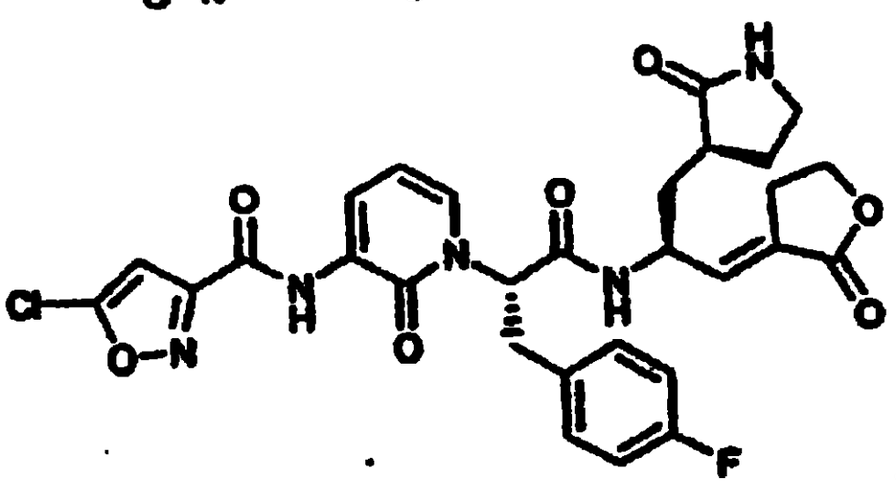
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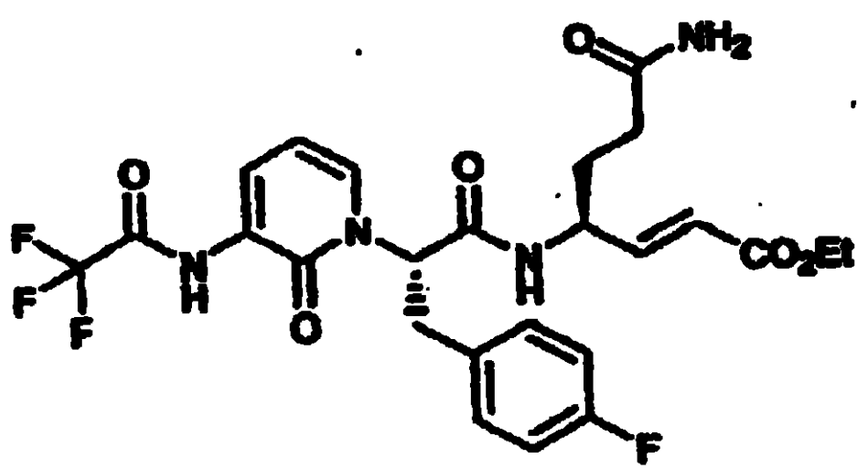
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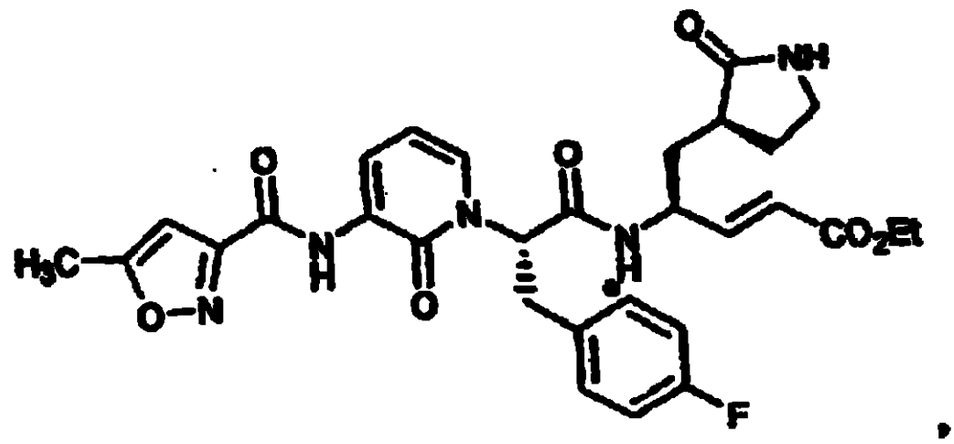
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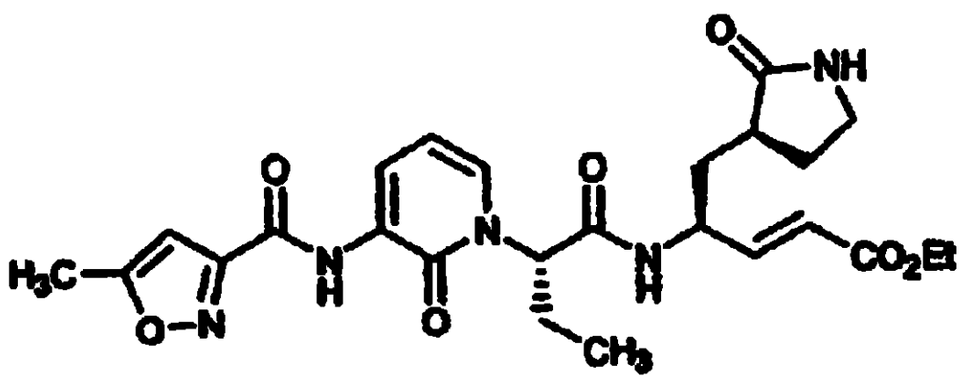


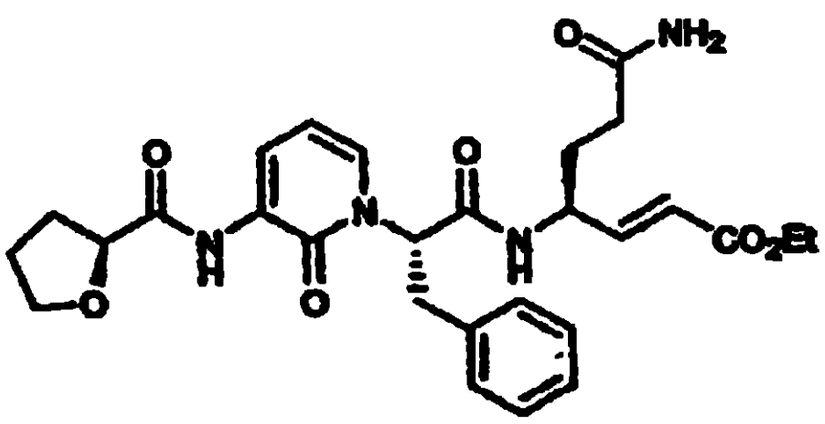
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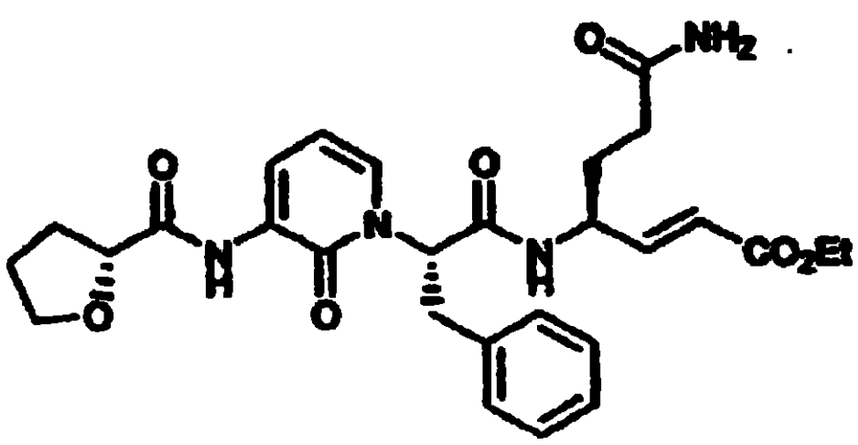
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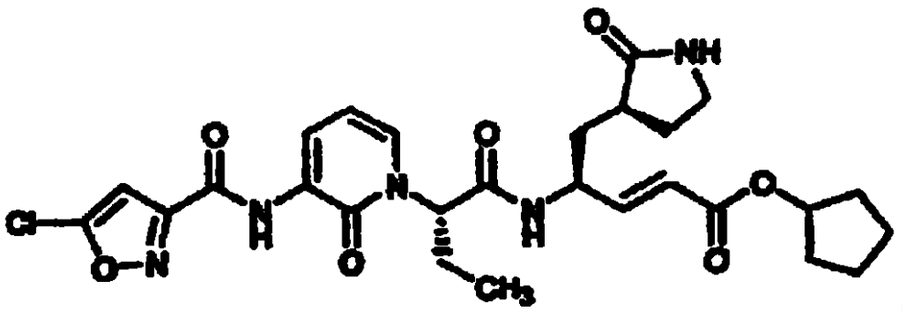


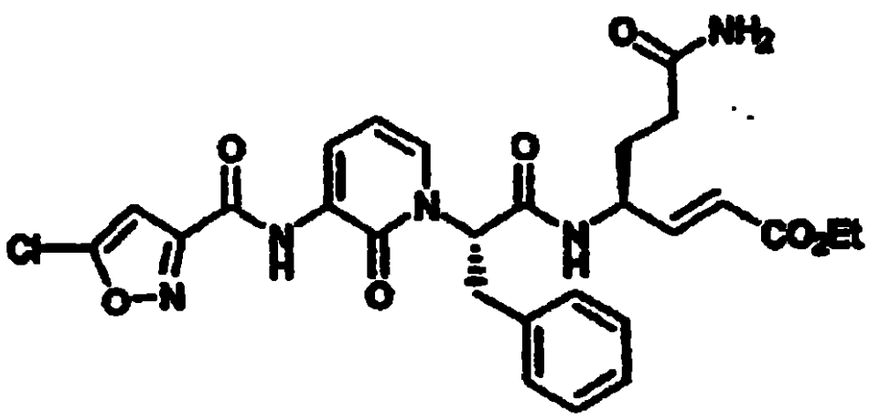


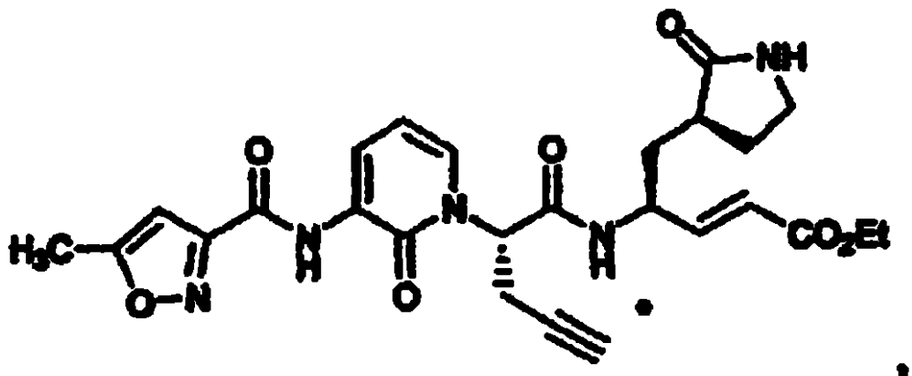


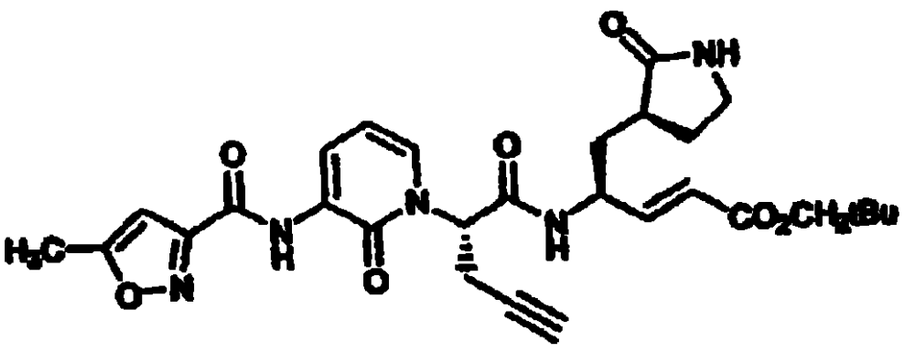
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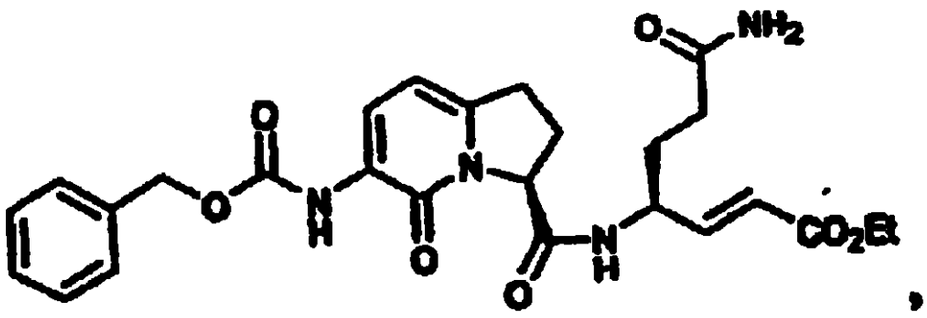




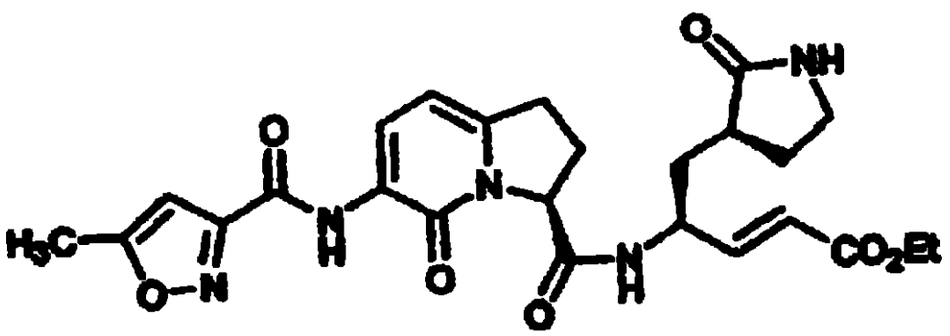


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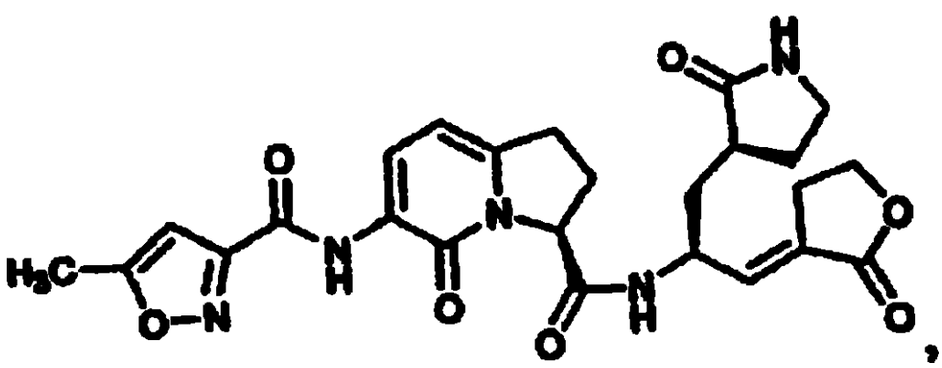
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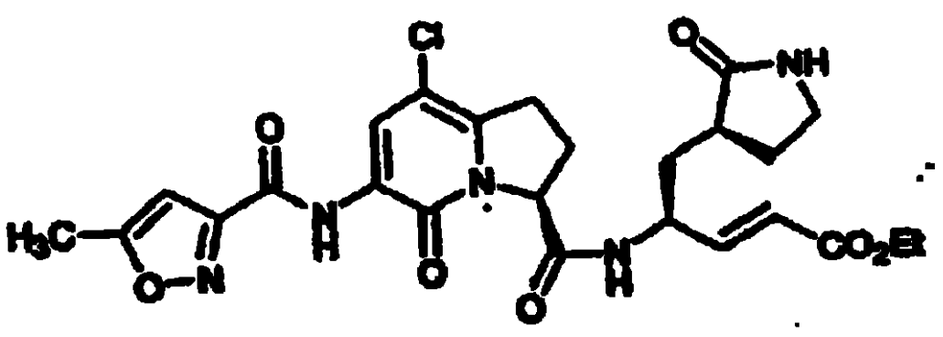
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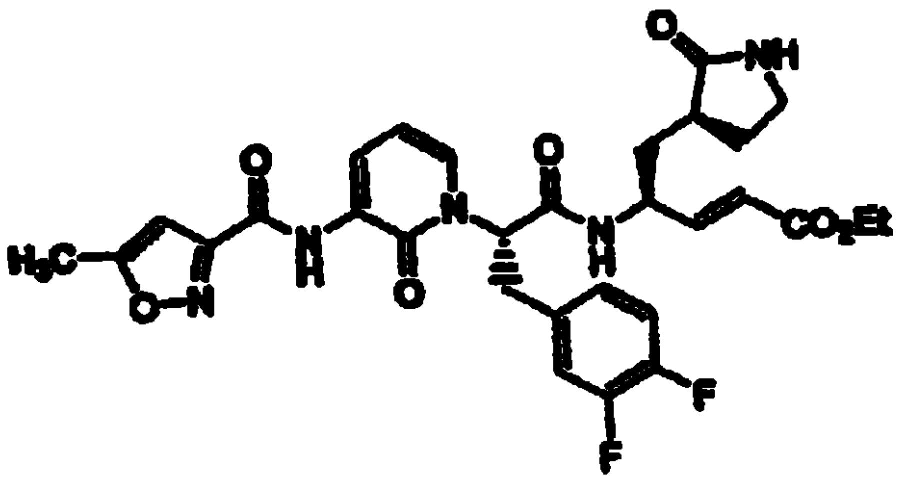


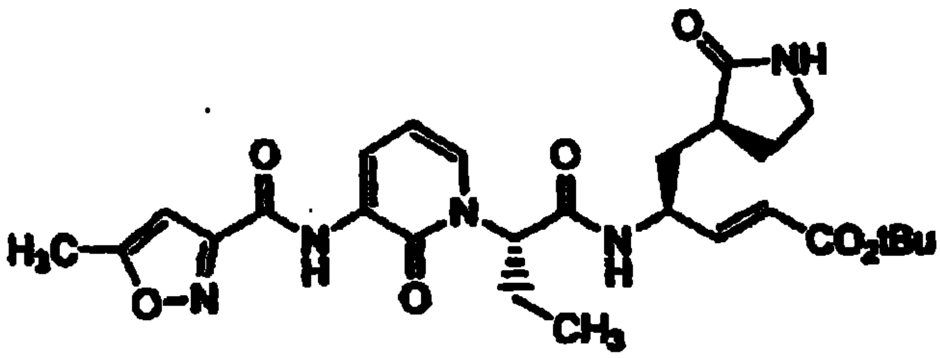
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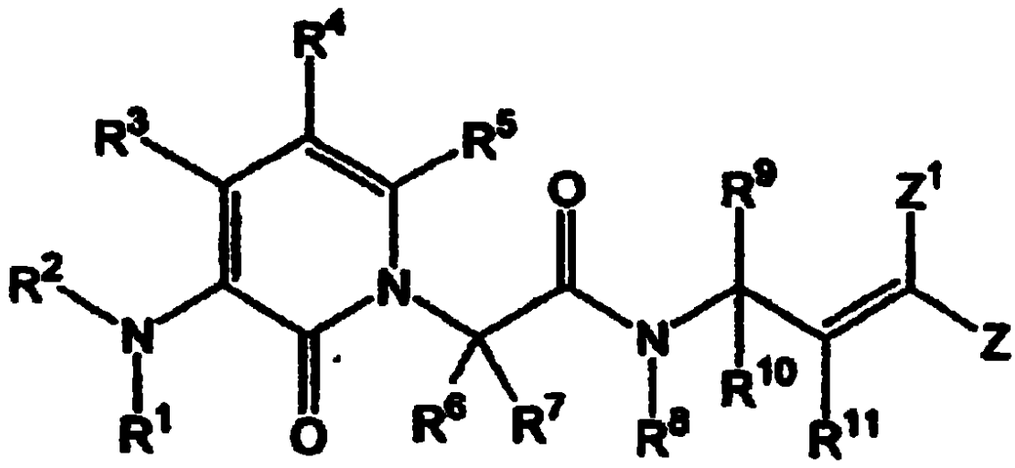


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RESUMEN DE LA REVELACION

Un compuesto que tiene la fórmula:



donde las variables de la fórmula son como se han definido en la revelación, ventajosamente inhiben o bloquean la actividad biológica de la proteasa picornaviral 3C. Esos compuestos, así como también las composiciones farmacéuticas que contienen esos compuestos, son útiles para el tratamiento de pacientes o huéspedes infectados con uno o más picornavirusos, tales como RVP. Los intermediarios y métodos sintéticos para preparar tales compuestos están también descritos.

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ES TRADUCCIÓN FIEL Y COMPLCETA DE LOS DOCUMENT S ADJUNTOS.

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PA 216798

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

October 17, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/192,052***
FILING DATE: ***March 24, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

W. Montgomery

W. MONTGOMERY
Certifying Officer

03-27-00

57 App. to 569

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

DOCKET NUMBER	2521.154-01 PVL	Type a plus sign (+) inside this box.	+

INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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PRINS	Thomas	J.	Cardiff, California
ZHOU	Ru		Carlsbad, California
JOHNSON, JR.	Theodore	O.	San Diego, California

TITLE OF THE INVENTION (280 characters max)

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS (check all that apply)

- [X] Specification — Number of Pages 161 — [ ] Small Entity Statement
- [ ] Drawing(s) — Number of Sheets ____ — [ ] Other (specify) ____

METHOD OF PAYMENT (check one)

- [X] A check or money order is enclosed to cover the Provisional filing fees
- [X] The Commissioner is hereby authorized to charge any deficiencies in the payment of the filing fees and credit any overpayment to Deposit Account Number: 06-1205

PROVISIONAL FILING FEE AMOUNT ($): $150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No.

[ ] Yes, the name of the U.S. Government agency and the Government contract number are: ____

Respectfully submitted,

SIGNATURE Kathryn L. Siebuerth — DATE March 24, 2000

TYPED or PRINTED NAME Kathryn L. Siebuerth — REGISTRATION NO. 40,072 (if appropriate)

[ ] Additional inventors are being named on separately numbered sheets attached hereto.

"Express Mail" mailing label number EL 582469851US

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KATHRYN L. SIEBUERTH
(Typed or printed name of person mailing paper or fee)

Kathryn L. Siebuerth
(Signature of person mailing paper or fee)

PROVISIONAL APPLICATION FILING ONLY

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2521.194-01 PVL

UNITED STATES PROVISIONAL APPLICATION FOR PATENT

60192026 "03240 00

TITLE

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

Inventors: Peter S. Dragovich
Thomas J. Prins
Ru Zhou
Theodore O. Johnson, Jr.

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Kathryn L. Sieburth
(Typed or printed name of person mailing paper or fee)

Kathryn L. Sieburth
(Signature of person mailing paper or fee)

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TITLE

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to pyridone-containing 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 these compounds in pharmaceutical compositions, methods of treatment of rhinoviral infections using these compounds and compositions, and processes for the synthesis of these compounds and compounds useful in the syntheses thereof.

Related Background Art

The picornaviruses are a family of tiny non-enveloped positive-stranded RNA-containing viruses that infect humans and other animals. These viruses include the

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 picornaviral 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 viral 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.

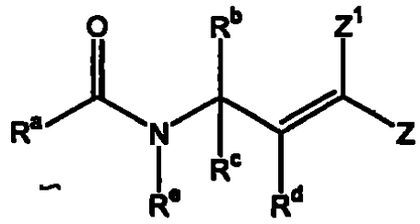
Some small-molecule inhibitors of the enzymatic activity of picornaviral 3C proteases (i.e., antipicornaviral compounds) have been recently discovered. See, for example: U.S. Patent No. 5,856,530; U.S Patent No. 5,962,487; U.S. Patent Application No. 08/991,282, filed December 16, 1997, by Dragovich et al.; and U.S. Patent Application No. 09/301,977, filed April 29, 1999, by Dragovich et al. See also: Dragovich et al., "Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ," *J. Med. Chem.* (1999), Vol. 42, No. 7, 1203-1212, 1213-1224; and Dragovich et al., "Solid-phase Synthesis of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ," *Bioorg. & Med. Chem.* (1999), Vol. 7, 589-598. There is still a desire, however, to discover small-molecule compounds that are especially potent antipicornaviral agents.

Inhibitors of other related cysteine proteases such as cathepsins have been described in, e.g., U.S. Patent No. 5,374,623; U.S. Patent No. 5,498,616; and WIPO International Publication Nos. WO 94/04172, WO 95/15749, WO 97/19231, and WO 97/49668. There yet remains a need for inhibitors targeting the picornaviral 3C cysteine protease with desirable pharmaceutical properties, such as high specificity.

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SUMMARY OF THE INVENTION

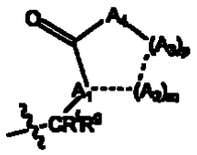
This invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the general formula:



wherein:

R^a is substituted or unsubstituted heterocycloalkyl or heterocycloalkylalkyl;

R^b is a substituent having the formula:



wherein:

R^f and R^g are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, or O; where each R^h, R^i and R^j is independently H or lower alkyl;

each A_3 present is independently $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, or O; where each R^h, R^i and R^j is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^h)$, $C(R^h)(R^i)$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^h)(R^i)$, $C(R^h)(R^i)(R^j)$, and $O(R^i)$, where each R^h, R^i and R^j is independently H or lower alkyl, each R^k is H, alkyl, aryl, or acyl, and each R^l is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0);

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R^c is H, halogen or a substituted or unsubstituted lower alkyl group;

R^d is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

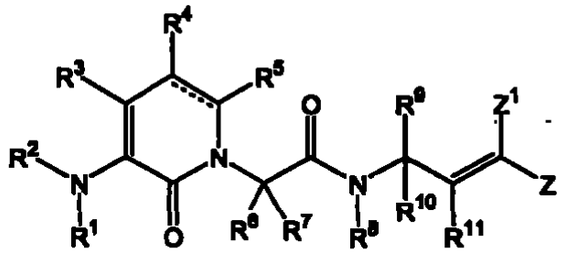
R^e is H or a substituted or unsubstituted alkylgroup; and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^a$, $-CO_2R^a$, -CN, $-C(O)NR^aR^e$, $-C(O)NR^aOR^e$, $-C(S)R^a$, $-C(S)NR^aR^e$, $-NO_2$, $-SOR^e$, $-SO_2R^a$, $-SO_2NR^aR^e$, $-SO_2(NR^a)(OR^e)$, $-SONR^a$, $-SO_3R^a$, $-PO(OR^a)_2$, $-PO(OR^a)(OR^e)$, $-PO(NR^aR^e)(OR^e)$, $-PO(NR^aR^e)(NR^eR^f)$, $-C(O)NR^aNR^eR^f$, $-C(S)NR^aNR^eR^f$, wherein R^a, R^e, R^f and R^g are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^a, R^e, R^f and R^g, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

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.

Preferably, when R^a is substituted or unsubstituted heterocycloalkylalkyl, the alkyl moiety thereof is a substituted or unsubstituted saturated alkyl moiety.

Specifically, this invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the general Formula I:



I

wherein:

R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl

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group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group;

R^3 is H or a suitable substituent; or

R^1 together with R^2 form a suitable nitrogen protecting group; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is H or a suitable substituent;

the dotted line represents an optional bond;

R^5 is H or a suitable substituent;

R^6 is H or a substituted or unsubstituted alkyl group; or

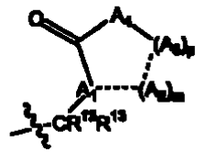
R^5 together with R^6 form a heterocycloalkyl group, which may be optionally substituted;

R^7 and R^{10} are independently H, halogen or a substituted or unsubstituted lower alkyl group;

R^8 is H or a substituted or unsubstituted lower alkyl group;

R^{11} is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

R^9 is a substituent having the formula:



wherein:

R^{12} and R^{13} are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

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when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, and $O(R^{18})$, where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, each R^{17} is H, alkyl, aryl, or acyl, and each R^{18} is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0); and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

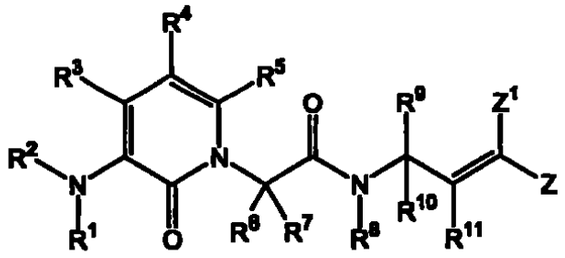
or Z and Z^1, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above except for moieties that cannot form the cycloalkyl or heterocycloalkyl group.

In addition to compounds of the Formula I, antipicornaviral agents of the invention include prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates of such compounds.

DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

In one embodiment, the compounds of this invention useful for inhibiting the activity of picornaviral 3C proteases have the Formula I-A:

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I-A

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Z and Z^1, and the variables contained therein, are as defined above, or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof.

Preferably, in the compounds of Formula I-A:

R^1, R^7, R^8, R^{10} and R^{11} are independently H or a substituted or unsubstituted lower alkyl group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

R^3 is H or a suitable substituent; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is H or a suitable substituent;

R^5 is H or a suitable substituent;

R^6 is H or an unsubstituted alkyl group or a lower alkyl group optionally substituted with a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkoxyl group, an aryloxy group, an alkylthio group, an arylthio group, wherein each alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety thereof may be optionally substituted; or

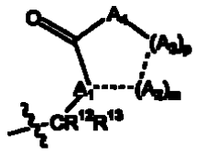
R^5 together with R^6 form a substituted or unsubstituted five- or six-membered heterocycloalkyl group;

wherein when R^3, R^4 and R^5 are suitable substituents, said suitable substituents may be independently selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl,

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nitro, amino, cyano, halogen, haloalkyl (trifluoromethyl), hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio and heteroarylthio, wherein any of the alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted with a suitable substituent;

R^9 is an aminocarbonylalkyl group, an alkylcarbonylaminoalkyl group, an alkylaminocarbonylalkyl group or a substituent having the formula:



wherein:

R^{12} and R^{13} are independently H or lower alkyl;

m is 1;

p is 1 or 2;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O;

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each A_2 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O;

A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O ;

wherein each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, and each R^{17} is H, alkyl, aryl, or acyl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond; and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{19}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

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.

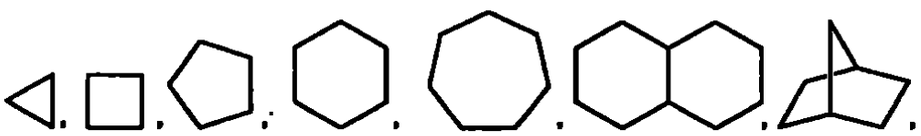
Preferably, R^3, R^4 and R^5 may be independently selected from H, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, amino, halogen, haloalkyl (trifluoromethyl), hydroxyl, alkoxy, aryloxy, cycloalkoxy, heterocycloalkoxy, alkyloxycarbonyl, aryloxycarbonyl, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaryl carbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, alkylamino, arylamino, dialkylamino, alkylaminocarbonyl, alkylsulfonyl, or arylsulfonyl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

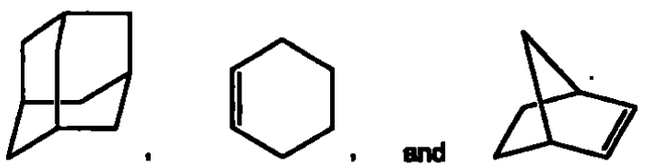
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In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

As used herein, the term "alkyl" represents a straight- or branched-chain saturated or unsaturated hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary alkyl substituents include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, butynyl, propynyl (propargyl, isopropynyl), pentynyl, hexynyl and the like. The term "lower alkyl" refers to an alkyl group containing from 1 to 4 carbon atoms.

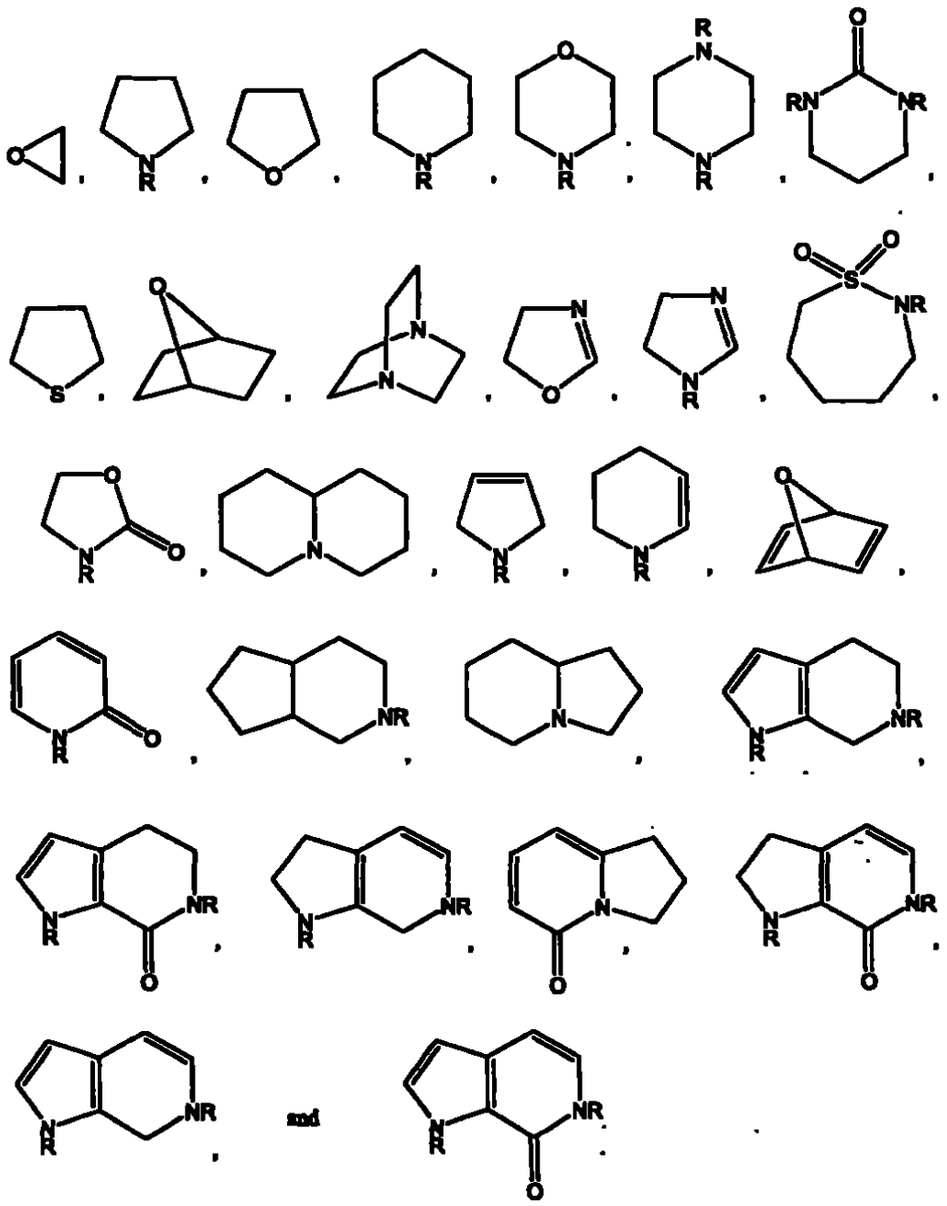
"Cycloalkyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below and may be saturated or unsaturated. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, that may be fully saturated or partially unsaturated. Illustrative examples of cycloalkyl groups include the following:





"Heterocycloalkyl" represents a group comprising a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or partially unsaturated, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heterocycloalkyl groups include,

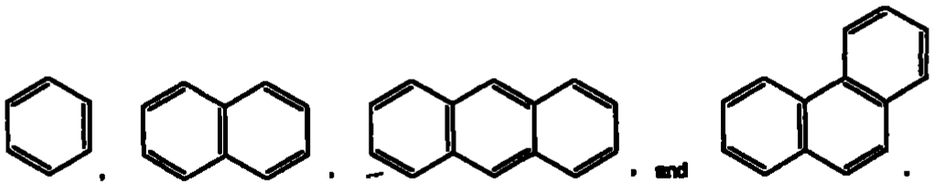
but are not limited to, azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Illustrative examples of heterocycloalkyl groups include the following moieties:



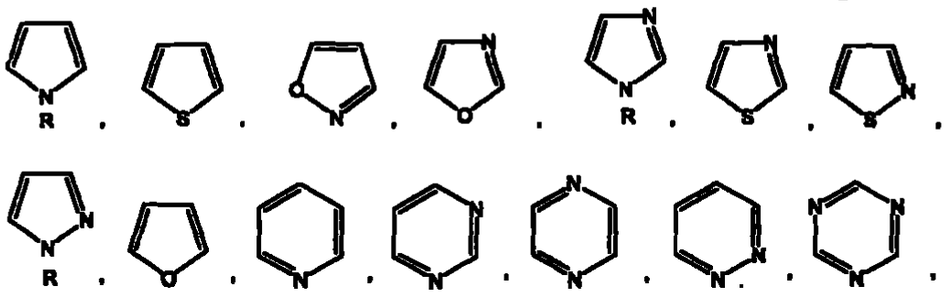
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"Aryl" represents a group comprising an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing from 6 to 18 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents described below, and to 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:



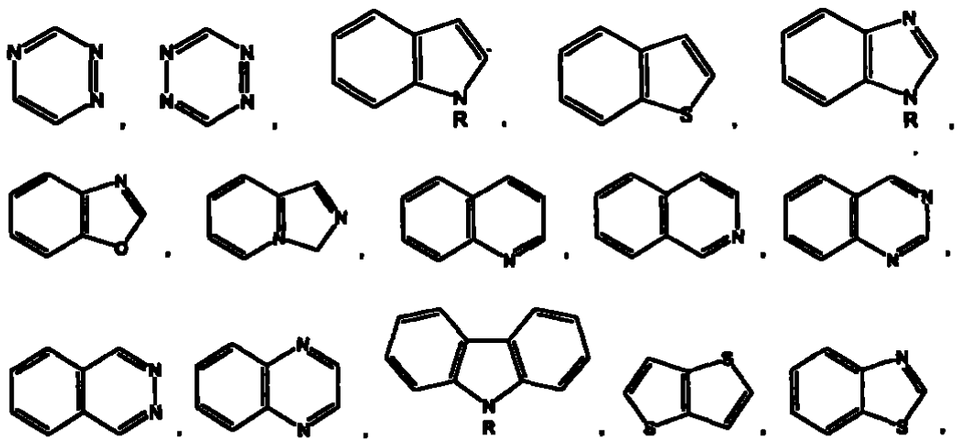
"Heteroaryl" represents a group comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Further examples of heteroaryl groups include the following moieties:



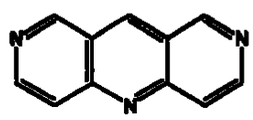
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and



Exemplary "suitable substituents" that may be present on any of the above alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl groups are described herein and include alkyl (except for alkyl), aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino,

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cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio, heteroarylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. Preferred "suitable substituents" include alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heteroaryloxy, and carboxyl. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the compounds of this invention, R^1 and R^2, independently or taken together, may be a suitable nitrogen protecting group. As indicated above, nitrogen protecting groups are well known in the art and any nitrogen protecting group that is useful in the methods of preparing the compounds of this invention or may be useful in the antipicornaviral compounds of this invention may be used. Exemplary nitrogen protecting groups include alkyl, substituted alkyl, carbamate, urea, amide, imide,

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enamine, sulfenyl, sulfonyl, nitro, nitroso, oxide, phosphinyl, phosphoryl, silyl, organometallic, borinic acid and boronic acid groups. Examples of each of these groups, methods for protecting nitrogen moieties using these groups and methods for removing these groups from nitrogen moieties are disclosed in T. Greene and P. Wuts, *supra*.

Preferably, when R^1 and/or R^2 are independently suitable nitrogen protecting groups, suitable R^1 and R^2 substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc: t-butyloxycarbonyl) and aryloxycarbonyl (e.g., Cbz: benzyloxycarbonyl, or FMOC: fluorene-9-methyloxycarbonyl), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl), and the like. When R^1 and R^2 taken together are a suitable nitrogen protecting group, suitable R^1/R^2 substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene).

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group. "Acyl" is intended to mean a -C(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Acyloxy" is intended to mean an -OC(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Thioacyl" is intended to mean a -C(S)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Sulfonyl" is intended to mean an $-SO_2-$ biradical. "Sulfenyl" is intended to mean an -SO- biradical. "Sulfo" is intended to mean an $-SO_3H$ radical. "Hydroxy" is intended to mean the radical -OH. "Amine" or "amino" is intended to mean the radical $-NH_2$. "Alkylamino" is intended to mean the radical $-NHR_a$, where R_a is an alkyl group. "Dialkylamino" is intended to mean the radical $-NR_aR_b$, where R_a and R_b are each independently an alkyl group, and is intended to include heterocycloalkyl groups, wherein R_a and R_b, taken together, form a heterocyclic ring that includes the amine nitrogen. "Alkoxy" 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. "Lower alkoxy" groups have alkyl moieties having from 1 to 4 carbons. "Alkoxycarbonyl" is intended to mean the radical $-C(O)OR_a$, where R_a is an alkyl group. "Alkylsulfonyl" is intended to mean the radical $-SO_2R_a$, where R_a is an alkyl group. "Alkylenedioxy" is intended to mean the divalent radical $-OR_aO-$ which is bonded to

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adjacent atoms (e.g., adjacent atoms on a phenyl or naphthyl ring) , wherein R_a is a lower alkyl group. "Alkylaminocarbonyl" is intended to mean the radical $-C(O)NHR_a$, where R_a is an alkyl group. "Dialkylaminocarbonyl" is intended to mean the radical $-C(O)NR_aR_b$, where R_a and R_b are each independently an alkyl group. "Mercapto" is intended to mean the radical -SH. "Alkylthio" is intended to mean the radical $-SR_a$, where R_a is an alkyl group. "Carboxy" is intended to mean the radical -C(O)OH. "Keto" or "oxo" is intended to mean the diradical =O. "Thioketo" is intended to mean the diradical =S. "Carbamoyl" is intended to mean the radical $-C(O)NH_2$. "Cycloalkylalkyl" is intended to mean the radical –alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined as above, and is represented by the bonding arrangement present in the groups $-CH_2$-cyclohexane or $-CH_2$-cyclohexene. "Arylalkyl" is intended to mean the radical –alkylaryl, wherein alkyl and aryl are defined as above, and is represented by the bonding arrangement present in a benzyl group. "Aminocarbonylalkyl" is intended to mean the radical –alkylC(O) NH_2 and is represented by the bonding arrangement present in the group $-CH_2CH_2C(O)NH_2$. "Alkylaminocarbonylalkyl" is intended to mean the radical –alkylC(O)NHR_a, where R_a is an alkyl group and is represented by the bonding arrangement present in the group $-CH_2CH_2C(O)NHCH_3$. "Alkylcarbonylaminoalkyl is intended to mean the radical –alkylNHC(O)-alkyl and is represented by the bonding arrangement present in the group $-CH_2NHC(O)CH_3$. "Dialkylaminocarbonylalkyl" is intended to mean the radical –alkylC(O)NR_aR_b, where R_a and R_b are each independently an alkyl group. "Aryloxy" is intended to mean the radical $-OR_c$, where R_c is an aryl group. "Heteroaryloxy" is intended to mean the radical $-OR_d$, where R_d is a heteroaryl group. "Arylthio" is intended to mean the radical $-SR_c$, where R_c is an aryl group. "Heteroarylthio" is intended to mean the radical $-SR_d$, where R_d is a heteroaryl group.

If an inventive compound is a base, a desired salt may be prepared by any suitable method known in 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

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or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-tohuenesulfonic acid or ethanesulfonic acid, or the like.

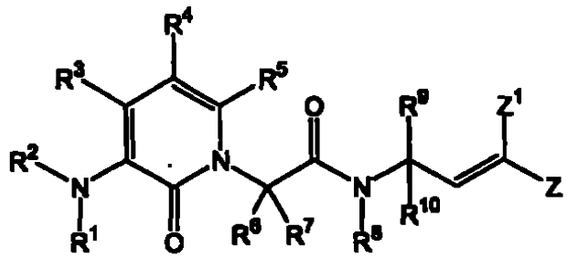
If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative 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.

The inventive compounds may exist as single stereoisomers and/or diastereomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, diastereomers, racemates, and mixtures thereof are intended to be encompassed within the broad scope of the present invention. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral carbon. Preferably, however, the inventive compounds are used in optically pure form. When used describe a particular compound, the term "optically pure" is used herein to that the compound is substantially enantiomerically or diastereomerically pure. Compounds that are substantially enatiomerically pure contain at least 90% of a single isomer and preferably contain at least 95% of a single isomer. Compounds that are substantially diastereomerically pure contain at least 90% of a single isomer of each chiral carbon center present in the diastereomer, and preferably contain at least 95% of a single isomer of each chiral carbon.. More preferably, the optically active compounds in this invention contain at least 97.5% of a single isomer and most preferably contain at least 99% of a single isomer. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least 90% of a single isomer. The term "racemic" or "racemic mixture" refers to a mixture of equal amounts of enantiomeric compounds, which encompasses mixtures of enantiomers and mixtures of enantiomeric diastereomers.

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Another embodiment of this invention comprises the compounds depicted by Formula I-a (as represented by Formula I, wherein the dotted line represents a bond):



I-a

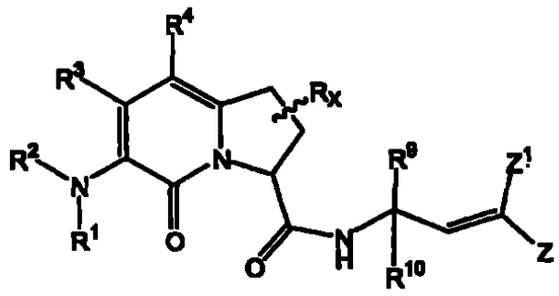
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

R^3, R^4, R^5 are independently H or a suitable substituent described above, and

R^1, R^6, R^7, R^8, R^9, R^{10}, Z and Z^1, and the variables contained therein, are as defined above.

Yet another embodiment of this invention comprises the compounds depicted by Formula I-b:



I-b

wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl,

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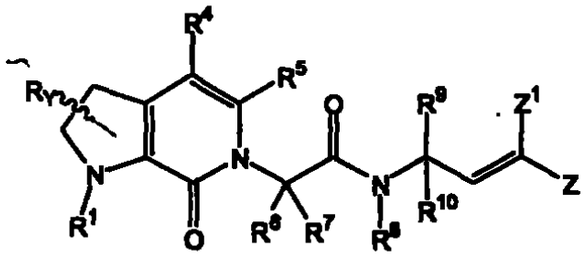
heterocycloalkyl or heteroaryl moieties of the above groups may be substituted or unsubstituted;

R_X represents H or one or more suitable substituents;

R^3 and R^4 are independently H or a suitable substituent described above; and

R^1, R^9, R^{10}, Z and Z^1, and the variables contained therein, are as defined above.

A further embodiment of this invention comprises the compounds depicted by Formula I-c:



I-c

wherein:

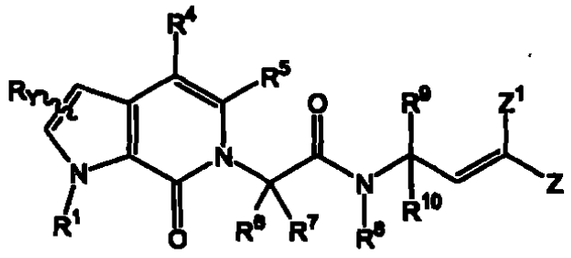
R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R_Y represents H or one or more suitable substituents;

R^4 and R^5 are independently H or a suitable substituent described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined above.

Another embodiment of this invention comprises the compounds depicted by Formula I-d:



I-d

wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

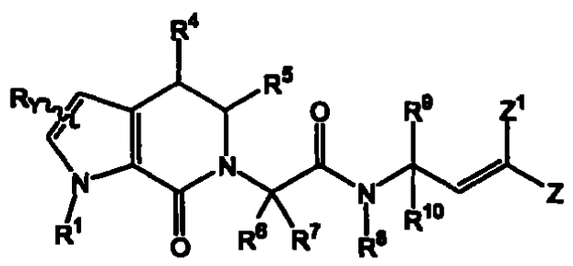
R_Y represents H or one or more suitable substituents;

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R^4 and R^5 are independently H or a suitable substituent described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined above.

Yet another embodiment of this invention comprises the compounds depicted by Formula I-e (as represented by Formula I, wherein the dotted line does not represent a bond):



I-e

wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R_Y represents H or one or more suitable substituents;

R^4 and R^5 are independently H or a suitable substituent described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined above.

In preferred embodiments of Formulas I-a and I-b, R^2 is selected from a substituted or unsubstituted alkyloxycarbonyl group, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocycloalkylcarbonyl or heteroarylcarbonyl group. Preferably, when R^2 is a substituted alkyloxycarbonyl group, R^2 is an unsubstituted or substituted arylalkyloxycarbonyl group. Exemplary R^2 groups include, but are not limited to benzyloxycarbonyl, methylcarbonyl, t-butylcarbonyl, trifluoromethylcarbonyl, cyclopentylcarbonyl, tetrahydrofuran-2-carbonyl, 1,3-dithiolane-2-carbonyl and the like. Preferably, R^2 is a substituted or unsubstituted benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl group. Even more preferably, R^2 is an unsubstituted or substituted benzyloxycarbonyl or heteroarylcarbonyl group, wherein the heteroaryl moiety 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

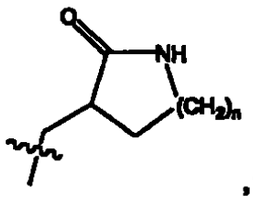
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(1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, or 1,2,5-oxadiazolyl). When the heteroaryl moiety is oxadiazolyl, unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl are preferred. In especially preferred embodiments, the heteroaryl moiety is 3-isoxazolyl or 5-isoxazolyl, either unsubstituted or substituted with one or two methyl groups and/or halogens (F, Cl, Br or I), with chlorine and fluorine being preferred. Accordingly, the heteroarylcarbonylgroup in the especially preferred embodiments is an unsubstituted or substituted 3-carbonyl-1,2-oxazolyl group (i.e., 3-carbonyl-isoxazolyl) or a 5-carbonyl-1,2-oxazolyl group (i.e., 5-carbonyl-isoxazolyl).

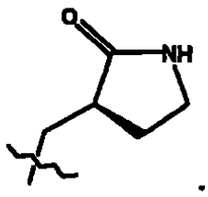
In especially preferred embodiments of Formulas I-a, I-c, I-d and I-e, R^6 is H or an unsubstituted alkyl group or an optionally substituted lower alkyl group, wherein these groups are comprised of a straight- or branched-chain saturated hydrocarbon group, a straight- or branched-chain substituted saturated hydrocarbon group, or group comprised of a straight- or branched-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety. When R^6 is a substituted alkyl group, the point of attachment of R^6 is via a saturated hydrocarbon moiety. When R^6 is a substituted saturated hydrocarbon group, the saturated hydrocarbon group may be optionally substituted with a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkoxy group, an aryloxy group, an alkylthio group, an arylthio group, wherein each alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety thereof may be optionally substituted. When R^6 is comprised of a saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety, the saturated hydrocarbon moiety may be bound to an unsaturated hydrocarbon moiety containing one or more double-bonds or triple-bonds, the terminal positions of which may be substituted by the substituents described above, or may contain additional straight- or branched-chain saturated hydrocarbon moieties. Preferably, the unsaturated hydrocarbon moiety contains one double-bond or one triple-bond, the terminal position(s) of which may optionally contain a straight- or branched-chain saturated hydrocarbon moiety. Preferably, if the unsaturated hydrocarbon moiety contains a double-bond, both terminal positions of the double bond contain a straight- or branched-chain saturated hydrocarbon moiety. In especially preferred embodiments, R^6 is H or a substituted or unsubstituted lower alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl group, or a group comprised of a straight-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety. Preferably, R^6 is H,

methyl, substituted methyl, ethyl, n-propyl, n-butyl, sec-butyl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, substituted or unsubstituted -methylthienyl or substituted or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino or halogen and the thienyl moiety of the substituted -methylthienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino or halogen. When R^6 is substituted methyl, the methyl (methylene) moiety may be substituted with an alkoxy group, an aryloxy group, an alkylthio group or an arylthio group. Most preferably, R^6 is H, ethyl, 2-propyn-1-yl, -methylcyclohexyl, or substituted. or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy and halogen.

In especially preferred embodiments of Formulas I-a, I-b, I-c, I-d and I-e, R^9 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alkyl; $-CH_2NHC(O)CH_3$; and



, where n is 1 or 2. More preferably, R^9 is

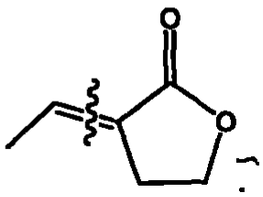


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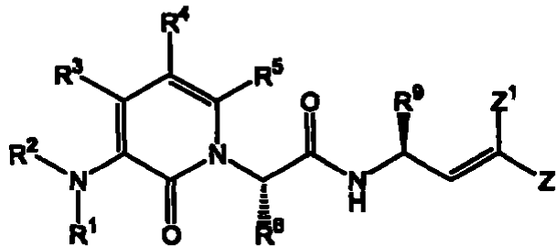
Preferably, in the compounds of Formulas I-a, I-b, I-c, I-d and I-e, Z and Z^1 are independently H, substituted or unsubstituted alkyl, $-CO_2R^{19}$, or taken together with the atom to which they are attached, form a heterocycloalkyl group, which may be optionally substituted. More preferably, Z and Z^1 are independently selected from H, $-CO_2H$, substituted or unsubstituted lower alkyl, $-CO_2$-alkyl, $-CO_2$-cycloalkyl or taken together with the atom to which they are attached form a heterocycloalkyl group , which may be optionally substituted. The heterocycloalkyl group may optionally contain O, N, S and/or P and may be substituted by one or more of oxo (keto) or thioketo. Most preferably, Z^1 is H or lower alkyl and Z is $-CO_2H$, substituted or unsubstituted-CO_2-alkyl, $-CO_2$-cycloalkyl or taken together with the atom to which they are attached form a heterocycloalkyl group , which may be optionally substituted.

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Exemplary Z groups include, but are not limited to substituted and unsubstituted $-CO_2$-alkyl groups, which include straight- and branched-chain alkyl groups such as ethoxycarbonyl, t-butoxycarbonyl, isopropoxycarbonyl, (2,2-dimethylpropyl)-oxycarbonyl, and the like, substituted and unsubstituted $-CO_2$-cycloalkyl groups such as $-CO_2$cyclopentyl or taken together with Z^1 and the atom to which they are attached form

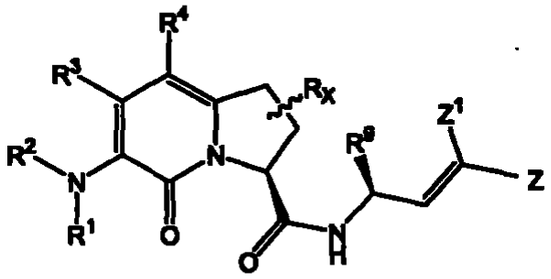


Especially preferred embodiments of this invention comprise compounds of Formulas I-a', I-b', I-c', I-d' and I-e' as follows:



I-a'

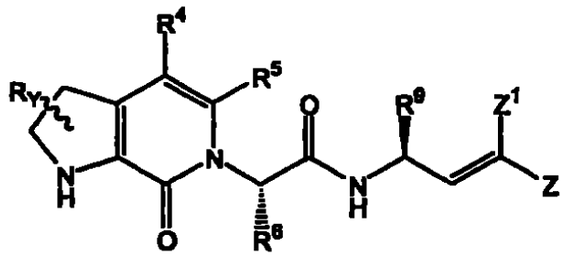
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z and Z^1 are as previously defined;



I-b'

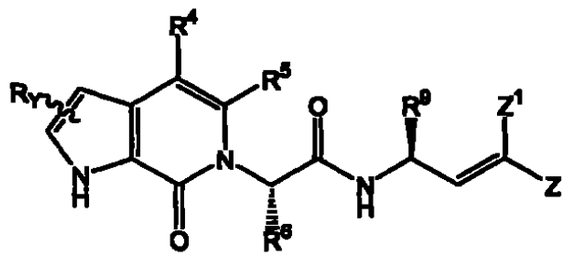
wherein R^1, R^2, R^3, R^4, R^9, R_x, Z and Z^1 are as previously defined;

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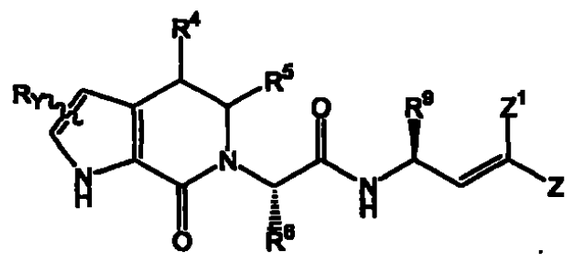
I-c'

wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as previously defined;



I-d'

wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as previously defined; and



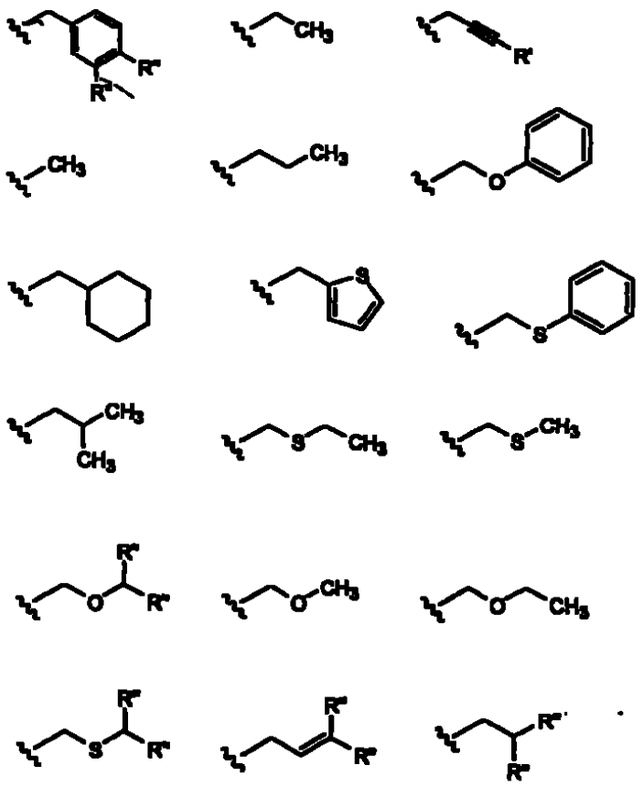
I-e'

wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as previously defined.

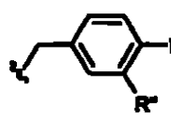
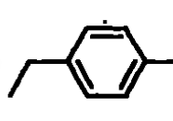
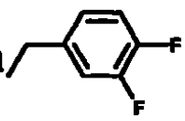
In especially preferred embodiments of Formulas I-a' and I-b', R^2 is unsubstituted or substituted benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl, more preferably heteroarylcarbonyl, where the heteroaryl moiety is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S. More preferably R^2 is heteroarylcarbonyl wherein the heteroaryl moiety is 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); preferred oxadiazolyls are unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl. In especially prefeared embodiments, the heteroaryl moiety is 3-isoxazolyl or 5-isoxazolyl, either unsubstituted or substituted with one or two substituents selected from methyl and halogen, with chloro and fluoro being preferred halogen substituents.

In the especially preferred embodiments of Formulas I-a', I-b', I-c', I-d' and I-e', R^6 is selected from H or:

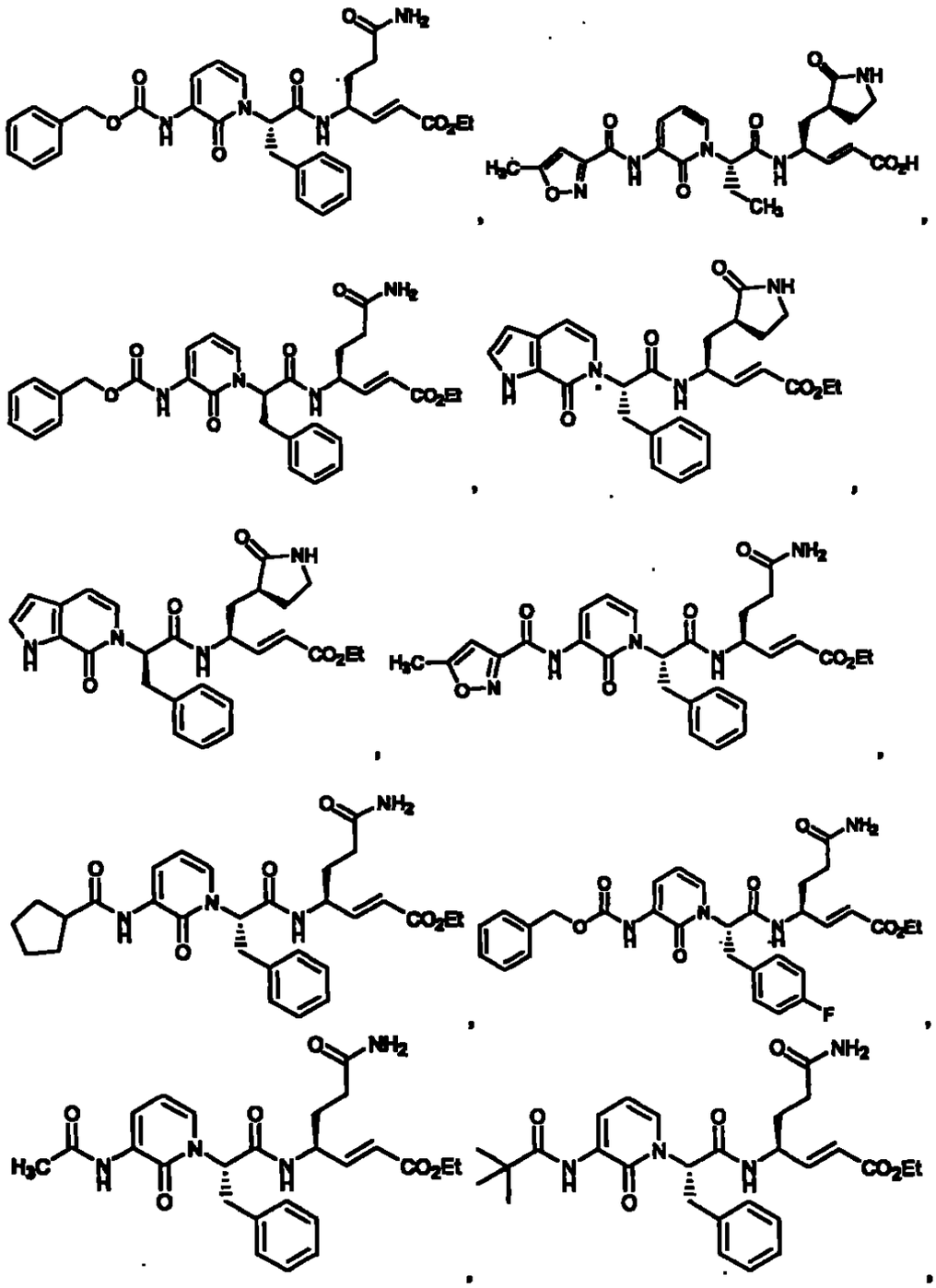


wherein R' may be H or alkyl and R" may be H or independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino, and halogen.

Preferred  groups are  and  .

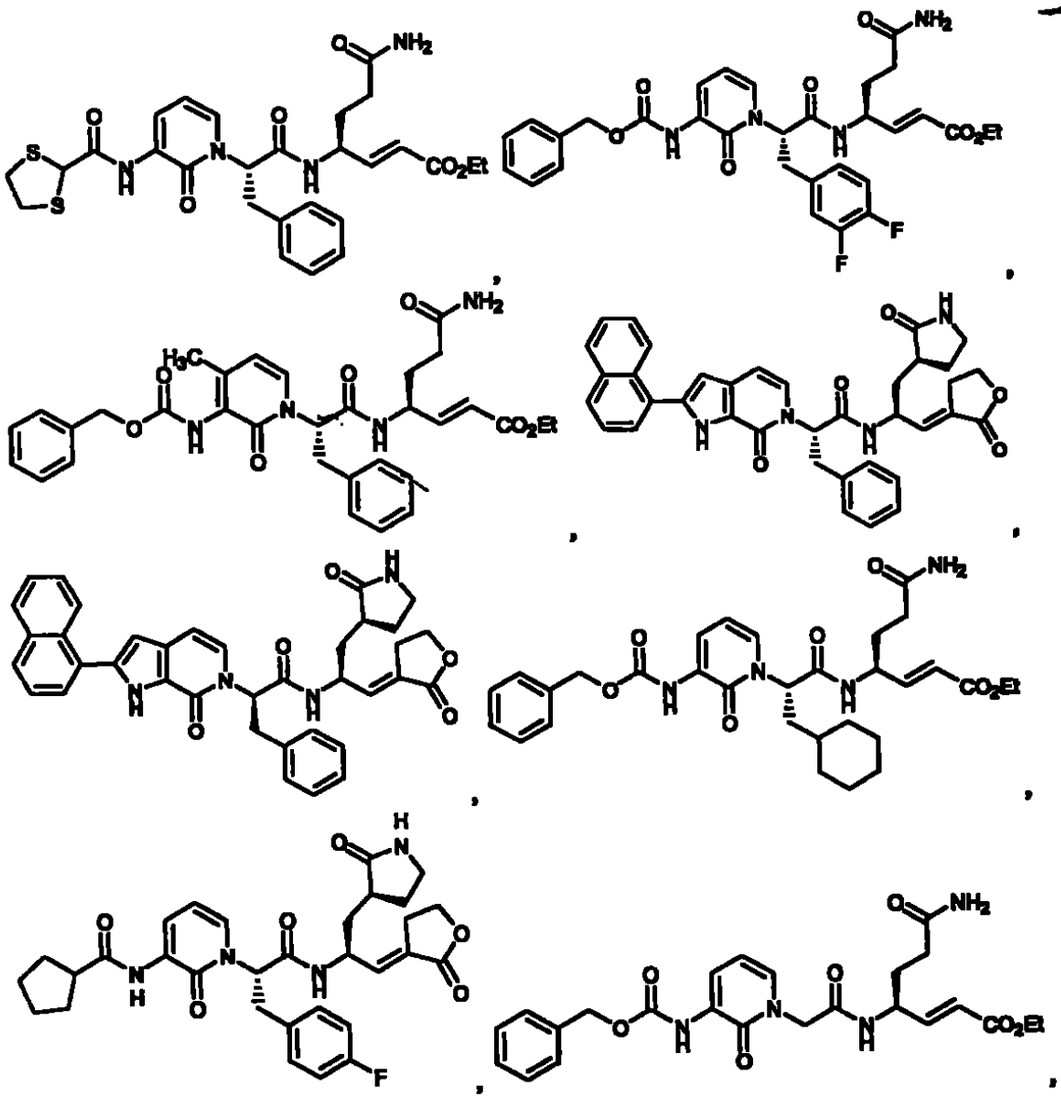
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Preferred specific compounds include those of the Examples below, especially:



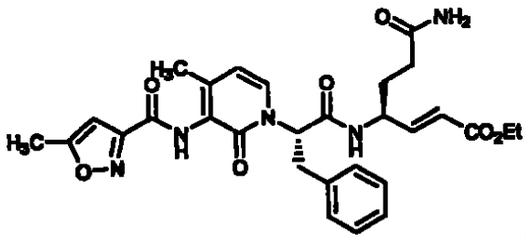
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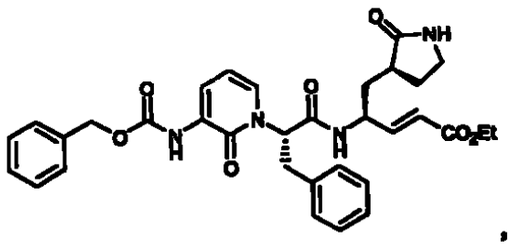


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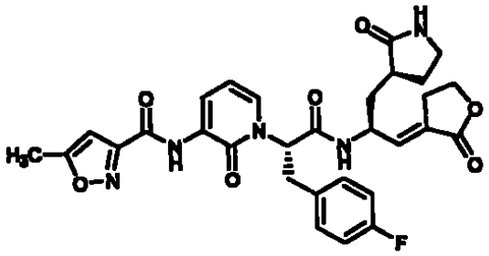
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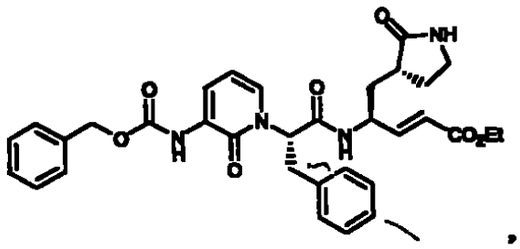
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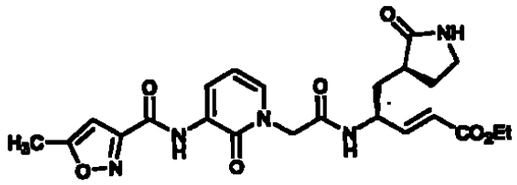
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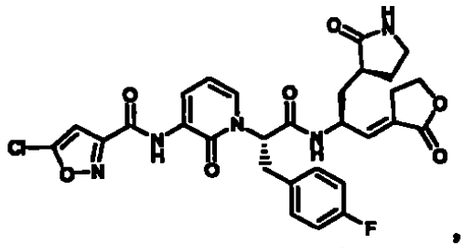
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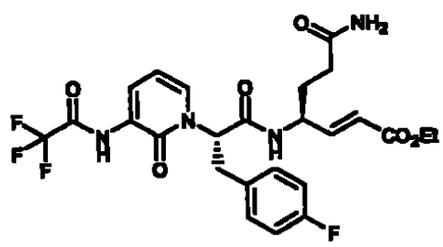
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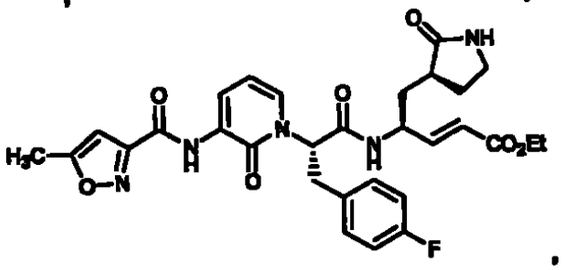
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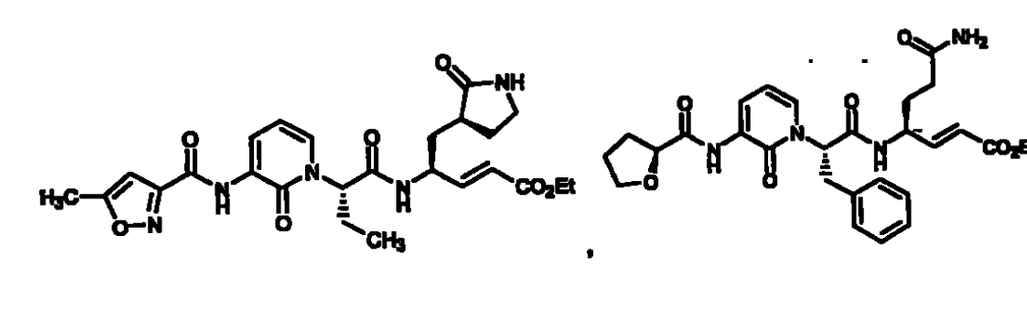
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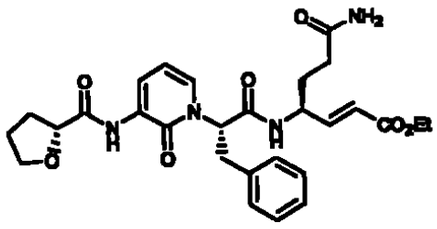
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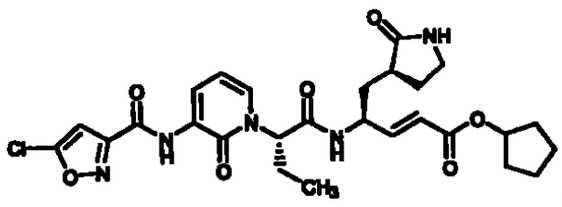
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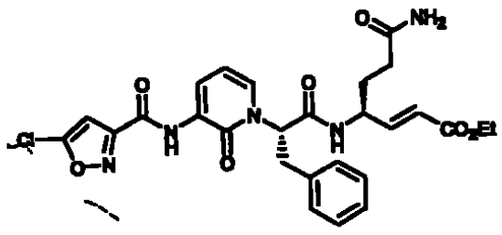
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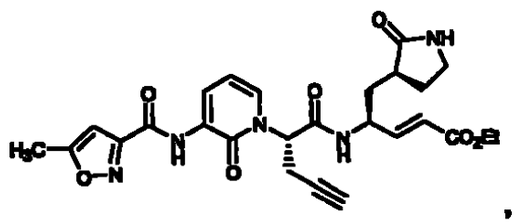
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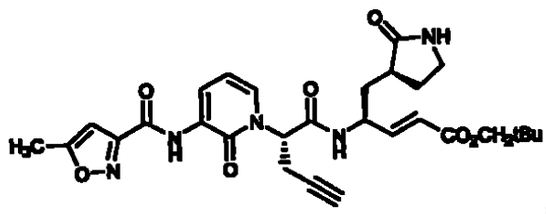
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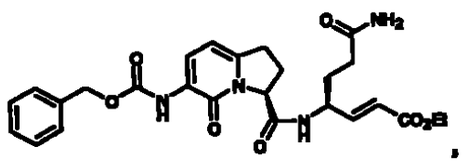
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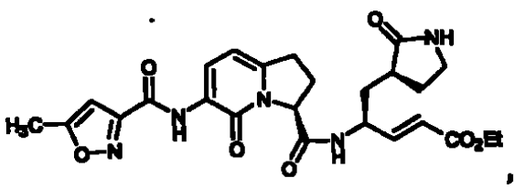
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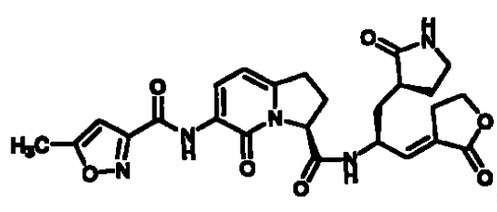
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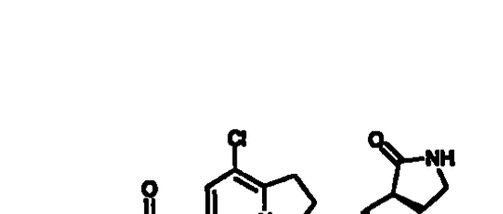
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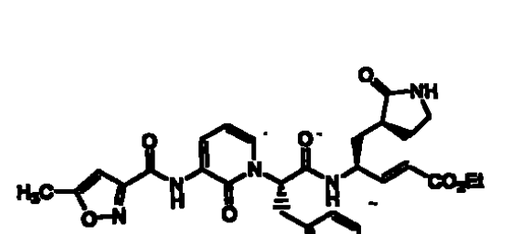
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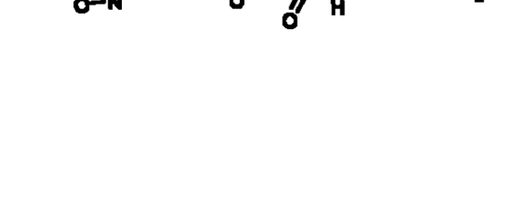
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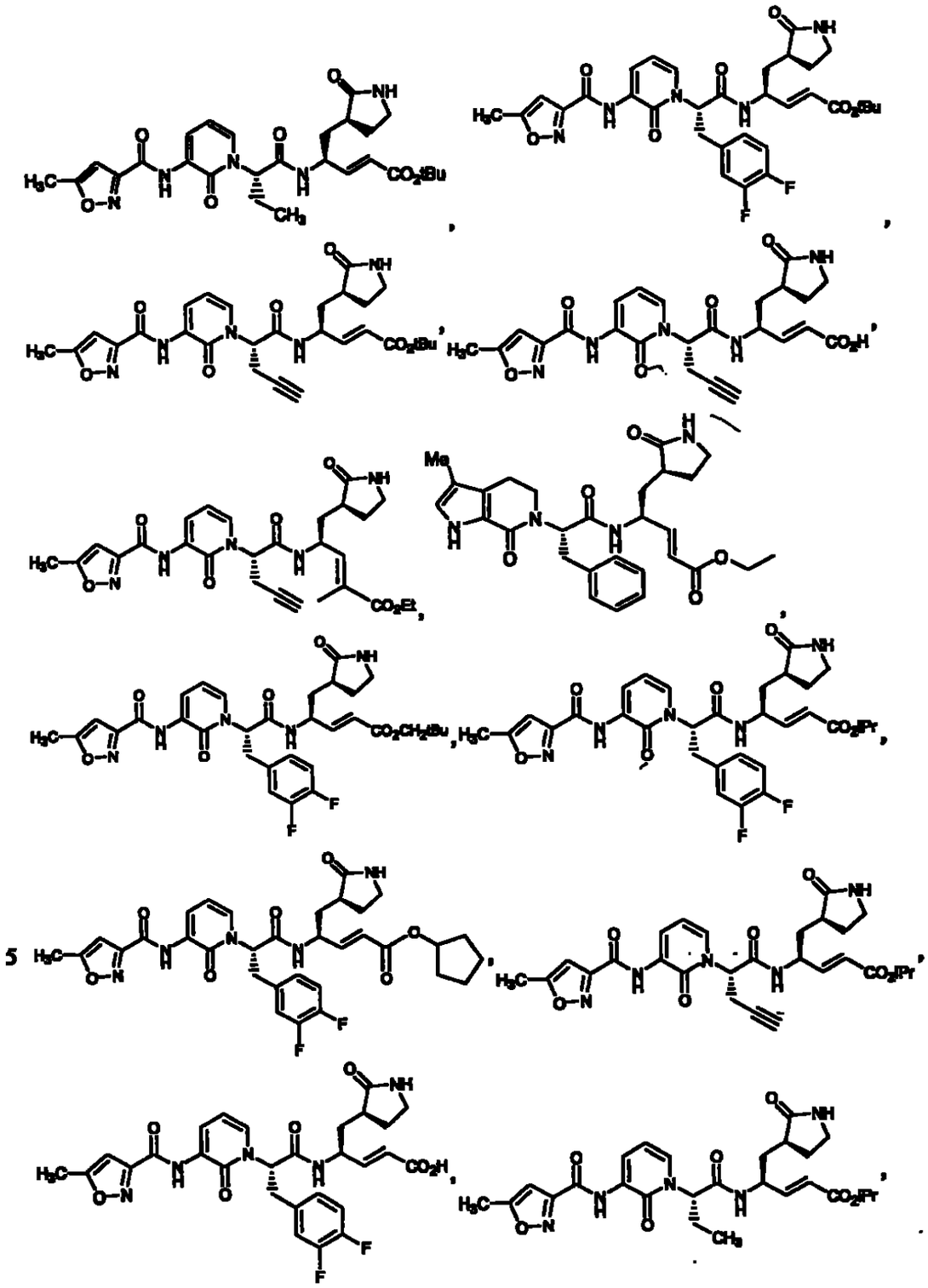


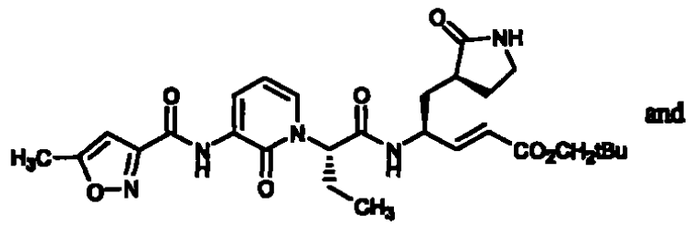
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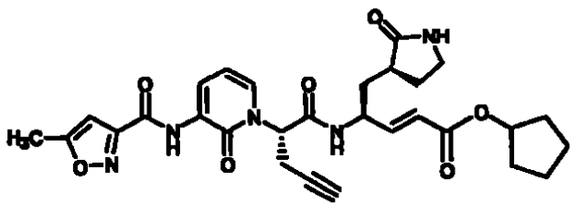
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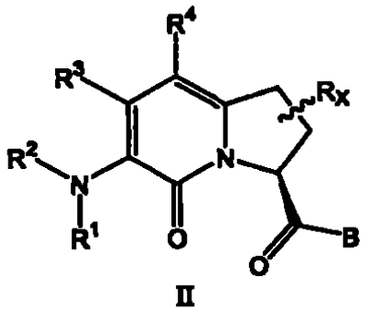




and



The invention is also directed to the intermediates of Formula II, which are useful in the synthesis of certain compounds of Formula I:



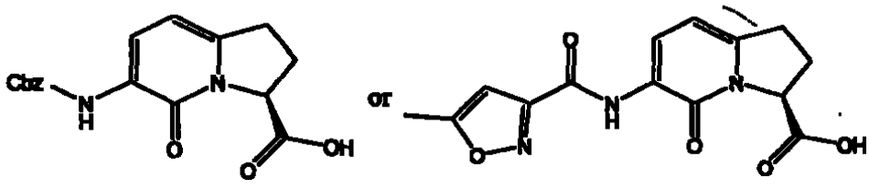
II

wherein the variables R^1, R^2, R^3, R^4 and R_X are as defined above, and B is H, $-OR^{24}$ When R^1 and/or R^2 are independently suitable nitrogen protecting groups, any suitable nitrogen-protecting group known in the art may be used (see, e.g., Greene & Wuts, *supra*). Suitable R^1 and R^2 substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc) and aryloxycarbonyl (e.g., Cbz or FMOC), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl) and the like. Preferably, when R^1 and R^2 are independently suitable nitrogen protecting groups, suitable R^1 and R^2 substituents include, but are not limited to, Boc, Cbz, FMOC, methyloxycarbonyl and trityl. When R^1 and R^2 taken together are a suitable nitrogen

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protecting group, suitable R^1/R^2 substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene). R^{24} may be H or a suitable protecting group for a carboxyl moiety. Suitable carboxyl protecting groups are also well known in the art, examples of which may be found in Greene and Wuts, *supra*, and include, but are not limited to, protecting groups where R^{24} is alkyl, substituted or unsubstituted aryl, alkyl and/or aryl substituted silyl (e.g., t-butyldimethylsilyl (TBS)), and the like.

The invention is also directed to pharmaceutically acceptable salts of the compounds of Formula II. Preferred examples of the Formula II useful as intermediates include the following:



and pharmaceutically acceptable salts thereof.

The antipicornaviral compounds of this invention include prodrugs, the pharmaceutically active metabolites, and the pharmaceutically acceptable salts and solvates thereof. In preferred embodiments, the compounds of Formula I, prodrugs, pharmaceutically acceptable salts, and pharmaceutically active metabolites and solvates thereof have an 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. 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 compound produced through metabolism in the body of a specified compound. A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of a 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,

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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, g-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. 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. 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 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, including, but not limited to human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, meningitis virus, and hepatitis A virus. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example, as a prophylactic. 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.

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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 generally 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.

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 or mode of administration. In preferred embodiments, the inventive pharmaceutical compositions are delivered orally, or intranasally in the form of suspensions. Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions 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

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(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, intraural, or intraocular infusion. A "therapeutically effective amount" is intended to mean the amount of an inventive agent 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.

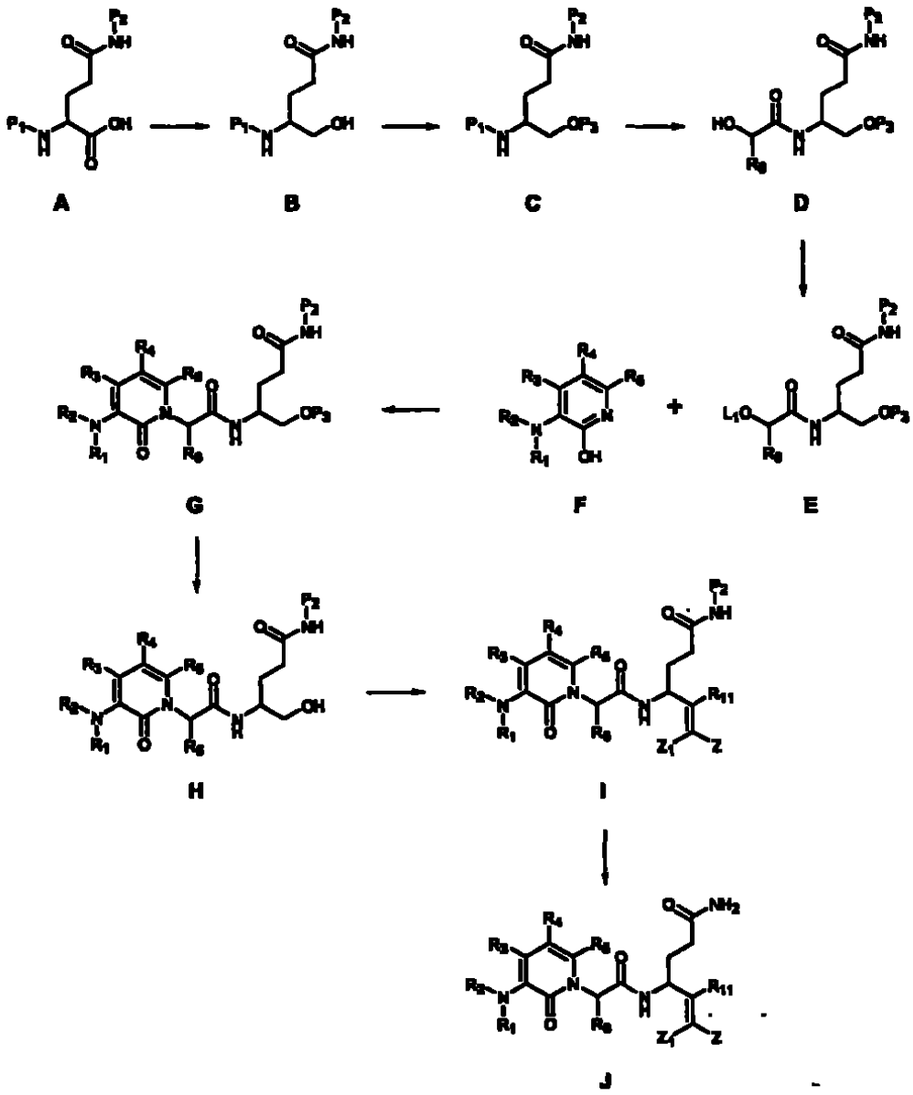
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GENERAL SYNTHETIC METHODS

Preferably, the inventive compounds of Formulas I and II are prepared by the methods of the present invention, including the General Methods shown below. When stereochemistry is not specified in chemical structures, either stereocenter may be utilized. Although several intermediates are described and depicted as 2-hydroxypyridines, it is understood that such entities may also exist as the corresponding 2-pyridone tautomers. The following abbreviations also apply: Boc (*tert*-butoxycarbonyl), Ac (acetyl), Cbz (benzyloxycarbonyl), DMB (2,4-dimethoxybenzyl), TBS (*tert*-butyldimethylsilyl), TBDPS (*tert*-butyldiphenylsilyl), Ms (methanesulfonate), Ts (toluenesulfonate), Bn (benzyl), and Tr (triphenylmethyl).

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General Method 1



In General Method 1, an amino acid A (commercially available or prepared by methods described in the chemical literature) where P_1 is an appropriate protecting group for the amine functionality (e.g, Cbz, Boc, or Ac), and P_2 is an appropriate protecting group for the amide nitrogen (e.g, Tr), is reductively transformed into alcohol B. Compound B is subsequently converted to compound C where P_3 is an appropriate protecting group for the alcohol functionality (e.g., TBS). At this point, the P_1 protecting group present in C is removed and the resulting amine or salt thereof (not shown) is

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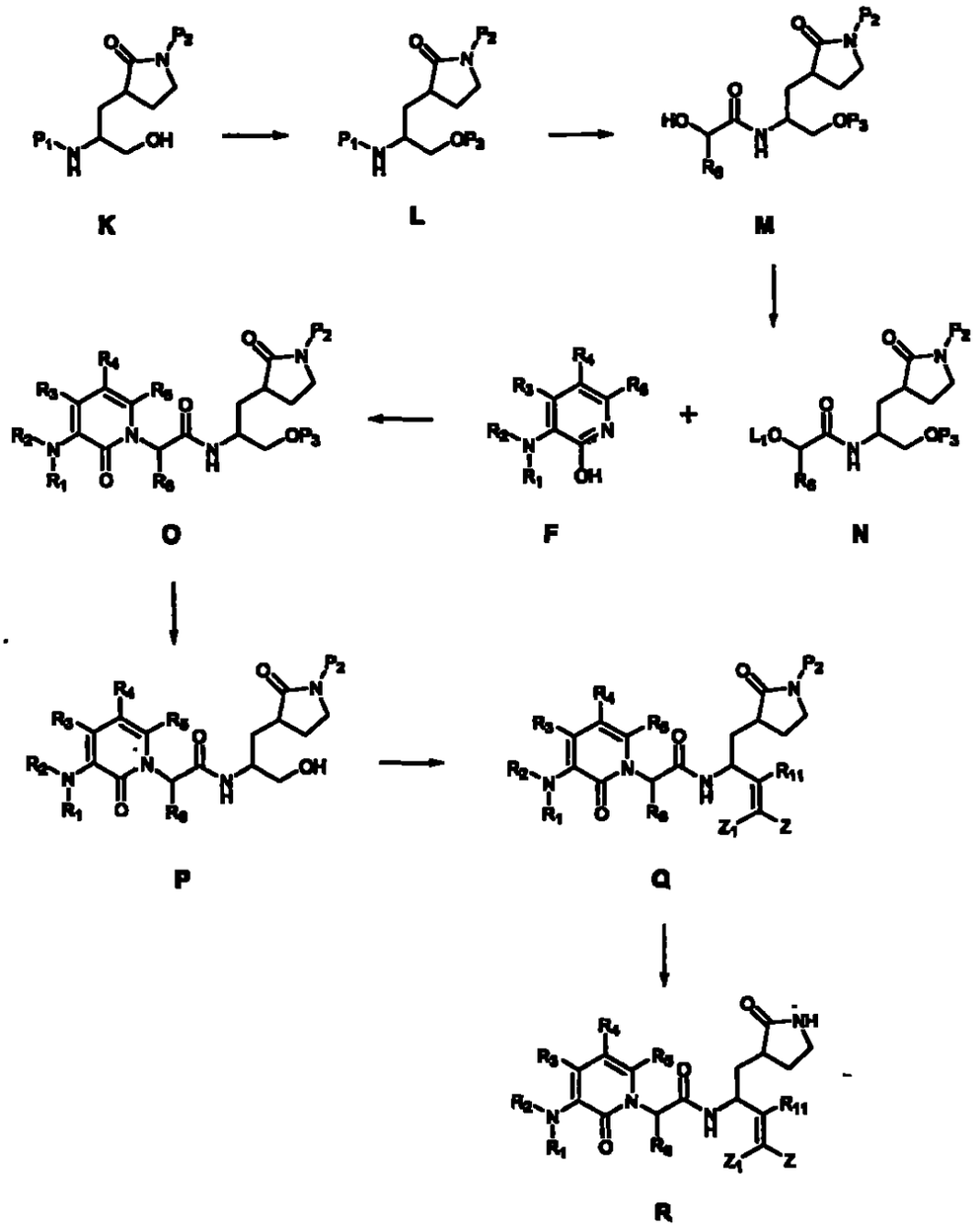
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subjected to an amide bond forming reaction with an appropriate α-hydroxycarboxylic acid (which incorporates R_6 and in which R_7 is H; also not shown) to provide imtermediate D. The alcohol functionality present in D is then converted to an appropriate leaving group (e.g., mesylate, tosylate) E and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate G. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting groups for the amine functionality. The P_3 protecting group is subsequently removed from G and the resulting alcohol (H) is oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to afford intermediate I (which incorporates R_{11}, Z, and Z_1). The P_2 protecting group present in I is then removed to give product J. If R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates G, H, or I or product J and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates G, H, or I or products J.

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General Method 2

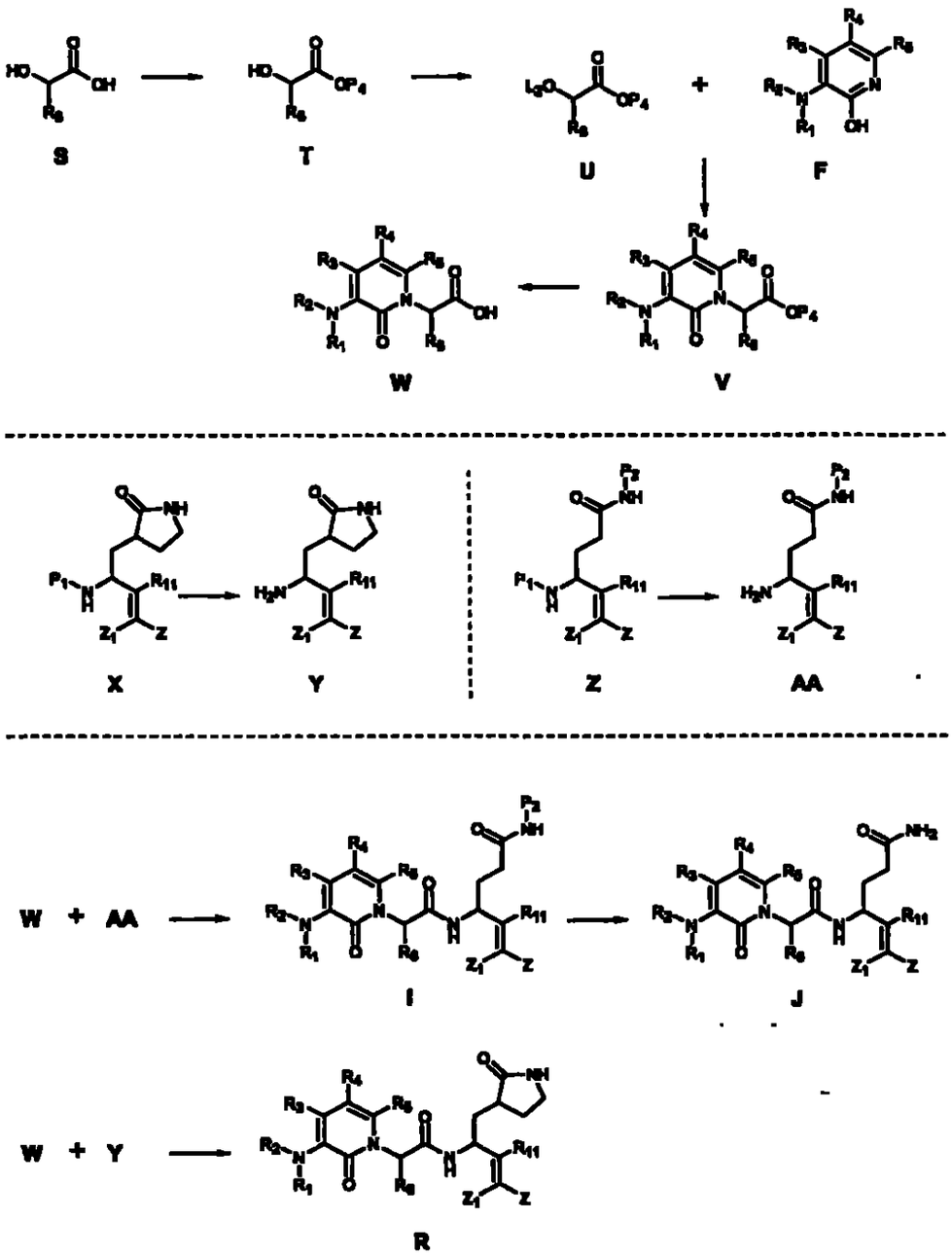


In General Method 2, amino alcohol K (prepared by methods described in the chemical literature), which incorporates R_9 and in which R_{10} is H, P_1 is an appropriate protecting group for amine functionality (e.g, Cbz, Boc, or Ac), and P_2 is an appropriate protecting group for the amide nitrogen (e.g, DMB), is converted to compound L where

P_3 is an appropriate protecting group for the alcohol functionality (e.g., TBDPS). The P_1 protecting group present in L is then removed and the resulting amine or salt thereof (not shown) is subjected to an amide bond forming reaction with an appropriate α-hydroxycarboxylic acid (which incorporates R_6 and in which R_7 is H; also not shown) to provide intermediate M. The alcohol functionality present in M is then converted to an appropriate leaving group (e.g., mesylate, tosylate) N and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate O. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting group for the amine functionality. The P_3 protecting group is subsequently removed from O and the resulting alcohol (P) is oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to afford intermediate Q (which incorporates R_{11}, Z, and Z_1). The P_2 protecting group present in Q is then removed to give product R. If R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates O, P, or Q or product R and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates O, P, or Q or products R.

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General Method 3



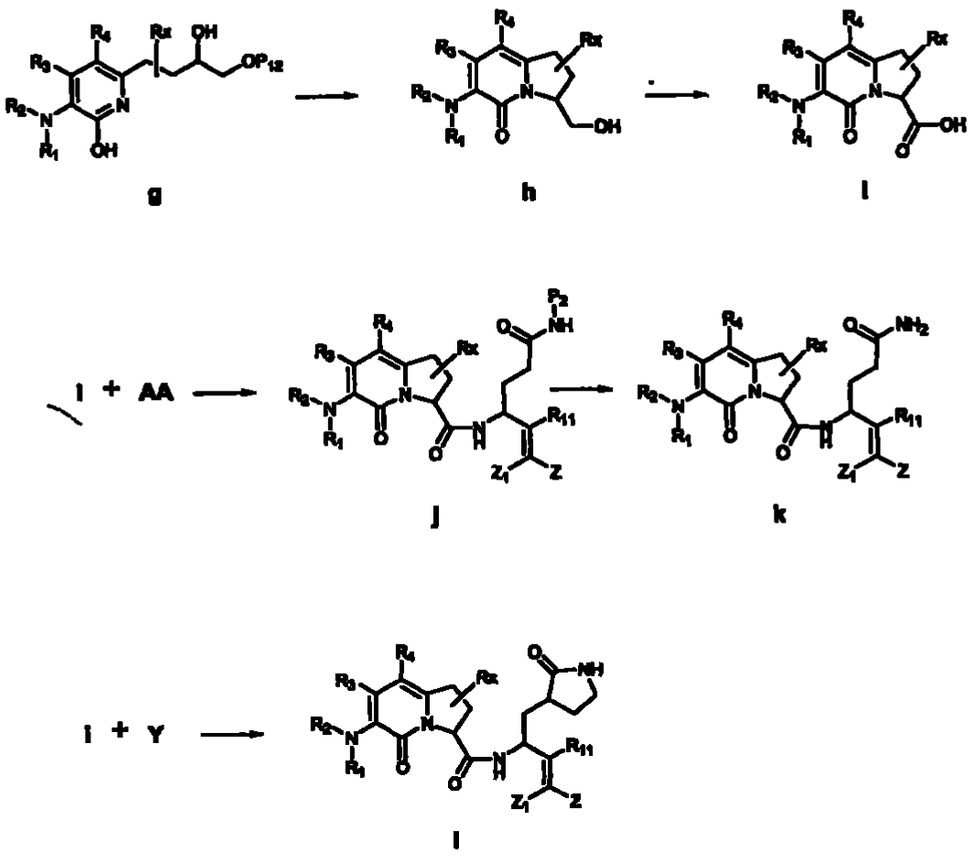
An alternate method for preparing either product J or product R is illustrated in General Method 3. An α-hydroxycarboxylic acid S (either commercially available or prepared by methods described in the chemical literature) which incorporates R_6 and in

which R_7 is H is converted to α-hydroxyester T where P_4 is an appropriate protecting group for the carboxylic acid functional group (e.g, methyl, benzyl, or *tert*-butyl). The alcohol functionality present in T is then converted to an appropriate leaving group (e.g., mesylate, tosylate, triflate) U and is coupled with 2-hydroxypyridine F (which incorporates R_1, R_2, R_3, R_4, and R_5) to give intermediate V. Note that the R_1 and R_2 moieties present in F may be an appropriate protecting group for the amine functionality. The P_4 protecting group is subsequently removed from V to afford carboxylic acid W. Independently, intermediates X and Z (prepared by methods described in the chemical literature) which incorporate R_{11}, Z, and Z_1 and in which P_1 is an appropriate protecting group for the amine functionality (e.g., Cbz, Boc, or Ac) and P_2 is an appropriate protecting group for the amide nitrogen (e.g., Tr), are converted to their corresponding amines Y and AA (or salts thereof), respectively. Amines AA and Y are then independently coupled with carboxylic acid W to afford intermediate I and product R, respectively. The P_2 protecting group present in intermediate I is subsequently removed to afford product J. Note that, although not depicted in General Method 3, the lactam nitrogen present in intermediate X may be protected with a suitable protecting group (e.g., DMB). If such a moiety is present in X, it may be removed after coupling of W with Y to afford product R.

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General Method 4



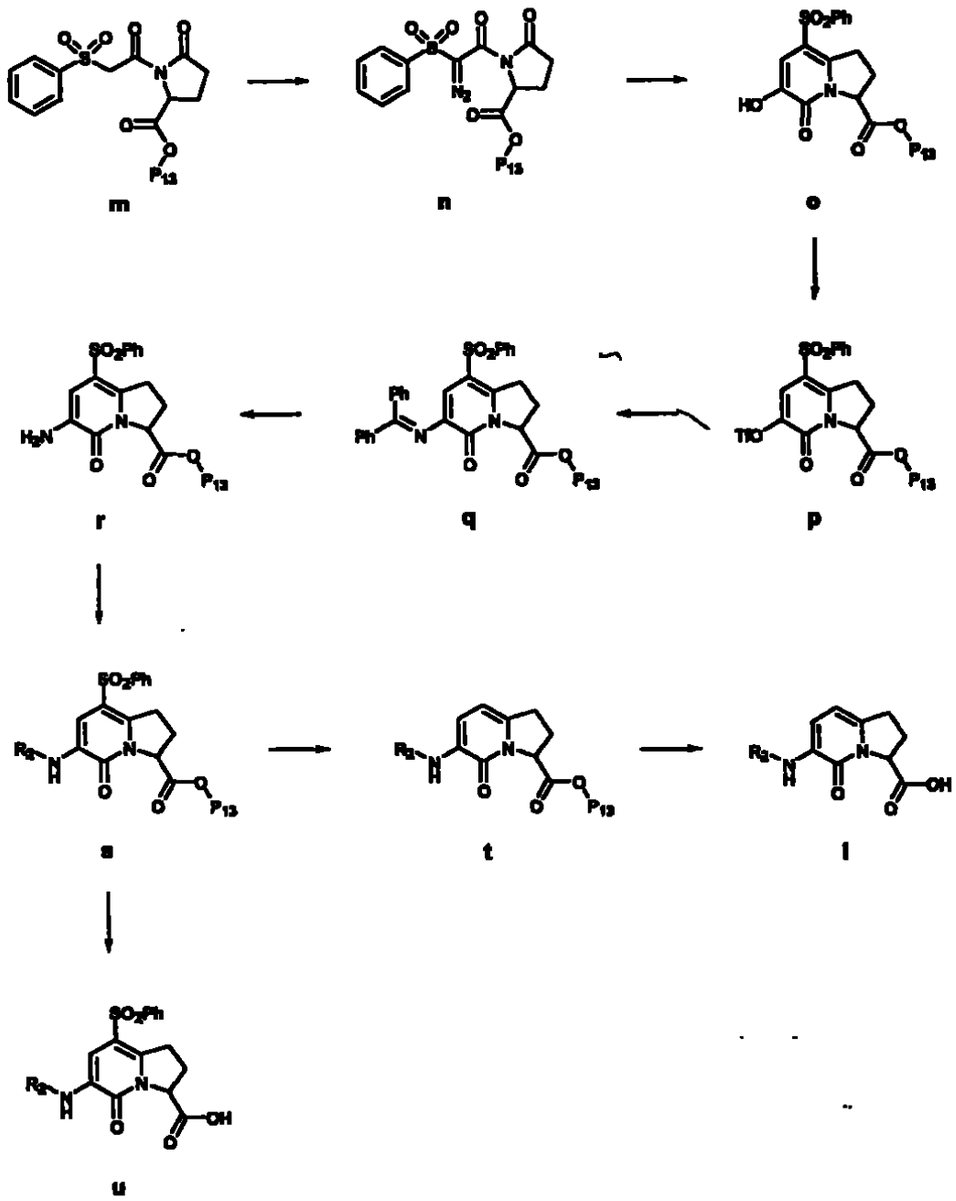
A method for preparing bicyclic products k and l is illustrated in General Method 4. Thus, an appropriate pyridine g (which incorporates R_1, R_2, R_3, and R_4, and which may be optionally substituted with R_x as shown) (an example of which may prepared as described in Specific Method 7 below) in which P_{11} and P_{12} are protecting groups for the alcohol functionality (e.g., silyl ether, methyl) is subjected to an intramolecular cyclization/deprotection protocol in which both P_{11} and P_{12} are removed to give pyridone h. Note that the R_1 and R_2 moieties present in g may be an appropriate protecting group for the amine functionality (e.g., Cbz). The alcohol moiety present in h is then oxidized to the corresponding carboxylic acid i. This oxidation may be accomplished via an aldehyde intermediate (not shown). Carboxylic acid i is then independently coupled with amines AA and Y (or salts thereof) (prepared as described in General Method 3 above) to afford intermediate j and product l, respectively. The P_2

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protecting group present in intermediate j is subsequently removed to afford product k. Note that, although not depicted in General Method 4, the lactam nitrogen present in intermediate Y may be protected with a suitable protecting group (e.g., DMB). If such a moiety is present in Y, it may be removed after coupling of i with Y to afford product l. In addition, if R_1 and/or R_2 is/are initially a protecting group for the amine functionality, it/they may be removed from intermediates g, h, i, or j or products k or l and replaced with a different R_1 and/or R_2 substituent to afford alternate intermediates g, h, i, or j or products k or l.

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General Method 5



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An alternate method for preparing a particular type of intermediate is illustrated in General Method 5. Thus, the sulfone m (which may be prepared by the method described in *Org. Lett.* 1999, *1*, 83) in which R_x is/are H and P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is transformed into diazo compound n. This intermediate is subjected to

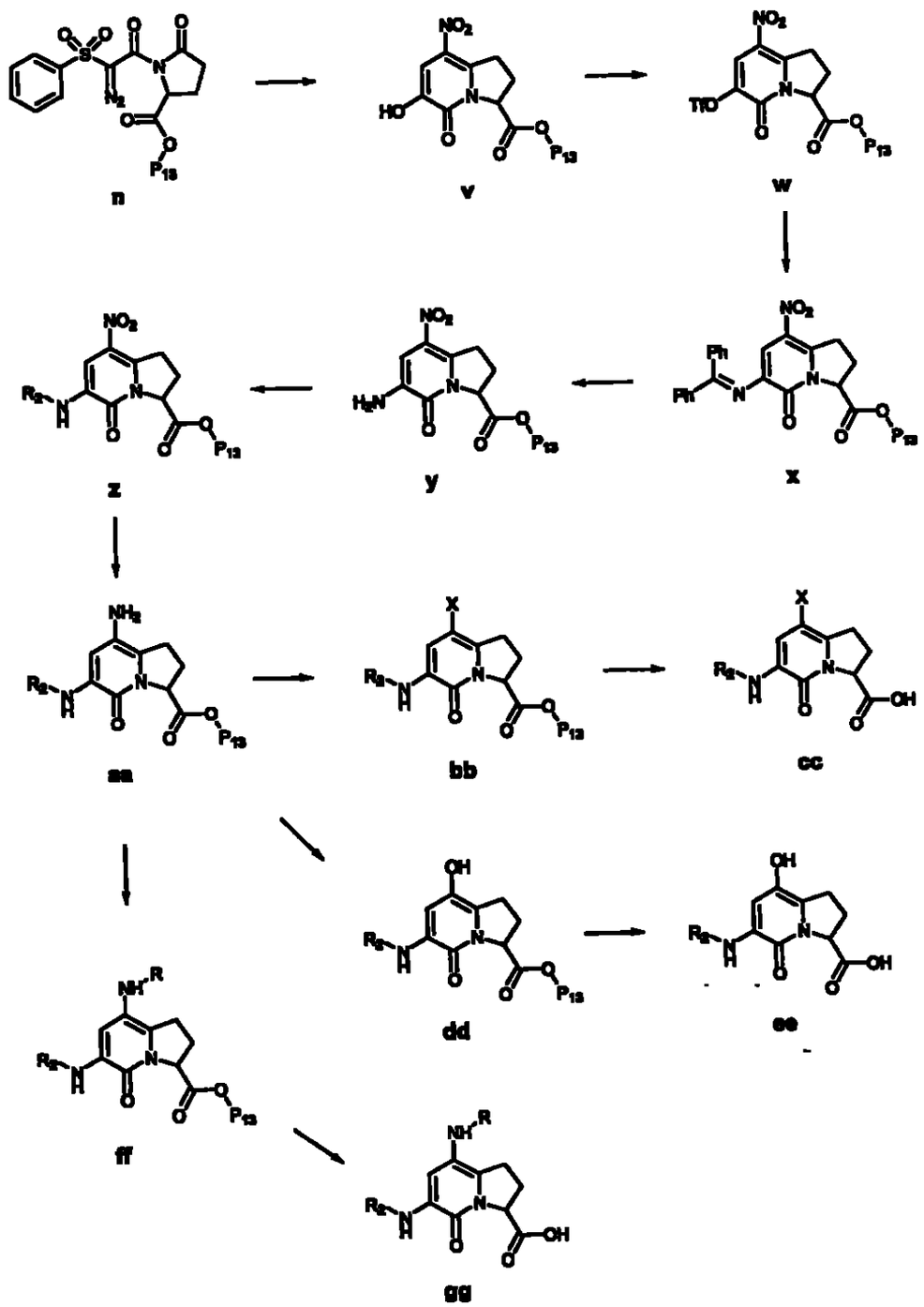
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a rhodium-catalyzed cyclization reaction involving phenylvinyl sulfone to give intermediate o (in which R_3 is H). The hydroxyl group present in o is converted to the corresponding trifluoromethane sulfonate (OTf) p, and this intermediate is further transformed to the amine r via imine q. The amine present in r is derivatized with an appropriate moiety to afford intermediate s (which contains the R_2 functional group and in which R_1 is H). Intermediate s is subjected to a desulfurization reaction to give intermediate t and this entity is deprotected to give carboxylic acid i (in which R_1, R_3, R_4, and R_x are H). Alternatively, intermediate s may be deprotected to give carboxylic acid u (in which R_1, R_3, and R_x are H) which may be utilized in place of i in General Method 4 above.

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General Method 6

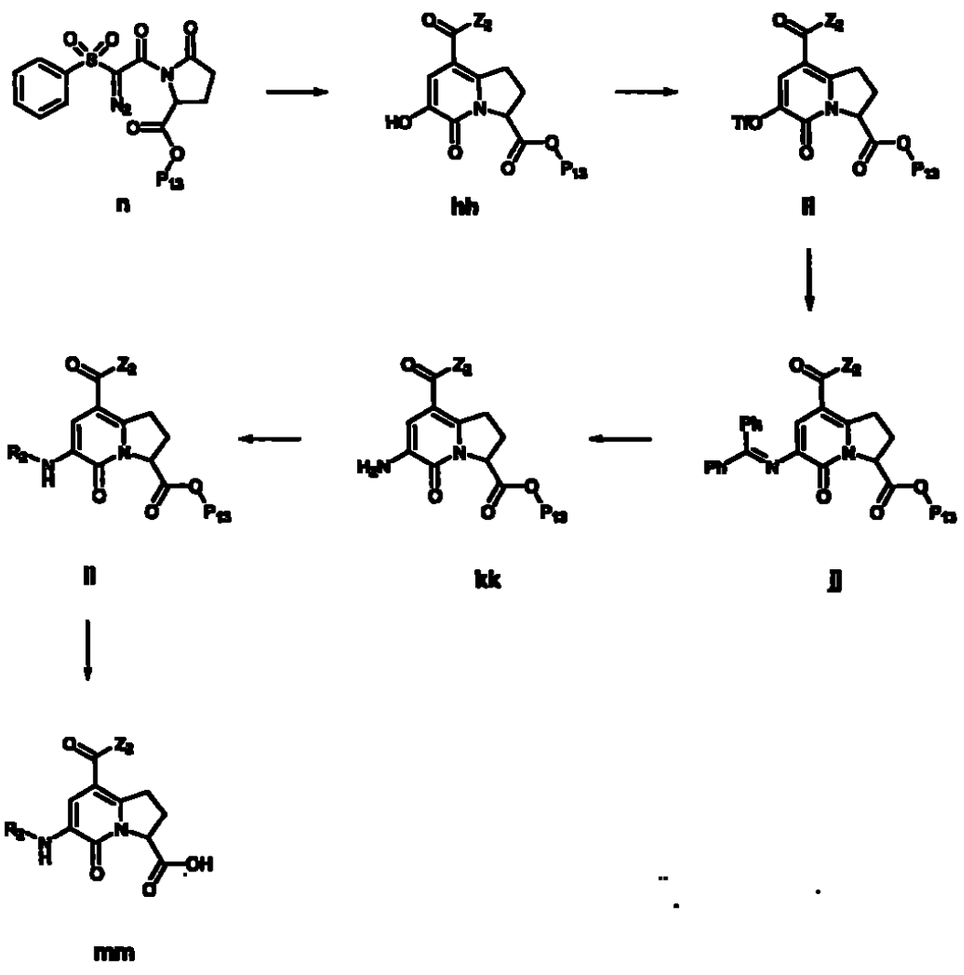


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An additional method for preparing intermediates related to i is illustrated in General Method 6. Thus, the diazo compound n (prepared in General Method 5 above) in which R_x is/are H and in which P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is subjected to a rhodium-catalyzed cyclization reaction involving nitroethylene to give intermediate v (in which R_3 is H). The hydroxyl group present in v is converted to the corresponding trifluoromethane sulfonate (OTf) w, and this intermediate is further transformed to the amine y via imine x. The amine present in y is derivatized with an appropriate moiety to afford intermediate z (which contains the R_2 functional group and in which R_1 is H). Intermediate z is reduced to give intermediate aa and this entity is transformed to intermediate bb in which X is a halogen. Intermediate bb is subsequently deprotected to give carboxylic acid cc. If desired, intermediate aa may also be transformed into intermediate t (General Method 5 above). Alternatively, intermediate aa is transformed to intermediate dd which is subsequently deprotected to give carboxylic acid ee. Alternatively, intermediate aa is transformed to intermediate ff in which R is alkyl, acyl, sulfonyl, or acyloxy. Intermediate ff is subsequently deprotected to give carboxylic acid gg. Carboxylic acids cc, ee, and gg may each be utilized in place of i in General Method 4 above.

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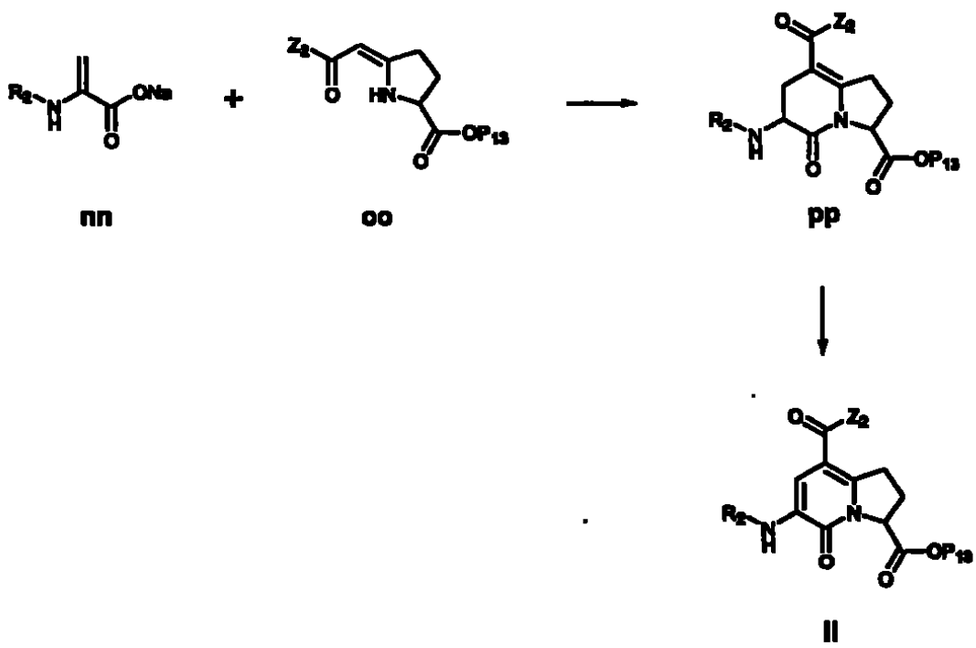
General Method 7



An additional method for preparing intermediates related to i is illustrated in General Method 7. Thus, the diazo compound n (prepared in General Method 5 above) in which R_x is/are H and in which P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) is subjected to a rhodium-catalyzed cyclization reaction involving acrylate esters or vinyl ketones to give intermediate hh (in which R_3 is H and Z_2 is alkyl, aryl, alkoxy, and benzyloxy). The hydroxyl group present in hh is converted to the corresponding trifluoromethane sulfonate (OTf) ii, and this intermediate is further transformed to the amine kk via imine jj. The amine present in kk is derivatized with an appropriate moiety to afford intermediate ll (which contains the R_2 functional group and in which R_1 is H).

Intermediate ll is subsequently deprotected to give carboxylic acid mm which may be utilized in place of i in General Method 4 above. At any point in the above sequence, if Z_2 is alkoxy or benzyloxy it may be replaced with a hydroxyl functionality. The resulting carboxylic acid may subsequently be rearranged to the corresponding amine using established methods and the amine-containing intermediates may be utilized as depicted in General Method 6. For example, intermediate ll (when Z_2 is OH) may be rearranged to intermediate aa (General Method 6).

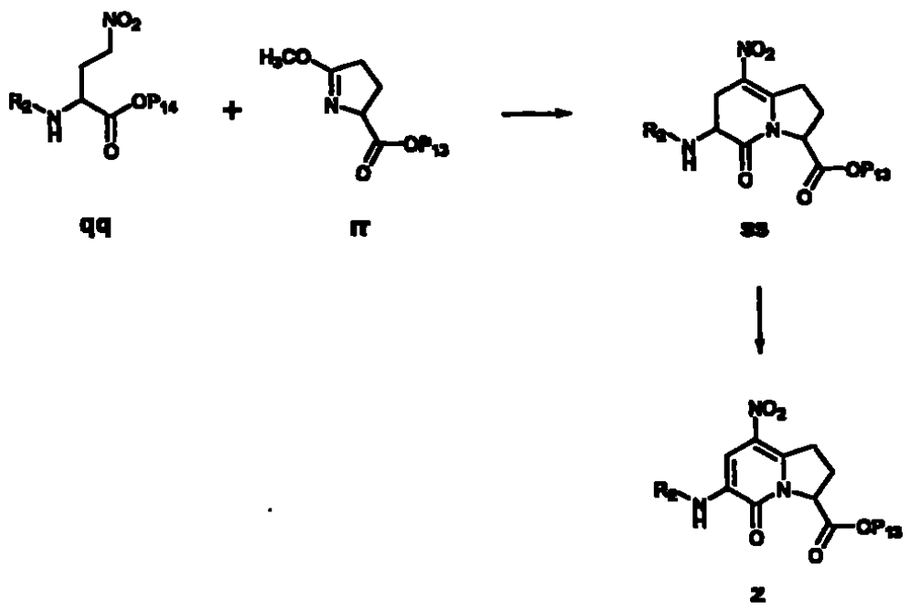
General Method 8



Yet another method for preparing intermediate ll is depicted in General Method 8. Thus the sodium salt of α-dehydroalanine derivative nn (which incorporates R_2 and in which R_1 is H) (which is either commercially available or may be prepared from serine by a variety of literature techniques) is condensed with intermediate oo (which may be prepared as described in *Tetrahedron Lett.* 1989, *30*, 3621) in which R_x is/are H and P_{13} is an appropriate protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl ester) and in which Z_2 is alkyl, aryl, alkoxy, or benzyloxy to give intermediate pp. Intermediate pp is subsequently oxidized (by a variety of literature

methods) to afford intermediate ll which may be utilized as described above in General Method 7.

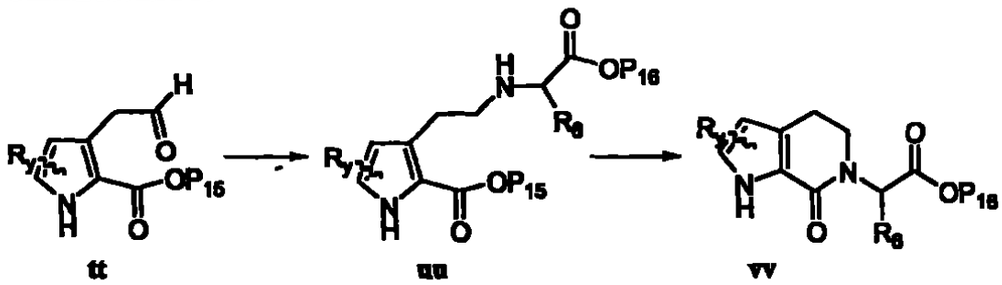
General Method 9



An alternate method for preparing intermediate z (from General Method 6 above) is depicted in General Method 9. Thus the nitro compound qq (prepared by analogy with the method described in: *J. Chem. Soc., Perkin Trans. 1* 1998, 1113) which incorporates R_2 and in which R_1 is H and P_{14} is a suitable protecting group for the carboxylic acid functionality (e.g., methyl or ethyl) is condensed with intermediate rr (prepared according to: *J. Heterocyclic Chem.* 1992, *29*, 1285) in which R_2 is/are H and P_{13} is a suitable protecting group for the carboxylic acid functionality (e.g., methyl, ethyl, benzyl, or *tert*-butyl) to give intermediate ss. Intermediate ss is subsequently oxidized (by a variety of literature methods) to afford intermediate z which may be utilized as described above in General Method 6.

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General Method 10



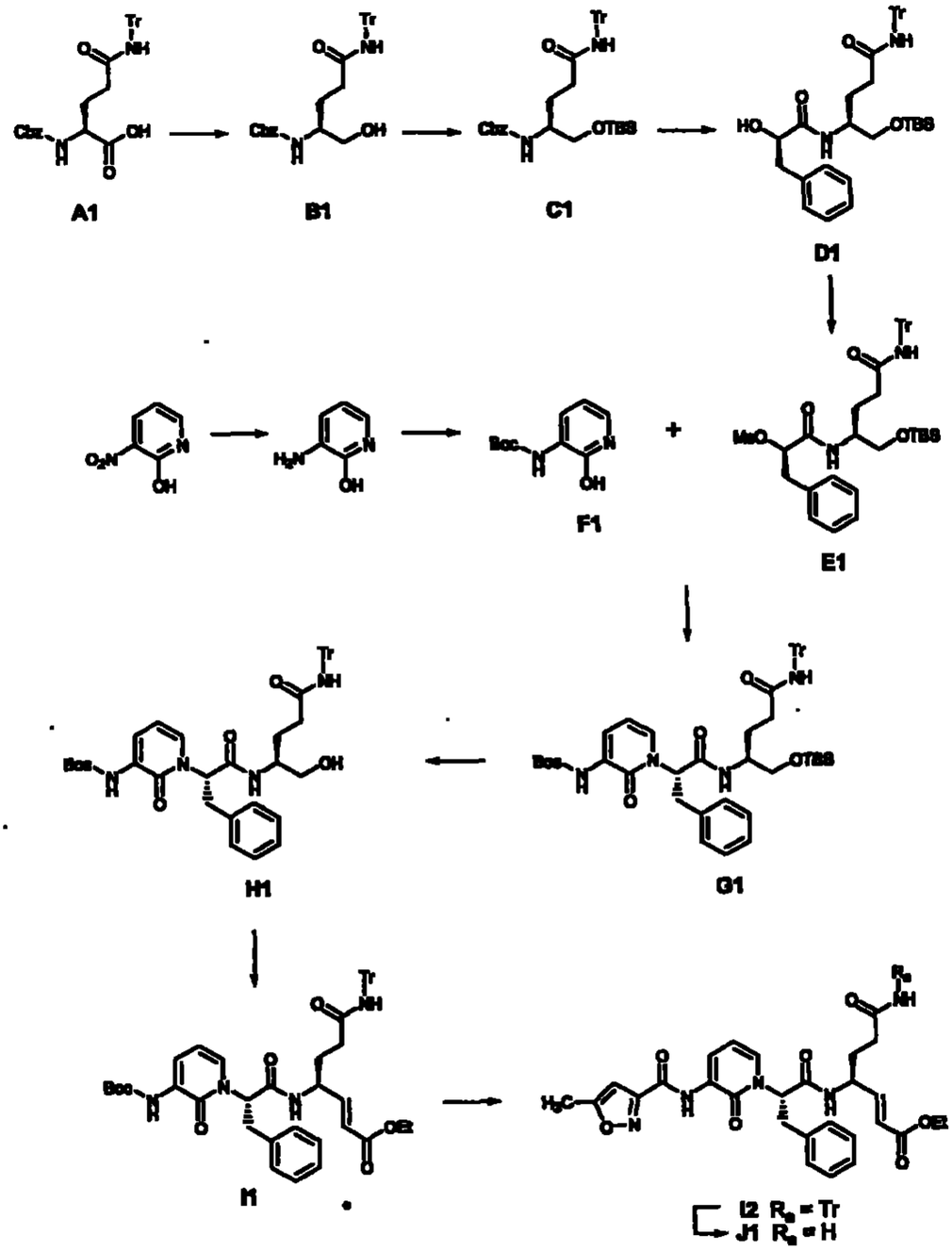
General Method 10 depicts the preparation of the bicyclic pyrrole vv, starting with aldehyde tt, prepared according to the procedure described in Smith, K. M., *J. Chem. Soc., Perkin Trans. I*, 1973, p. 516. This compound is subjected to reductive amination conditions with an amine to give compound uu. The carboxylic acid protecting group P_{16} is removed, and the resulting acid is condensed intramolecularly with the secondary amine to give bicycle vv. This bicyclic compound may be coupled to amine Y or AA according to the method described in General Method 3.

SPECIFIC METHODS

The following Specific Methods may also be utilized to prepare some of the compounds described in this invention.

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Specific Method 1



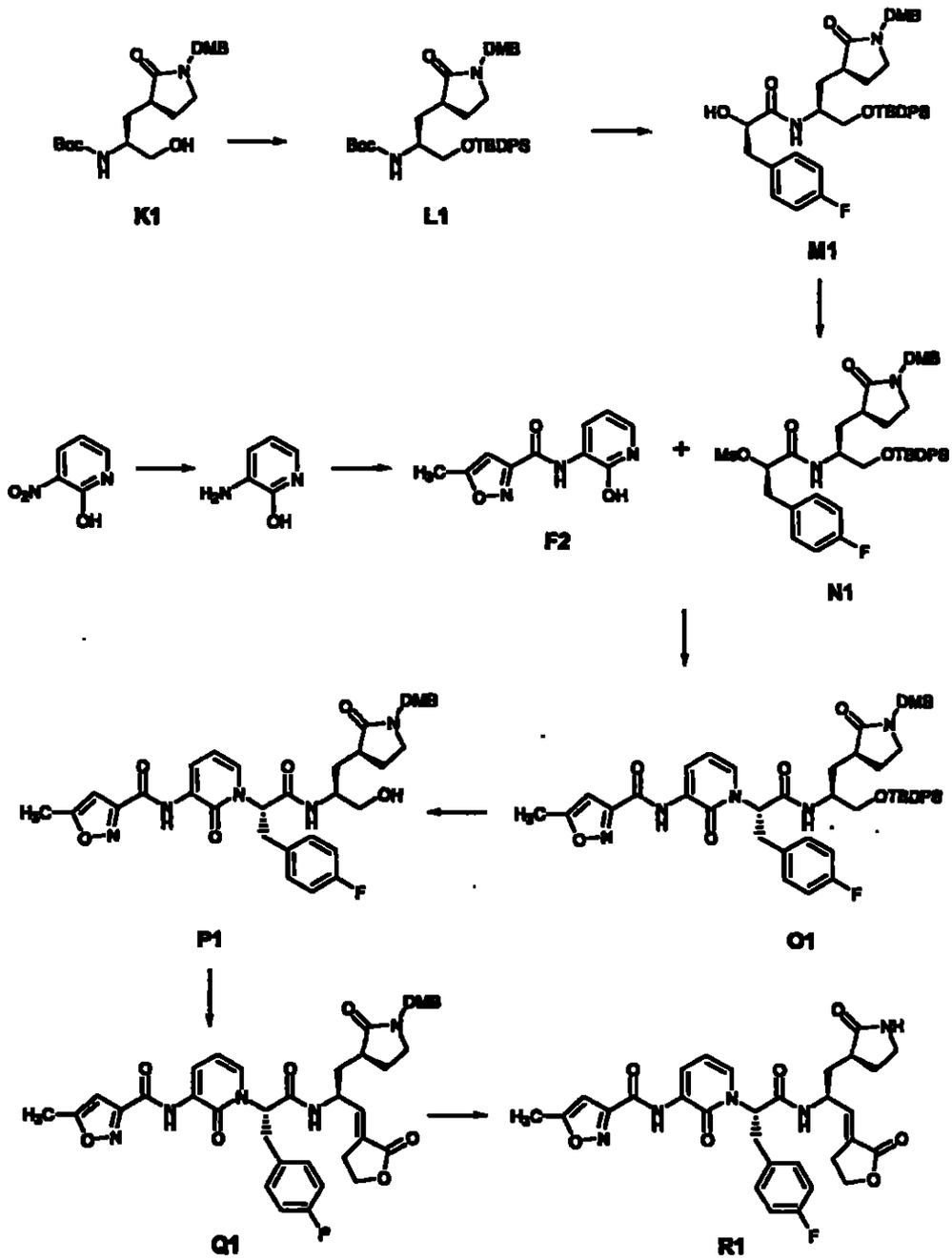
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Specific Method 1 describes the preparation of specific compound J1 (compound 5). Thus, commercially available amino acid A1 was reduced to alcohol B1 which, in turn, was transformed into compound C1. The Cbz moiety present in C1 was removed by hydrogenation and the resulting amine (not shown) was coupled with D-3-phenyllactic acid (commercially available) to afford intermediate D1. This latter entity was subsequently transformed to the corresponding methanesulfonate (mesylate) (E1) and was coupled with the sodium salt of 2-hydroxypyridine F1 to provide intermediate G1. The 2-hydroxypyridine F1 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent Boc protection of the resulting amine. The silyl protecting group present in G1 was removed and the alcohol thus obtained (H1) was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate I1. The Boc moiety contained in I1 was then thermally deprotected and the resulting amine (not shown) was derivatized with commercially available 5-methylisoxazole-3-carbonyl chloride to give intermediate I2. The trityl protecting group present in I2 was subsequently removed under acidic conditions to complete the preparation of specific compound J1 (compound 5).

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Specific Method 2



Specific Method 2 describes the preparation of specific compound R1 (compound 20). Thus, alcohol K1 (prepared as described in Dragovich, et al., *J. Med Chem.* 1999, ...

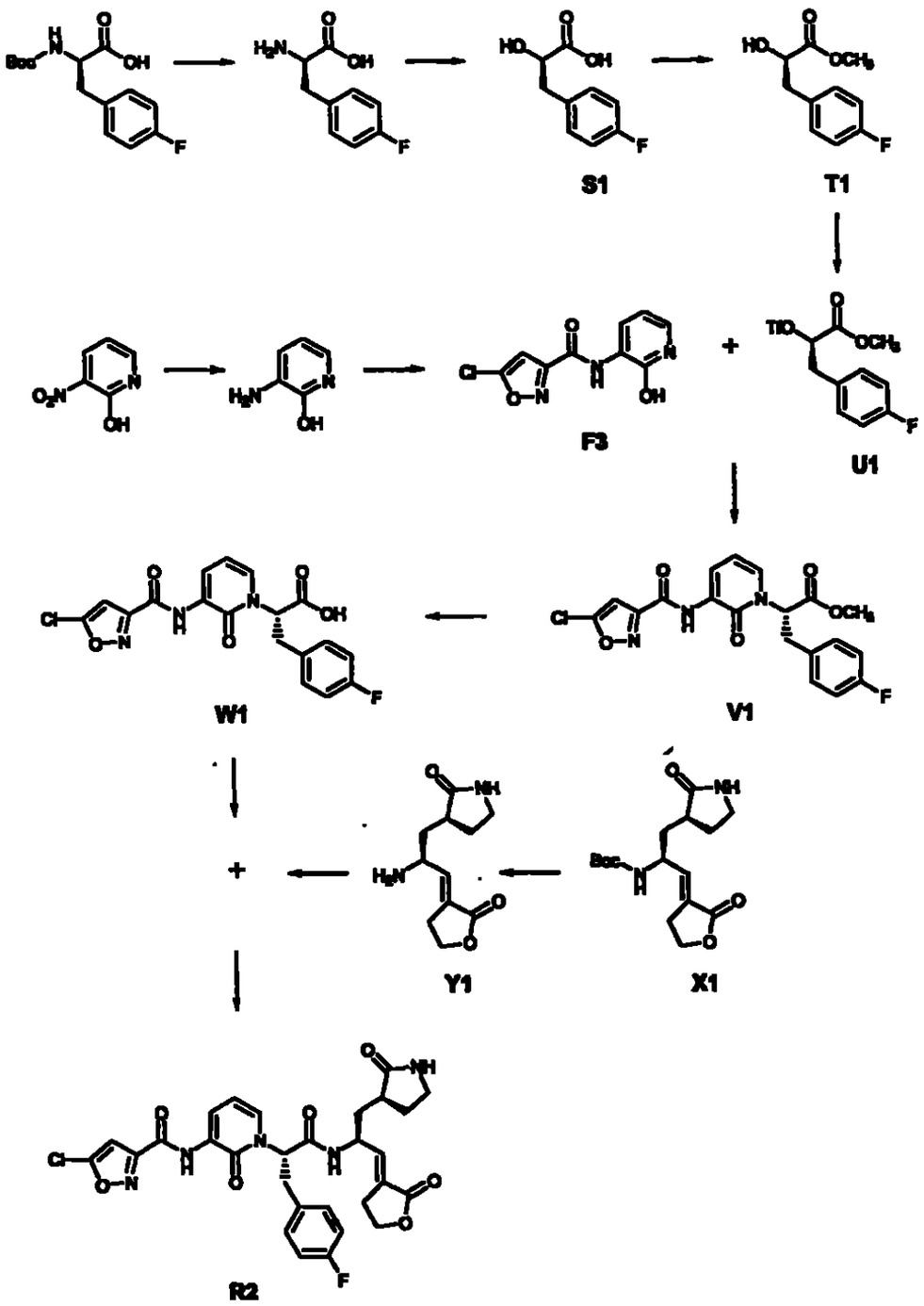
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42, 1213) was protected to give intermediate L1. The Boc protecting group present in L1 was removed under acidic conditions and the resulting amine salt (not shown) was coupled with (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1, prepared as described in Specific Method 3 below) to afford intermediate M1. This latter entity was subsequently transformed to the corresponding methanesulfonate (mesylate) (N1) and was coupled with the sodium salt of 2-hydroxypyridine F2 to provide intermediate O1. The 2-hydroxypyridine F2 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with commercially available 5-methylisoxazole-3-carbonyl chloride. The silyl protecting group present in O1 was removed and the alcohol thus obtained (P1) was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate Q1. The DMB moiety contained in Q1 was then deprotected to complete the preparation of specific compound R1 (compound 20).

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Specific Method 3



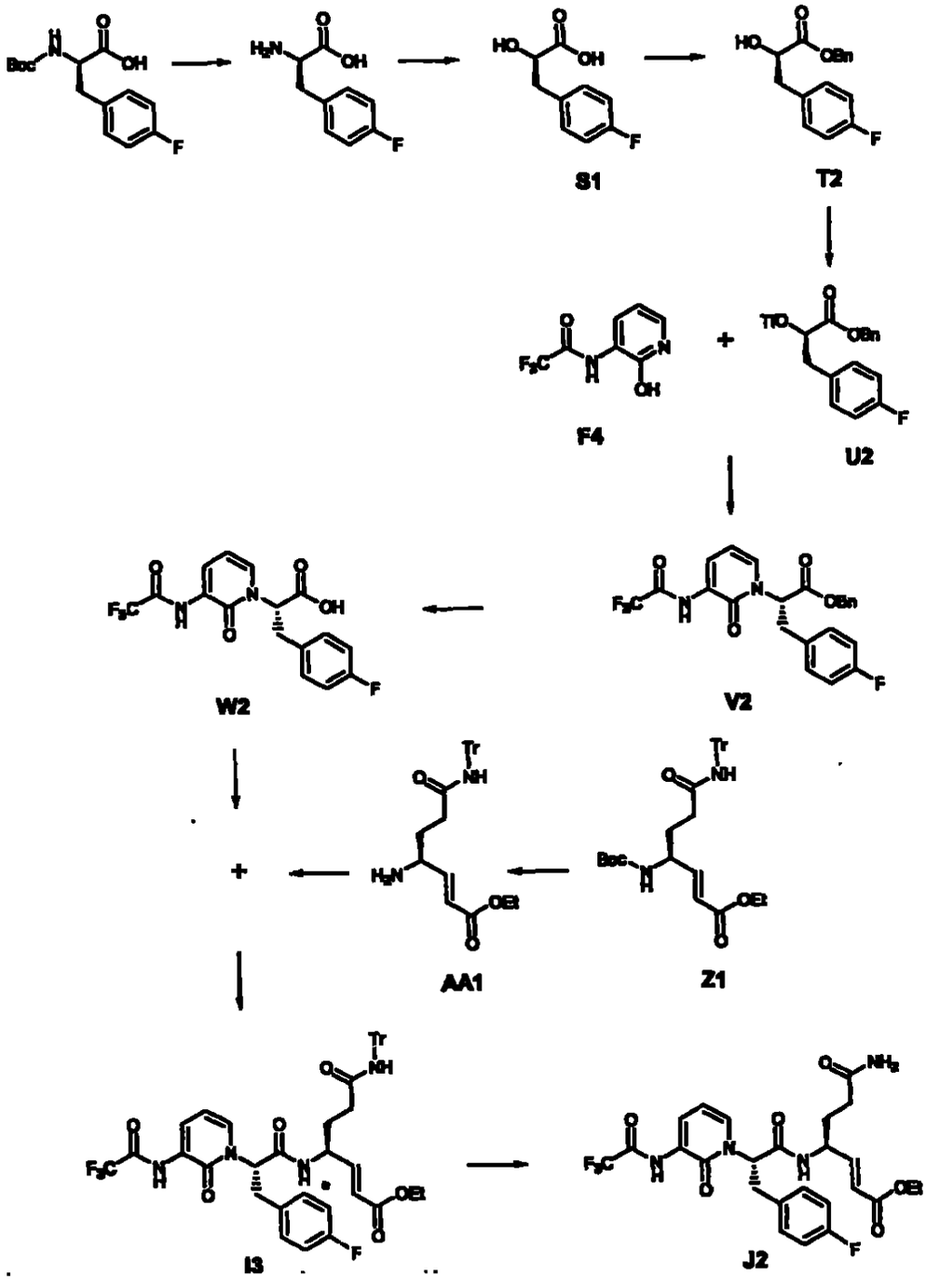
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Specific Method 3 describes the preparation of specific compound R2 (compound 23). Thus, commercially available Boc-D-(4-F)Phe-OH was deprotected under acidic conditions and the resulting amine salt was subjected to a diazotization/displacement protocol to provide (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1). This material was subsequently transformed into the corresponding trifluoromethane sulfonate (triflate) U1 via the methyl ester T1 and was coupled with the sodium salt of 2-hydroxypyridine F3 to provide intermediate V1. The 2-hydroxypyridine F3 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with 5-chloroisoxazole-3-carbonyl chloride (prepared as described in the Experimental Section of this work). The methyl ester present in V1 was subsequently hydrolyzed under basic conditions and the resulting carboxylic acid (W1) was coupled with amine Y1 (or salt thereof) to complete the preparation of specific compound R2 (compound 23). Amine Y1 (or salt thereof) was prepared by deprotection of intermediate X1 (prepared in a manner analogous to that described in Baldwin et al., *J. Org. Chem.* 1971, *36*, 1441).

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Specific Method 4



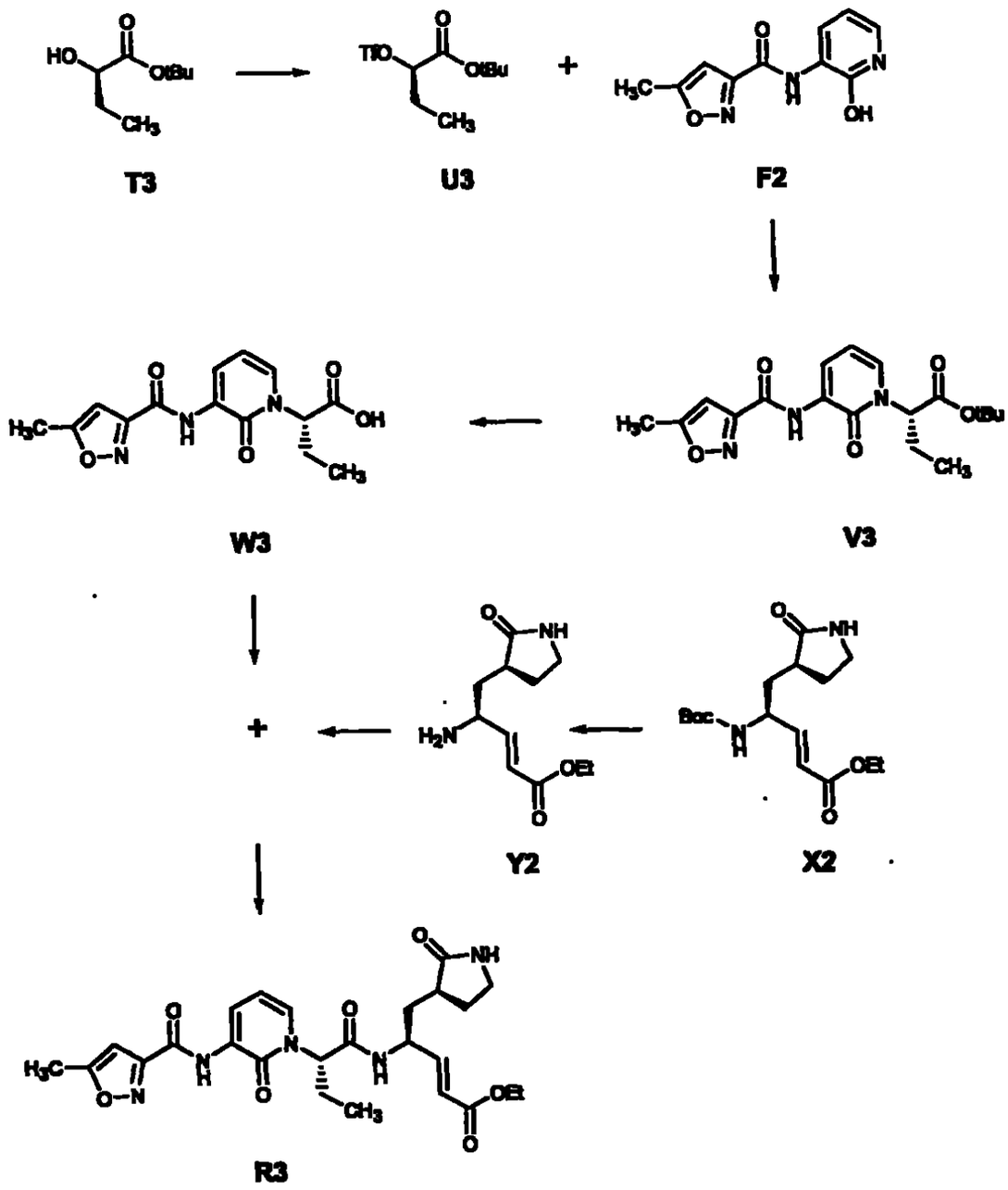
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Specific Method 4 describes the preparation of specific compound J2 (compound 24). Thus, (2*R*)-3-(4'-fluorophenyl)-2-hydroxypropionic acid (S1, prepared as described above in Specific Method 3) was transformed into the corresponding trifluoromethane sulfonate (triflate) U2 via the benzyl ester T2 and was coupled with the sodium salt of 2-hydroxypyridine F4 to provide intermediate V2. The 2-hydroxypyridine F4 was prepared from commercially available 2-hydroxy-3-nitropyridine by reduction and subsequent derivatization of the resulting amine with trifluoroacetic anhydride. The benzyl ester present in V2 was subsequently removed by hydrogenation and the resulting carboxylic acid (W2) was coupled with amine AA1 (or salt thereof) to give intermediate I3. The trityl protecting group present in I3 was then removed under acidic conditions to complete the preparation of specific compound J2 (compound 24). Amine AA1 (or salt thereof) was prepared by deprotection of intermediate Z1 (prepared as described in Dragovich, et al. *J. Med. Chem.* 1998, *41*, 2806).

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Specific Method 5

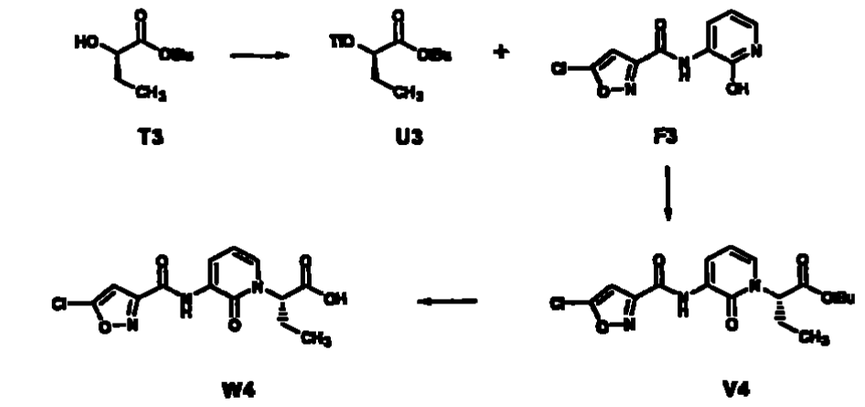


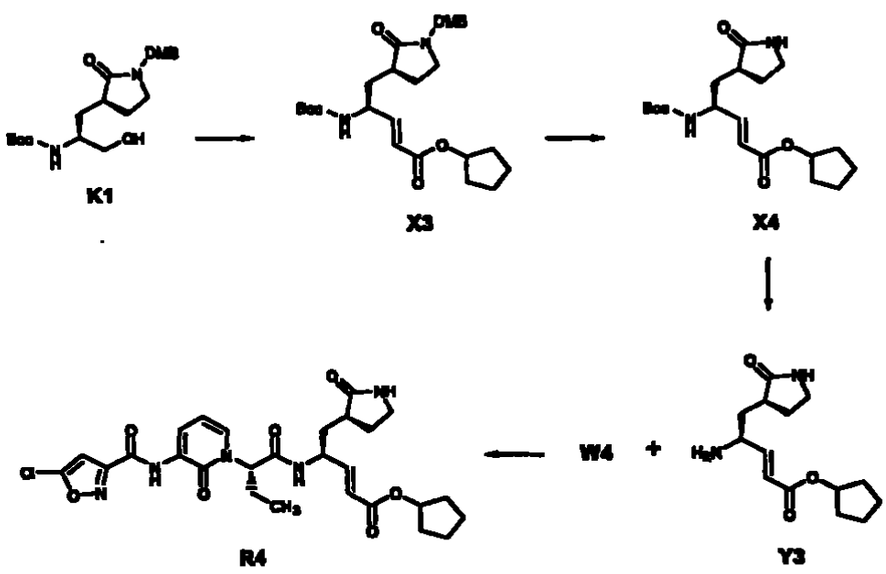
Specific Method 5 describes the preparation of specific compound R3 (compound 26). Thus, commercially available *tert*-butyl (*R*)-2-hydroxybutyrate (T3) was transformed into the corresponding trifluoromethane sulfonate (triflate) U3 and was

coupled with the sodium salt of 2-hydroxypyridine F2 (prepared as described in Specific Method 2 above) to provide intermediate V3. The *tert*-butyl ester present in V3 was subsequently hydrolyzed under acidic conditions and the resulting carboxylic acid (W3) was coupled with amine Y2 (or salt thereof) to complete the preparation of specific compound R3 (compound 26). Amine Y2 (or salt thereof) was prepared by deprotection of intermediate X2, prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999, the disclosure of which is incorporated herein by reference.

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Specific Method 6





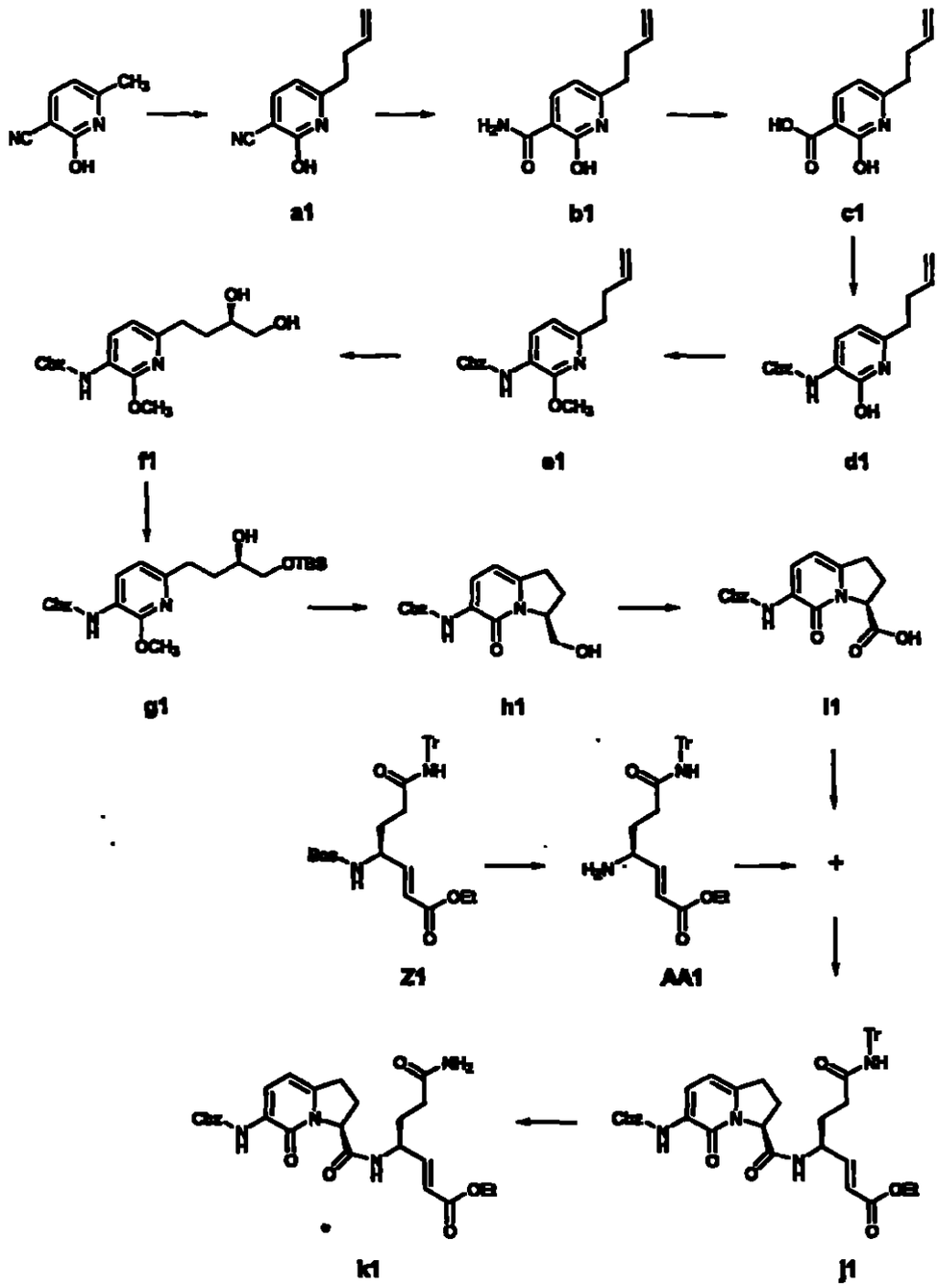
Specific Method 6 describes the preparation of specific compound R4 (compound 29). Thus, trifluoromethane sulfonate (triflate) U3 (prepared as described in Specific method 5 above) was coupled with the sodium salt of 2-hydroxypyridine F3 (prepared as described in Specific Method 3 above) to provide intermediate V4. The *tert*-butyl ester present in V4 was subsequently hydrolyzed under acidic conditions and the resulting carboxylic acid (W4) was coupled with amine Y3 (or salt thereof) to complete the preparation of specific compound R4 (compound 29). Amine Y3 (or salt thereof) was

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synthesized from alcohol K1 (prepared as described in Dragovich, et al., *J. Med Chem.* 1999, *42*, 1213) by the following method. Alcohol K1 was oxidized to the corresponding aldehyde (not shown) and subjected to an olefin-forming reaction to give intermediate X3. The DMB moiety contained in X3 was then deprotected to provide intermediate X4, and this entity was deprotected under acidic conditions to afford amine Y3 (or salt thereof).

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Specific Method 7

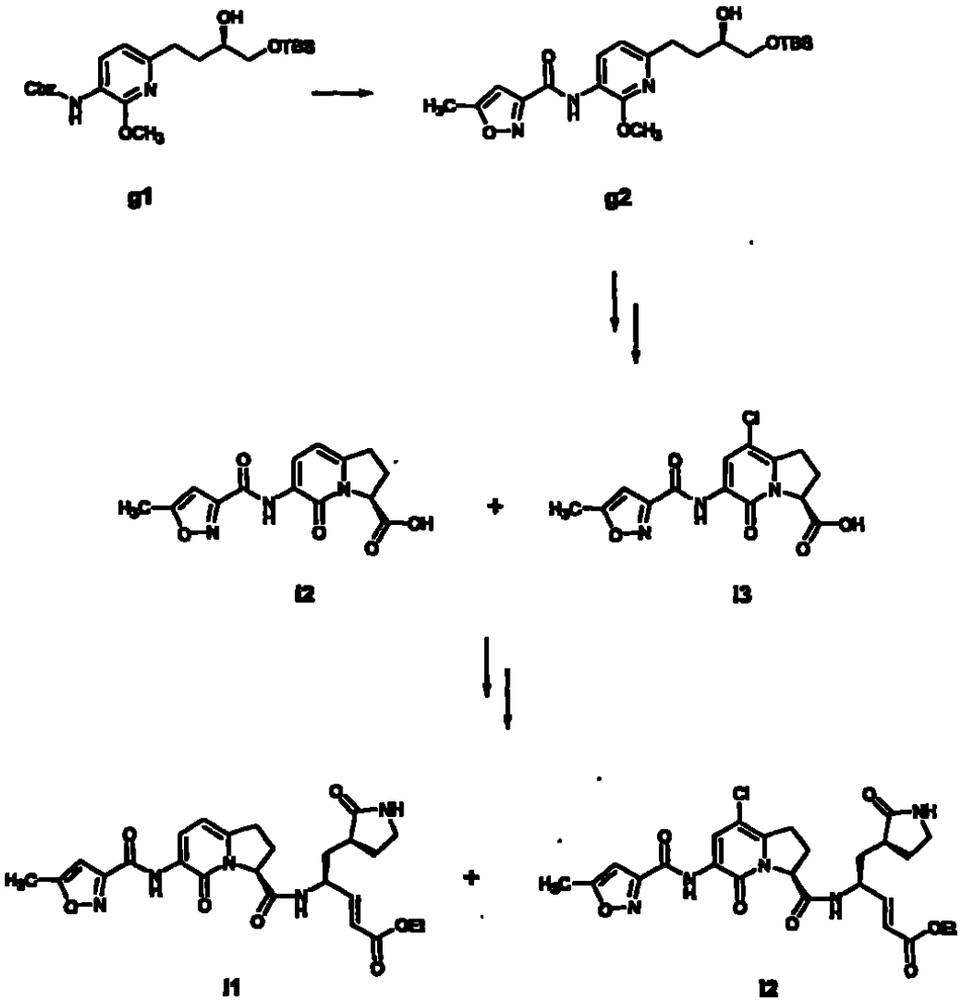


Specific Method 7 describes the preparation of specific compound k1 (compound 36). Thus, the diamion of commercially available 2-hydroxy-6-methylnicotinonitrile was

converted to intermediate a1 by methods related to those described in the literature (DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocyclic Chem.* 1983, *20*, 1295). The nitrile functionality present in this intermediate was then converted to the corresponding carboxylic acid c1 via the primary amide b1. Intermediate c1 was subjected to a Curtius rearrangement and the resulting isocyanate was trapped with benzyl alcohol to provide carbamate d1. The hydroxyl moiety contained in d1 was selectively methylated and the resulting methyl ether (e1) was subjected to an asymmetric dihydroxylation reaction to give diol f1. This asymmetric dihydroxylation reaction can be effected utilizing a variety of commercial and non-commercial chiral additives. The primary hydroxyl moiety contained in f1 was selectively protected as the corresponding *tert*-butyldimethylsilyl ether (g1). This intermediate was treated with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine at low temperature followed by exposure to tetrabutylammonium fluoride to effect (i) intramolecular cyclization and (ii) silyl ether deprotection and afford alcohol h1. Alcohol h1 was oxidized to the corresponding aldehyde (not shown), and this intermediate was further oxidized to the corresponding carboxylic acid i1. Acid i1 was coupled with amine AA1 (or salt thereof) to give intermediate j1. The trityl protecting group present in j1 was then removed under acidic conditions to complete the preparation of specific compound k1 (compound 36). Amine AA1 (or salt thereof) was prepared by deprotection of intermediate Z1 (prepared as described in Dragovich, et al. *J. Med. Chem.* 1998, *41*, 2806).

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Specific Method 8

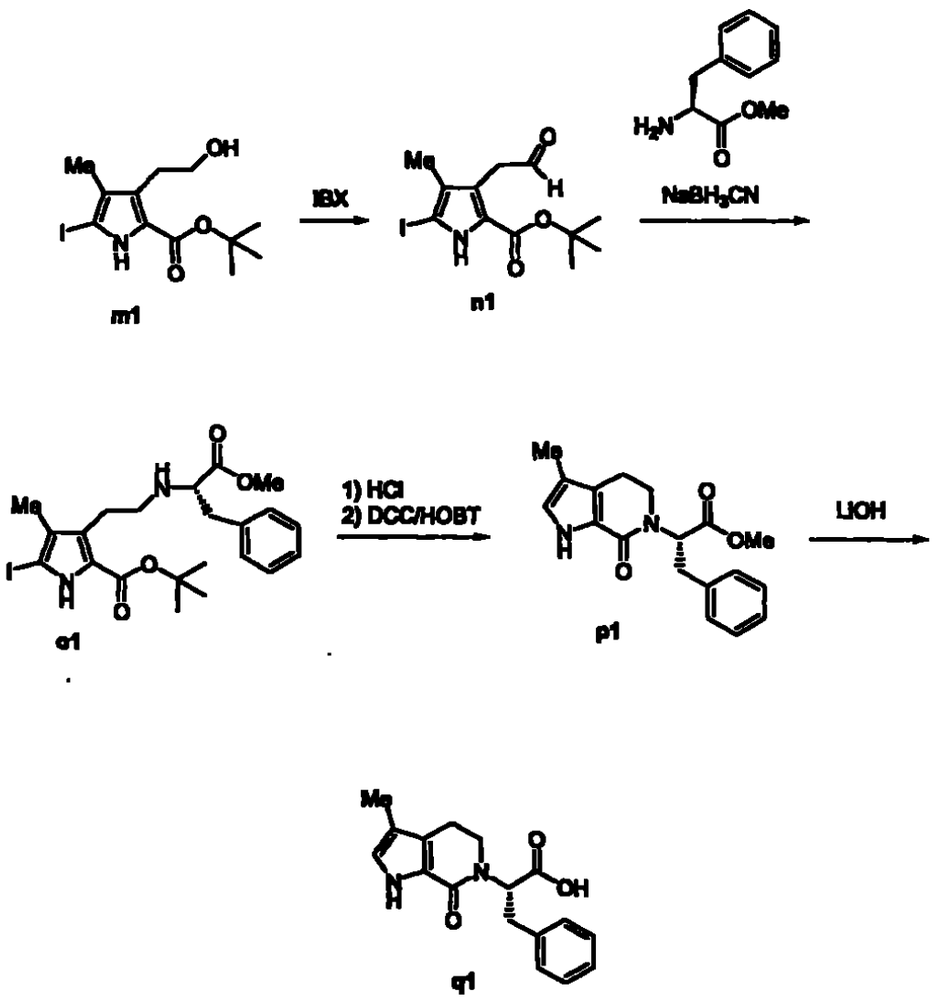


Specific Method 8 describes the preparation of specific compounds I1 and I2 (compounds 37 and 39, respectively). Thus, the Cbz moiety present in intermediate g1 (prepared as described in Specific Method 7 above) was removed and the resulting amine (not shown) was derivatized with commercially available 5-methylisoxazole-3-carbonyl chloride to provide intermediate g2. This intermediate was converted to specific compound I1 (compound 37) by a process analogous to that described in Specific Method 7 for the conversion of intermediate g1 to intermediate j1 utilizing amine Y2 (Specific Method 5) where appropriate. During this process, a small amount of intermediate i3 was also serendipitously generated. This intermediate was transformed

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to specific compound l2 (compound 39) by a process analogous to that described in Specific Method 7 for the conversion of intermediate g1 to intermediate j1 utilizing amine Y2 (Specific Method 5) where appropriate.

Specific Method 9



Specific Method 9 describes the synthesis of a bicyclic pyrrole. Alcohol m1 was oxidized with 2-iodoxybenzoic acid to give aldehyde n1, then reductively aminated with phenylalanine methyl ester and sodium cyanoborohydride to give amine o1. The t-butyl-protecting group was selectively removed, and the resulting amino acid was cyclized with DCC-HOBT to give p1. The methyl ester was cleaved with lithium hydroxide to

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give acid q1. Boc-protected 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester X2 was deprotected with HCl, then coupled to acid q1, using HATU, to complete the preparation of compound 43.

EXAMPLES

Examples of the processes used to make several of the compounds of Formulas I and II 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 and melting point. Proton magnetic resonance (^{1}H NMR) spectra were determined using either a Varian UNITY*plus* 300 or a General Electric QE-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; 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 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. Et_2O refers to diethyl ether. DMF refers to *N,N*-dimethylformamide. DMSO refers to dimethylsulfoxide. 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.

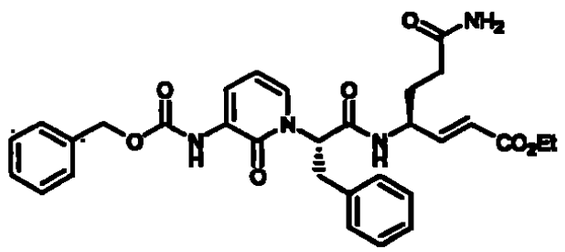
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(*tert*-butoxycarbonyl), TFA (trifluoroacetic acid), DIEA (*N,N*-diisopropylethylamine), TMEDA (*N,N,N',N'*-tetramethylethylenediamine), AcOH (acetic acid), Ac_2O (acetic anhydride), NMM (4-methylmorpholine), HOBt (1-hydroxybenzotriazole hydrate), HATU [*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate], EDC [1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride], DCC (dicyclohexyl-carbodiimide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), DMAP (4-dimethylaminopyridine), Gln (glutamine), Leu (leucine), Phe (phenylalanine), Phe(4-F) (4-fluorophenylalanine), Val (valine), amino-Ala (2,3-diaminopropionic acid), and (*S*)-Pyrrol-Ala [(2*S*,3'*S*)-2-amino-3-(2'-oxopyrrolidin-3'-yl)-propionic acid]. Additionally, "L" represents the configuration of naturally occurring amino acids.

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EXAMPLE 1

Preparation of Compound 1: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-phenylpropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2-Hydroxypyridin-3-yl)carbamic Acid Benzyl Ester

A suspension of 10% palladium on carbon (0.20 g) and 2-hydroxy-3-nitropyridine (3.00 g, 21.4 mmol, 1 equiv) in EtOH (100 mL) was subjected to one atmosphere of hydrogen for 4 hours. After purging the reaction vessel with argon, the mixture was filtered and the filtrate evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was stirred in THF (70 mL) at 23 °C. Benzyl chloroformate (3.37 mL, 23.6 mmol, 1.1 equiv) and Na_2CO_3 (5.00 g, 47.2 mmol, 2.2 equiv) were added and the reaction mixture was stirred for 60 h then diluted with EtOAc (250 mL) and washed sequentially with saturated $NaHCO_3$ and brine (50 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (gradient elution, 3→5%

CH_3OH in CH_2Cl_2) to provide the title intermediate (3.69 g, 71%) as a white solid: ^1H NMR ($CDCl_3$) δ 5.21 (s, 2H), 6.33 (t, 1H, J = 6.8), 7.00 (dd, 1H, J = 6.8, 1.6), 7.31-7.43 (m, 5H), 7.80 (s, 1H), 8.12-8.17 (m, 1H), 12.97 (s, 1H).

Preparation of Intermediate 5-(3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)-6-phenyl-4-[2-(tritylcarbamoyl)ethyl]hex-2-enoic Acid Ethyl Ester

(2-Hydroxypyridin-3-yl)carbamic acid benzyl ester was converted to the title intermediate via condensation with B1 (see Example 5) by a process analogous to that described in Example 5 for the conversion of F1 to intermediate I1: ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2), 1.55-1.69 (m, 1H), 1.86-2.00 (m, 1H), 2.06-2.23 (m, 2H), 3.12 (dd, 1H, J = 13.6, 7.8), 3.46 (dd, 1H, J = 13.6, 8.2), 4.17 (q, 2H, J = 7.2), 4.43-4.54 (m, 1H), 5.14 (d, 1H, J = 12.1), 5.18 (d, 1H, J = 12.1), 5.49-5.57 (m, 1H), 5.62 (dd, 1H, J = 15.7, 1.7), 6.14 (t, 1H, J = 7.3), 6.59-6.75 (m, 3H), 7.08-7.41 (m, 26H), 7.73 (s, 1H), 7.93-7.98 (m, 1H).

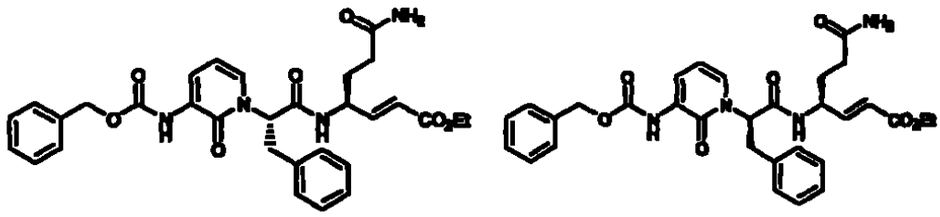
Preparation of Compound 1

The preceding intermediate was converted to compound 1 by a process analogous to that described in Example 5 for the conversion of I2 to product J1: IR (cm^{-1}) 3298, 1713, 1655, 1590, 1508, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.65-1.96 (m, 2H), 2.02-2.19 (m, 2H), 3.15 (dd, 1H, J = 13.8, 7.6), 3.49 (dd, 1H, J = 13.8, 8.3), 4.18 (q, 2H, J = 7.1), 4.42-4.53 (m, 1H), 5.17 (s, 2H), 5.62-5.81 (m, 4H), 6.28 (t, 1H, J = 7.2), 6.66 (dd, 1H, J = 15.6, 5.4), 7.12-7.40 (m, 12H), 7.81 (s, 1H), 7.97-8.04 (m, 1H); Anal. $C_{31}H_{34}N_4O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 2

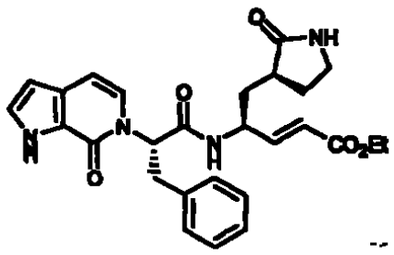
Preparation of a 1:1 mixture of Compound 1 (above) and Compound 2: *trans*-(2'*R*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-phenylpropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



The title products were prepared from commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid by a process analogous to that described in Example 22 for the conversion of S1 to product R2 utilizing intermediates (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 1) and AA1 (Example 23) where appropriate: ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 1.20 (t, *J* = 7.0), 1.29 (t, *J* = 7.2), 1.64-2.25 (m), 3.08 (dd, *J* = 13.6, 6.4), 3.14 (dd, *J* = 13.6, 7.8), 3.41-3.52 (m), 4.09 (q, *J* = 7.2), 4.18 (q, *J* = 7.0), 4.39-4.50 (m), 5.16 (s), 5.18 (s), 5.59-5.82 (m), 6.12-6.22 (m), 6.25-6.34 (m), 6.65 (dd, *J* = 15.6, 5.6), 6.70 (dd, *J* = 15.6, 5.3), 7.10-7.41 (m), 7.47-7.58 (m), 7.79-7.86 (m), 7.97-8.07 (m).

EXAMPLE 3

Preparation of Compound 3: *trans*-(2'*S*,3"'*S*,4*S*)-4-[2'-(7"-Oxo-1",7"-dihydropyrrolo[2",3"-c-pyridin-6"-yl)-3'-phenylpropionylamino]-5-(2"'-oxopyrrolidin-3"'-yl)pent-2-enoic Acid Ethyl Ester



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Preparation of Intermediate (2*S*)-2-(2',2'-Diethyloxyethylamino)-3-phenylpropionic Acid Ethyl Ester

A solution of L-phenylalanine ethyl ester (8.37 g, 46.8 mmol, 1 equiv), bromoacetaldehyde diethyl acetal (10.6 mL, 70.1 mmol, 1.5 equiv), and DIEA (16.2 mL, 93.4 mmol, 2.0 equiv) in DMF (100 mL) was heated at 80 °C for 2 d. The resulting solution was cooled to 23 °C, taken up in chloroform (200 mL), washed with 10% aqueous potassium carbonate (3 x 50 mL), dried over potassium carbonate, and concentrated. Purification of the residue by silica gel chromatography yield 7.4 g (54%) of product. ^{1}H NMR ($CDCl_3$) δ 1.13-1.23 (m, 9H), 2.61 (dd, 1H, *J* = 11.8, 5.9), 2.78 (dd, 1H, *J* = 11.8, 5.9), 2.96-3.03 (m, 2H), 3.46-3.53 (m, 1H), 3.55-3.70 (m, 4H), 4.18 (q, 2H, *J* = 7.1), 4.57 (t, 1H, *J* = 5.5), 7.19-7.33 (m, 5H).

Preparation of Intermediate (2*S*)-2-[(2,2-Diethoxyethyl)-(1H-pyrrole-2-carbonyl)-amino]-3-phenylpropionic Acid Ethyl Ester

Pyrrole-2-carboxylic acid (0.82 g, 7.41 mmol, 1.42 equiv) in CH_2Cl_2 (30 mL) was treated with oxalyl chloride (1.0 mL, 11.1 mmol, 2.13 equiv), followed by DMF (1 drop). The reaction mixture was held at 23 °C overnight, then was concentrated under reduced pressure. The resulting solid was taken up in CH_2Cl_2 (30 mL), and was treated with the preceding intermediate (1.60 g, 5.2 mmol, 1 equiv), and collidine (1.96 mL, 14.8 mmol, 2.85 equiv). The resulting solution was held at 23 °C overnight, then was taken up in EtOAc (100 mL), and washed sequentially with saturated aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (2 x 20 mL). The organic layer was dried over $MgSO_4$, then was concentrated to yield 2.18 g of crude product. The product was purified by silica gel chromatography to give 1.42 g (68%) of product. ^{1}H NMR ($CDCl_3$) δ 1.15-1.30 (m, 9H), 3.24 (d, 2H, *J* = 5.8), 3.75-4.43 (m, 2H), 4.15-4.28 (m, 6H), 4.50-4.57 (m, 1H), 5.05 (dd, 1H, *J* = 13.6, 5.8), 6.22-6.24 (m, 1H), 6.56-6.59 (m, 1H), 6.94-6.96 (m, 1H), 7.19-7.33 (m, 5H), 9.76 (s, 1H).

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Preparation of Intermediate (2*S*)-(7-Oxo-1,7-dihydropyrrolo[2,3-c]pyridin-6-yl)-3-phenylpropionic Acid Ethyl Ester

A solution of the preceding intermediate (1.04 g, 2.59 mmol) in toluene (30 mL) was treated with PTSA (5 mg), then heated to reflux for 1 h. The solution was taken up in EtOAc (100 mL), washed with saturated aqueous sodium bicarbonate (30 mL), then brine (30 mL), then concentrated. Purification of the residue by silica gel chromatography gave 0.14 g (18%) of product. ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.1), 3.25 (dd, 1H, J = 14.2, 9.8), 3.49 (dd, 1H, J = 14.2, 5.7), 4.11 (q, 2H, J = 7.1), 5.57 (dd, 1H, J = 9.6, 5.7), 6.26 (t, 1H, J = 2.3), 6.42 (d, 1H, J = 7.2), 6.70 (d, 1H, J = 7.2), 7.00-7.20 (m, 6H), 10.33 (s, 1H),.

Preparation of Compound 3

A solution of the preceding intermediate (0.14 g, 0.45 mmol, 1 equiv) in 1:1 1,4-dioxane-water (5 mL) was treated with LiOH-hydrate (28 mg, 0.68 mmol, 1.42 equiv), and heated to reflux for 30 min. The resulting solution was taken up in ethyl acetate (50 mL), washed with saturated aqueous citric acid (10 mL), followed by brine (2 x 15 mL), dried over $MgSO_4$, then evaporated to yield 61 mg of the corresponding acid. This was taken up in DMF (5 mL), treated with intermediate Y2 (Example 25, 49 mg, 0.22 mmol, 0.48 equiv), DIEA (0.07 mL, 0.43 mmol, 0.95 equiv), and HATU (82 mg, 0.22 mmol, 0.49 equiv), then held at 23 °C overnight. The solution was taken up in ethyl acetate (30 mL), washed with brine (10 mL), then evaporated. Purification of the residue by silica gel chromatography yielded 0.12 g (56%) of product as a 2:1 mixture of 2*S* : 2*R* diastereomers (Compounds 3 and 4, respectively). The diastereomers were separated by preparative reverse phase HPLC (acetonitrile-H_2O gradient). Compound 3: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.42-1.65 (m, 2H), 1.90-2.10 (m, 2H), 2.20-2.35 (m, 1H), 2.82-2.95 (m, 1H), 3.05-3.25 (m, 2H), 3.53 (dd, 1H, J = 13.8, 7.8), 4.17 (q, 2H, J = 7.1), 4.45-4.58 (m, 1H), 5.76-5.90 (m, 2H), 6.32 (t, 1H, J = 2.1), 6.63 (d, 1H, J = 7.3), 6.69-6.78 (m, 2H), 7.08-7.35 (m, 7H), 8.11 (d, 1H, J = 7.1), 11.22 (s, 1H).

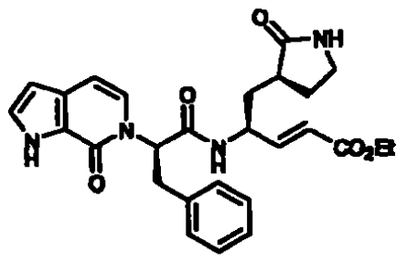
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EXAMPLE 4

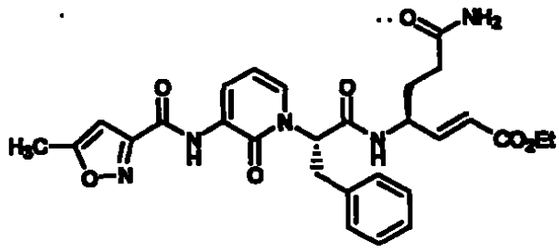
Preparation of Compound 4: *trans*-(2'*R*,3'''*S*,4*S*)-4-[2'-(7''-Oxo-1'',7''-dihydropyrrolo[2'',3''-c-pyridin-6''-yl)-3'-phenylpropionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester



See Preceding Example for preparation: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.1), 1.42-1.52 (m, 1H), 1.58-1.70 (m, 1H), 1.90-2.28 (m, 3H), 3.12 (dd, 1H, J = 13.3, 7.1), 3.20-3.28 (m, 2H), 3.57 (dd, 1H, J = 13.3, 9.0), 4.07 (q, 2H, J = 7.0), 4.45-4.58 (m, 1H), 5.80 (d, 1H, J = 15.7), 6.04 (t, 1H, J = 7.7), 6.37 (t, 1H, J = 2.3), 6.48 (s, br, 1H), 6.60-6.80 (m, 2H), 7.00-7.40 (m, 6H), 8.11 (d, 1H, J = 7.8), 10.61 (s, 1H).

EXAMPLE 5

Preparation of Compound 5: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3''-[(5'''-methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester (J1)



Preparation of Intermediate (1*S*)-[1-Hydroxymethyl-3-(tritylcarbamoyl)propyl]carbamic Acid Benzyl Ester (B1)

4-Methylmorpholine (1.89 mL, 17.2 mmol, 1 equiv) and ethyl chloroformate (1.65 mL, 17.3 mmol, 1 equiv) were added to a mixture of commercially available Cbz-Gln(Trt)-OH (9.00 g, 17.2 mmol, 1 equiv) in THF (23 mL) at –10 °C. After stirring 20 min, the reaction mixture was filtered and the filtrate was added dropwise to a

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suspension of $NaBH_4$ (1.47 g, 38.9 mmol, 2.25 equiv) in H_2O (10 mL) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 5 h. It was then cooled again to 0 °C, quenched by the careful addition of 1 N HCl (30 mL) and then partitioned between MTBE (500 mL) and brine (2 x 100 mL). The organic phase was dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (1*S*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-3-(tritylcarbamoyl)propyl]carbamic Acid Benzyl Ester (C1)

Intermediate B1, prepared above, was dissolved in DMF (10 mL). Imidazole (2.69 g, 39.5 mmol, 2.3 equiv) and *tert*-butyldimethylsilyl chloride (2.86 g, 19.0 mmol, 1.1 equiv) were added. The reaction mixture was stirred overnight, then diluted with MTBE (500 mL) and washed sequentially with 2.5% $KHSO_4$, H_2O, $NaHCO_3$, H_2O, and brine (100 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 25→40% EtOAc in hexanes) to provide the title intermediate (7.6 g, 71%) as a white amorphous solid: IR (cm^{-1}) 3307, 1708, 1660, 1496, 1249; ^1H NMR ($CDCl_3$) δ -0.01-0.05 (m, 6H), 0.89 (s, 9H), 1.76-1.93 (m. 2H), 2.29-2.40 (m, 2H), 3.56-3.77 (m, 3H), 5.03-5.16 (m, 3H), 7.00 (s, 1H), 7.18-7.39 (m, 20 H); Anal. $C_{38}H_{46}N_2O_4Si$: C, H, N.

Preparation of Intermediate (2'*R*,4*S*)-5-(*tert*-Butyldimethylsilanyloxy)-4-(2'-hydroxy-3'-phenylpropionylamino)pentanoic Acid Tritylamide (D1)

Intermediate C1 from above (7.6 g, 12 mmol, 1 equiv) and 10% palladium on carbon (0.45 g) were suspended in EtOH (140 mL) and hydrogenated at 50 psi overnight. The reaction mixture was filtered through Whatman #3 paper, the paper was washed with EtOH (120 mL) and the combined filtrates were evaporated. The residue was combined with D-3-phenyllactic acid (1.42 g, 12.2 mmol, 1 equiv), iPr_2NEt (4.25 mL, 24.4 mmol, 2 equiv) and HATU (4.64 g, 12.2 mmol, 1 equiv) in DMF (35 mL) at 0 °C. After stirring 1 h, the reaction mixture was allowed to warm to 23 °C and stirred 20 min more. Then 5% $KHSO_4$ (80 mL) and MTBE (600 mL) were added and the phases were separated. The organic phase was washed with H_2O (80 mL) and brine (70 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (50% EtOAc

in hexanes) to provide the title intermediate as a white foam (4.85 g, 62%): IR (cm^{-1}) 3394, 3295, 1666, 1649, 1519, 1255, 1114, 1085; ^1H NMR ($CDCl_3$) δ -0.03-0.02 (m, 6H), 0.85 (s, 9H), 1.70-1.89 (m, 2H), 2.18-2.42 (m, 3H), 2.83 (dd, 1H, J = 13.8, 8.1), 3.15 (dd, 1H, J = 13.8, 4.0), 3.40 (dd, 1H, J = 10.0, 4.7), 3.51 (dd, 1H, J = 10.0, 3.1), 3.83-3.94 (m, 1H), 4.17-4.23 (m, 1H), 6.79 (d, 1H, J = 8.7), 7.09 (s, 1H), 7.17-7.32 (m, 20H); Anal. $C_{39}H_{48}N_2O_4Si \cdot 0.30H_2O$: C, H, N.

Preparation of Intermediate (1'*S*,2*R*)-Methanesulfonic Acid 1-[1'-(*tert*-butyldimethylsilanyloxymethyl)-3'-(tritylcarbamoyl)propylcarbamoyl]-2-phenylethyl Ester (E1)

Intermediate D1 from above (1.96 g, 3.08 mmol, 1 equiv) and iPr_2NEt (0.752 mL, 4.32 mmol, 1.4 equiv) were dissolved in CH_2Cl_2 (30 mL) and cooled to –10 °C. Methanesulfonyl chloride (0.286 mL, 3.70 mmol, 1.2 equiv) was added dropwise, slowly, with vigorous stirring. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with brine (50 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (2-Hydroxypyridin-3-yl)carbamic acid *tert*-Butyl Ester (F1)

A suspension of 10% palladium on carbon (0.35 g) and 2-hydroxy-3-nitropyridine (5.00 g, 35.7 mmol, 1 equiv) in EtOH (170 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was stirred in THF (100 mL) at 23 °C. Di-*tert*-butyl dicarbonate (7.79 g, 35.7 mmol, 1 equiv) was added and the reaction mixture was heated to reflux for 4 h. More di-*tert*-butyl dicarbonate (6.0 g, 27 mmol, 0.8 equiv) was added and the reaction mixture was heated to reflux overnight. The solvent was evaporated and the residue was purified by flash column chromatography (gradient elution, 50→60% EtOAc in hexanes) to provide the title intermediate as a white solid (6.48 g, 83%): IR (cm^{-1}) 3225, 1725, 1649, 1514; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.33 (dd, 1H, J = 7.4, 6.6), 7.01 (dd, 1H, J = 6.6, 1.8), 7.56 (s, 1H), 8.11 (d, 1H, J = 7.1), 12.61 (s, 1H); Anal. $C_{10}H_{14}N_2O_3$: C, H, N.

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Preparation of Intermediate (1"*S*,2'*S*)-(1-{1'-[1"-(*tert*-Butyldimethylsilanyloxymethyl)-3"-(tritylcarbamoyl)propylcarbamoyl]-2'-phenylethyl}-2-oxo-1,2-dihydropyridin-3-yl)-carbamic Acid *tert*-Butyl Ester (G1)

Intermediate F1 from above (0.838 g, 3.99 mmol, 1.3 equiv) was stirred in THF (20 mL). Sodium hydride (60% dispersion in mineral oil, 0.148 g, 3.70 mmol, 1.2 equiv) was added. After stirring 20 min, a solution of intermediate E1 from above (1 equiv based on D1) in THF (15 mL) was added. The resulting mixture was heated to reflux for 40 h, but thin layer chromatography showed the reaction to be only 50% complete. In a separate flask, more sodium hydride (60% dispersion in mineral oil, 0.111 g, 2.78 mmol, 0.9 equiv) was added to a suspension of F1 (0.647 g, 3.08 mmol, 1 equiv) in THF (10 mL). After stirring 20 min, this mixture was added to original reaction vessel and the resulting mixture was heated to reflux for 21 h. After stirring at 23 °C over the weekend, the crude reaction mixture was diluted with MTBE (600 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 80 mL) and brine (80 mL), then dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (gradient elution, 30→35% EtOAc in hexanes) to provide the desired intermediate G1 as a white foam (1.98 g, 77%): IR (cm^{-1}) 3389, 3307, 1725, 1678, 1649, 1590, 1502; ^1H NMR ($CDCl_3$) δ -0.02-0.04 (m, 6H), 0.86 (s, 9H), 1.52 (s, 9H), 1.55-1.88 (m, 2H), 2.08-2.14 (m, 2H), 3.19 (dd, 1H, J = 13.7, 8.1), 3.39-3.51 (m, 2H), 3.53 (dd, 1H, J = 14.2, 7.8), 3.82-3.93 (m, 1H), 5.60-5.67 (m, 1H), 6.17 (t, 1H, J = 7.3), 6.44 (d, 1H, J = 8.3), 7.04 (s, 1H), 7.12-7.36 (m, 21H), 7.59 (s, 1H), 7.94 (d, 1H, J = 7.1); Anal. $C_{49}H_{60}N_4O_6Si$: C, H, N.

Preparation of Intermediate (1"*S*,2'*S*)-(1-{1'-[1"-Hydroxymethyl-3"-(tritylcarbamoyl)propylcarbamoyl]-2'-phenylethyl}-2-oxo-1,2-dihydropyridin-3-yl)carbamic Acid *tert*-Butyl Ester (H1)

Intermediate G1 from above (1.92 g, 2.32 mmol, 1 equiv) was dissolved in a mixture of CH_3CN (30 mL) and H_2O (3 mL) in a plastic tube. Triethylamine trihydrofluoride (21 drops) was added and the reaction solution was stirred overnight. It was then diluted with EtOAc (750 mL), washed with brine (3 x 80 mL), dried over $MgSO_4$ and evaporated to provide the title intermediate which was used without further purification.

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Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-[2'-(3"-*tert*-Butoxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-phenylpropionylamino]-6-(tritylcarbamoyl)-hex-2-enoic Acid Ethyl Ester (I1)

Intermediate H1 from above (1 equiv based on G1) was dissolved in CH_2Cl_2 (20 mL). Commercially available Dess-Martin periodinane (1.09 g, 2.55 mmol, 1.1 equiv) was added. After stirring 2 h, the solvent was evaporated and the residue was suspended in toluene and again evaporated (70 mL, then 2 x 20 mL) to give a yellow foam. One half of this material (1.16 mmol based on G1) was dissolved in THF (17 mL). (Carbethoxymethylene) triphenylphosphorane (0.563 g, 1.62 mmol, 1.4 equiv) was added and the reaction mixture was heated to reflux for 1 h and then stirred at 23 °C overnight. After evaporating the solvent, the residue was purified by flash column chromatography (gradient elution, 40→50% EtOAc in hexanes) to provide the title intermediate (0.710 g, 77%): IR (cm^{-1}) 3378, 3284, 1719, 1649, 1596, 1508, 1267; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.47 (s, 9H), 1.54-1.69 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.22 (m, 2H), 3.12 (dd, 1H, J = 13.7, 7.7), 3.47 (dd, 1H, J = 13.7, 8.1), 4.17 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.51-5.58 (m, 1H), 5.64 (dd, 1H, J = 15.7, 1.6), 6.12 (t, 1H, J = 7.2), 6.60-6.68 (m, 3H), 7.08-7.31 (m, 21H), 7.51 (s, 1H), 7.90 (d, 1H, J = 7.1); Anal. $C_{47}H_{50}N_4O_7 \cdot 0.50H_2O$: C, H, N.

Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-(2'-{3"-[(5"'-Methylisoxazole-3"'-carbonyl)amino]-2"-oxo-2"*H*-pyridin-1"-yl}-3'-phenylpropionylamino)-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (I2)

Intermediate I1 from above (0.088 g, 0.11 mmol, 1 equiv) was heated (neat) to between 190 and 200 °C for 65 minutes, then allowed to cool providing the crude amine as a dark residue which was dissolved in CH_3CN (2 mL) and cooled to 0 °C. 5-Methylisoxazole-3-carbonyl chloride (0.033 g, 0.23 mmol, 2 equiv) and 4-methylmorpholine (0.025 mL, 0.23 mmol, 2 equiv) were added and the reaction mixture was allowed to warm to 23 °C. After stirring 40 min, a mixture of 10% $KHSO_4$ and brine (1:1, 15 mL) and EtOAc (70 mL) were added. The phases were separated and the organic phase was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to provide the title intermediate (0.049 g, 55%): IR (cm^{-1}) 3331, 1678 (br), 1590, 1525; ^1H NMR

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($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.58-1.72 (m, 1H), 1.87-2.03 (m, 1H), 2.10-2.26 (m, 2H), 2.48 (s, 3H), 3.15 (dd, 1H, J = 13.7, 7.8), 3.47 (dd, 1H, J = 13.7, 8.1), 4.17 (q, 2H, J = 7.1), 4.43-4.55 (m, 1H), 5.54-5.61 (m, 1H), 5.65 (dd, 1H, J = 15.8, 1.5), 6.17 (t, 1H, J = 7.3), 6.45 (s, 1H), 6.65 (dd, 1H, J = 15.8, 5.4), 6.72 (s, 1H), 6.84 (d, 1H, J = 8.0), 7.08-7.32 (m., 22 H), 8.35 (dd, 1H, J = 7.3, 1.5), 9.49 (s, 1H); Anal. $C_{47}H_{46}N_5O_7 \cdot 0.25H_2O$: C, H, N.

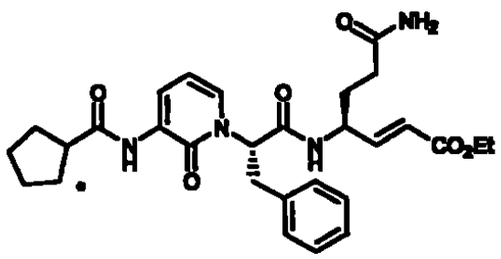
Preparation of Product J1 (Compound 5)

Intermediate I2 from above (0.047 g, 0.059 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 mL). Triisopropylsilane (0.036 mL, 0.176 mmol, 3 equiv) and TFA (2 mL) were added. The bright yellow solution was stirred 25 min, then diluted with CCl_4 (3 mL) and all the volatiles were evaporated. The residue was purified by flash column chromatography (3% CH_3OH in CH_2Cl_2) to give the desired product J1 (0.028 g, 85%): IR (cm^{-1}) 3342, 1666 (br), 1590, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.17-2.24 (m, 2H), 2.48 (s, 3H), 3.18 (dd, 1H, J = 13.7, 7.8), 3.50 (dd, 1H, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.68 (dd, 1H, J = 15.7, 1.3), 5.74-5.82 (m, 1H), 6.00 (s, 1H), 6.19 (s, 1H), 6.32 (t, 1H, J = 7.3), 6.46 (s, 1H), 6.69 (dd, 1H, J = 15.7, 5.5), 7.13-7.30 (m, 5H), 7.48 (dd, 1H, J = 7.3, 1.6), 7.62 (d, 1H, J = 7.6), 8.39 (dd, 1H, J = 7.3, 1.6), 9.46 (s, 1H); Anal. $C_{28}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 6

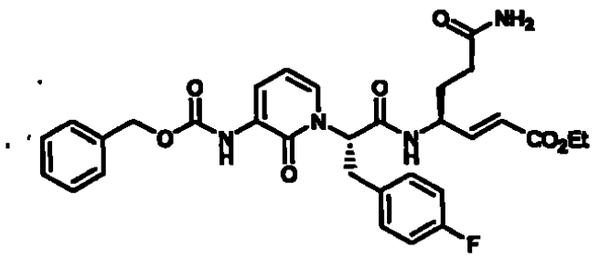
Preparation of Compound 6: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{2'-[3"-cyclopentanecarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl]-3'-phenylpropionylamino}hex-2-enoic Acid Ethyl Ester



The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate cyclopentanecarbonyl chloride where appropriate: IR (cm^{-1}) 3319, 1713, 1666, 1590, 1514; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 1.55-2.02 (m, 10H), 2.04-2.22 (m, 2H)2.68-2.80 (m, 1H), 3.16 (dd, 1H, J = 13.7, 7.7), 3.51 (dd, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.45-4.56 (m, 1H), 5.57-5.74 (m, 4H), 6.29 (t, 1H, J = 7.4), 6.68 (dd, 1H, J = 15.8, 5.5), 7.10-7.32 (m, 7H), 8.30 (s, 1H), 8.35 (dd, 1H, J = 7.4, 1.7); Anal. $C_{29}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 7

Preparation of Compound 7: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-(4"'-fluorophenyl)propionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-(4"'-fluorophenyl)propionylamino]-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester

Intermediate C1 (Example 5) was converted to the title intermediate by a process analogous to that described in Example 5 for the conversion of C1 to intermediate I1 utilizing S1 (Example 22) where appropriate: IR (cm^{-1}) 3283, 1722, 1651, 1604, 1513; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 6.9), 1.62-1.71 (m, 1H), 1.94-2.01 (m, 1H), 2.17-2.24 (m, 2H), 3.06-3.13 (m, 1H), 3.43-3.50 (m, 1H), 4.21 (q, 2H, J = 6.9), 4.50-4.57 (m, 1H), 5.16-5.25 (m, 2H), 5.52 (t, 1H, J = 8.1), 5.63 (dd, 1H, J = 15.6, 1.5), 6.18 (t, 1H, J = 7.2), 6.65 (s, br. 1H), 6.69 (dd, 1H, J = 15.6, 5.4), 6.84 (d, 1H, J = 8.4), 6.96 (t, 2H, J = 8.4), 7.09-7.18 (m, 7H), 7.21-7.33 (m, 12H), 7.38-7.42 (m, 4H), 7.76 (s, br. 1H), 7.99 (d, 1H, J = 7.5); Anal. $C_{50}H_{47}N_4O_7 \cdot 0.50H_2O$: C, H, N.

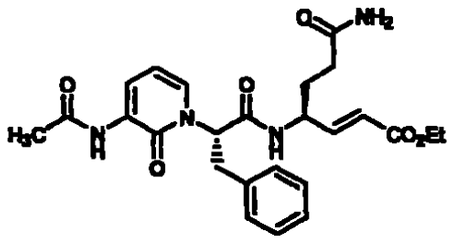
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Preparation of Compound 7

The preceding intermediate was converted to compound 7 by a process analogous to that described in Example 5 for the conversion of I2 to product J1: mp = 99-101 °C; IR (cm^{-1}) 3308, 1714, 1650, 1511, 1199; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 6.9), 1.72 –1.82 (m, 1H), 1.86-1.96 (m, 1H), 2.10-2.18 (m, 2H), 3.10-3.17 (m, 2H), 3.10-3.17 (m, 2H), 3.46-3.53 (m, 1H), 3.63-3.74 (m, 2H), 4.22 (q, 2H, J = 6.9), 4.48-4.57 (m, 1H), 5.21 (s, 2H), 5.58-5.65 (m, 2H), 5.91-5.97 (m, 1H), 6.19-6.22 (m, 1H), 6.35 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.6, 5.1), 6.98 (t, 2H, J = 8.7), 7.13-7.18 (m, 2H), 7.36-7.40 (m, 5H), 7.85 (s, br. 1H), 8.06-8.09 (m, 1H); Anal. $C_{33}H_{33}N_4O_7 \cdot 1.25H_2O$: C, H, N.

EXAMPLE 8

Preparation of Compound 8: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Acetylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-phenypropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



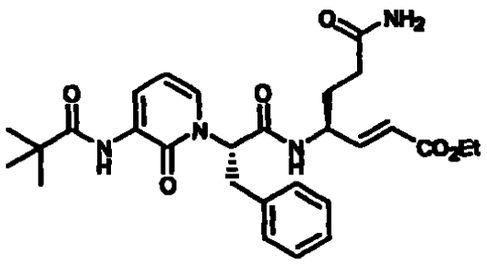
The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate acetyl chloride where appropriate: IR (cm^{-1}) 3307, 1708, 1666, 1643, 1590, 1519; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.70-1.86 (m, 2H), 2.05-2.24 (m, 5H), 3.15 (dd, 1H, J = 13.7, 8.1), 3.50 (dd, 1H, J = 13.7, 7.8), 4.19 (q, 2H, J = 7.1), 4.45-4.56 (m, 1H), 5.66-5.77 (m, 2H), 5.82 (s, 1H), 5.94 (s, 1H), 6.28 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.7, 5.6), 7.10-7.29 (m, 5H), 7.32-7.45 (m, 2H), 8.28-8.36 (m, 2H); Anal. $C_{25}H_{30}N_4O_6 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 9

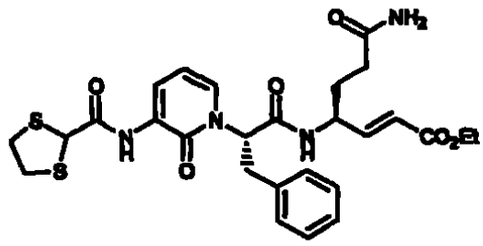
Preparation of Compound 9: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{2'-[3"-(2"',2"'-dimethylpropionylamino)-2"-oxo-2"*H*-pyridin-1"-yl]-3'-phenylpropionylamino}hex-2-enoic Acid Ethyl Ester



The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate 2,2-dimethylpropionyl chloride where appropriate: IR (cm^{-1}) 3378, 3307, 3213, 1713, 1666, 1643, 1590, 1514, 1273; ^1H NMR ($CDCl_3$) δ 1.18-1.37 (m, 12H), 1.67-1.98 (m, 2H), 2.05-2.20 (m, 2H), 3.17 (dd, 1H, J = 13.6, 7.7), 3.50 (dd, 1H, J = 13.6, 8.2), 4.19 (q, 2H, J = 7.1), 4.43-4.54 (m, 1H), 5.62-5.72 (m, 2H), 5.81-5.92 (m, 2H), 6.29 (t, 1H, J = 7.2), 6.66 (dd, 1H, J = 15.8, 5.7), 7.13-7.39 (m, 7H), 8.33-8.38 (m, 1H), 8.59 (s, 1H); Anal. $C_{28}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 10

Preparation of Compound 10: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3"-[([1"',3"']dithiolane-2"'-carbonyl)amino]-2"-oxo-2"*H*-pyridin-1"-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester

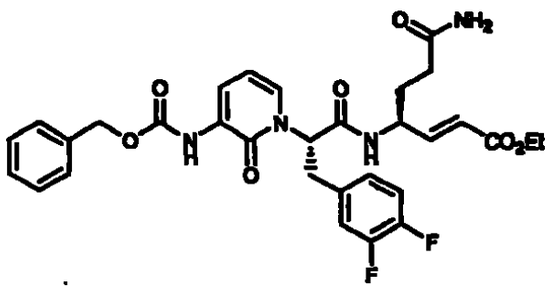


The title compound was prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate [1,3]dithiolane-2-carbonyl chloride (prepared as described in *Helv. Chim. Acta* 1975, *58*, 2509) where appropriate: IR (cm^{-1}) 3295, 1672 (br), 1590, 1519 (br), 1273; ^1H NMR

(CDCl$_3$) δ 1.30 (t, 3H, J = 7.1), 1.66-2.22 (m, 4H), 3.17 (dd, 1H, J = 13.7, 7.8), 3.28-3.45 (m, 4H), 3.52 (dd, 1H, J = 13.7, 8.1), 4.19 (q, 2H, J = 7.1), 4.43-4.55 (m, 1H), 5.01 (s, 1H), 5.66 (dd, 1H, J = 15.8, 1.5), 5.67 (s, 1H), 5.86 (s, 2H), 6.29 (t, 1H, J = 7.3), 6.67 (dd, 1H, J = 15.8, 5.5), 7.12-7.40 (m, 7H), 8.31 (dd, 1H, J = 7.3, 1.6), 9.57 (s, 1H); Anal. $C_{27}H_{32}N_4O_6S_4$·0.50H_2O: C, H, N.

EXAMPLE 11

Preparation of Compound 11: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-(3"',4"'-difluorophenyl)propionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2*R*)-3-(3',4'-Difluorophenyl)-2-hydroxypropionic Acid

Boc-D-3,4-Difluorophenylalanine (3.05 g, 11.0 mmol, 1 equiv) was dissolved in 1,4-dioxane (10 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added. The reaction was stirred at 23 °C for 5 h, then the solvent was removed under reduced pressure. The residue was dissolved in 1 M H_2SO_4 (22 mL), cooled to 0 °C and 2 N $NaNO_2$ (22 mL) was added via addition funnel under argon. The reaction mixture was stirred at 0 °C for 3 h and warmed to room temperature overnight. The resulting mixture was extracted with MTBE (3 x 40 mL), dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether/petroleum ether to afford the title intermediate (1.29 g, 58%) as off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.82-0.86 (m, 2H), 1.10-1.27 (m, 4H), 1.40-1.48 (m, 2H), 1.63-1.78 (m, 5H), 3.95-4.00 (m, 1H).

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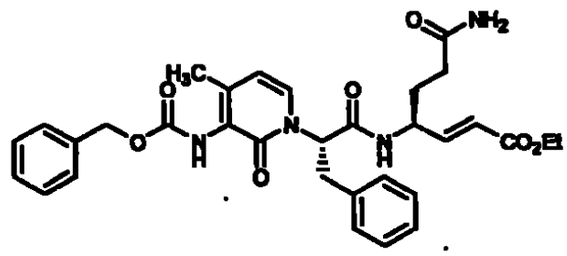
Preparation of Compound 11

Intermediate C1 (Example 5) was converted to compound 11 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing (2*R*)-3-(3',4'-difluorophenyl)-2-hydroxypropionic acid (Example 11) where appropriate: mp = 175-178 °C; IR (cm^{-1}) 3298, 1661, 1516, 1266; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.2), 1.74-1.95 (m, 2H), 2.12-2.20 (m, 2H), 3.05-3.12 (m, 1H), 3.42-3.50 (m, 1H), 4.21 (q, 2H, J = 7.2), 4.45-4.56 (m, 1H), 5.21 (s, 2H), 5.58-5.71 (m, 3H), 6.07-6.10 (m, 1H), 6.32-6.34 (m, 1H), 6.71 (dd, 1H, J = 15.6, 5.1), 6.88-6.91 (m, 1H), 6.99-7.11 (m, 2H), 7.30-7.33 (m, 1H), 7.36-7.39 (m, 5H), 7.53 (s, br. 1H), 7.86 (s, br. 1H), 8.04 (s, br. 1H); Anal. $C_{31}H_{32}N_4O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 12

Preparation of Compound 12: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-4"-methyl-2"-oxo-2"*H*-pyridin-1"-yl)-3'-phenylpropionylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (2-Hydroxy-6-methylphenyl)carbamic Acid Benzyl Ester

A suspension of 10% palladium on carbon (0.045 g) and 2-hydroxy-4-methyl-3-nitropyridine (0.600 g, 3.89 mmol, 1 equiv) in EtOH (20 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-4-methyl-3-aminopyridine which was used without further purification. This crude material was stirred in THF (18 mL) at 23 °C. Benzyl chloroformate (0.611 mL, 4.28 mmol, 1.1 equiv) and Na_2CO_3 (0.907 g, 8.56 mmol, 2.2 equiv) were added and the reaction mixture was stirred for 60 h, but TLC showed the reaction to be only 25% complete. The reaction mixture was heated to reflux for 24 h. More benzyl chloroformate (0.611 mL, 4.28 mmol, 1.1 equiv) and Na_2CO_3 (0.454 g, 4.28 mmol, 1.1

equiv) were added. The reaction mixture was heated to reflux for 24 h more, allowed to cool, diluted with EtOAc (200 mL), washed with half-saturated brine (2 x 40 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography (gradient elution, 3→5% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.363 g, 35%) as a white solid: ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 3.31-3.35 (m, 2H), 5.06 (s, 2H), 6.83 (d, 1H, J = 6.7), 7.17 (d, 1H, J = 6.7), 7.28-7.39 (m, 5H); Anal. $C_{14}H_{14}N_2O_3$: C, H, N.

Preparation of Compound 12

The preceding intermediate was converted to compound 12 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid and C1 (Example 5) where appropriate: IR (cm^{-1}) 3284, 1684 (br), 1596, 1327, (br), 1308, 1267, 1237; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1), 1.55-1.68 (m, 1H), 1.82-2.07 (m, 4H), 2.14 (s, 3H), 3.08 (dd, 1H, J = 13.6, 7.1), 3.47 (dd, J = 13.6, 8.8), 4.17 (q, 2H, J = 7.1), 4.41-4.52 (m, 1H), 5.06 (d, 1H, J = 12.3), 5.12 (d, 1H, J = 12.3), 5.59 (dd, 1H, J = 15.7, 1.6), 5.67-5.74 (m, 1H), 5.90 (s, 1H), 6.02 (s, 1H), 6.17 (d, 1H, J = 7.3), 6.68 (dd, 1H, J = 15.7, 5.1), 7.01 (s, 1H), 7.13-7.38 (m, 10H), 7.48 (d, 1H, J = 7.3); Anal. $C_{32}H_{36}N_4O_7 \cdot 0.75H_2O$: C, H, N.

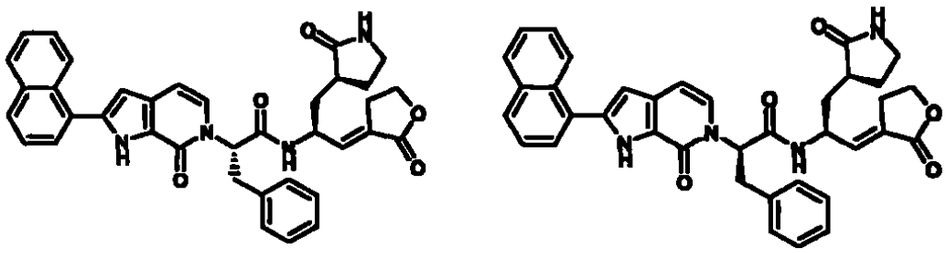
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EXAMPLE 13

Preparation of a 1:1 mixture of Compound 13: *trans*-(2*S*,2"*S*,3*S*)-2-(2'-Naphthalen-1'-yl-7'-oxo-1',7'-dihydropyrrolo[2',3'-c]pyridin-6'-yl)-*N*-[2"-(2"'-oxodihydrofuran-3"'-ylidene)-1"-(2""-oxopyrrolidin-3""-ylmethyl)ethyl]-3-phenylpropionamide and Compound 14: *trans*-(2*R*,2"*S*,3*S*)-2-(2'-Naphthalen-1'-yl-7'-oxo-1',7'-dihydropyrrolo[2',3'-c]pyridin-6'-yl)-*N*-[2"-(2"'-oxodihydrofuran-3"'-ylidene)-1"-(2""-oxopyrrolidin-3""-ylmethyl)ethyl]-3-phenylpropionamide



Preparation of Intermediate Pyrrole-2-carboxylic Acid Methyl Ester

Pyrrole-2-carboxylic acid (10.0 g, 90.0 mmol) in diethyl ether (200 mL) was treated with diazomethane (270 mmol, generated from *N*-nitroso-*N*-methyl urea), then back titrated with acetic acid until the yellow color dissipated. The solution was washed with saturated aqueous sodium bicarbonate (3 x 20 mL), followed by brine (3 x 20 mL), then was evaporated to obtain 10 g (88%) of product. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.26-6.29 (m, 1H), 6.91-6.94 (m, 1H), 6.65-6.98 (m, 1H), 9.14 (s, 1H).

Preparation of Intermediate 5-Bromo-1H-pyrrole-2-carboxylic Acid Methyl Ester

A solution of the preceding intermediate (10.0 g, 79.9 mmol, 1 equiv) in carbon tetrachloride (300 mL) was heated to 70 °C, then treated dropwise with a solution of bromine (126.0 mL, 99.9 mmol, 1.25 equiv) in carbon tetrachloride (200 mL). The reaction was initiated by the addition of iodine (40 mg). After the addition was complete, the reaction was held at 70 °C for 10 min, then cooled to 23 °C using an ice bath. The mixture was washed with 10% aqueous sodium carbonate (100 mL), followed by water (100 mL). The volatiles were evaporated, and the residue was purified by silica gel chromatography to obtain 4.5 g (27%) of product: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.23 (dd, 1H, J = 3.8, 2.6), 6.80 (dd, 1H, J = 3.9, 2.7), 9.29 (s, 1H).

Preparation of Intermediate 5-Naphthalene-1-yl-1H-pyrrole-2-carboxylic Acid Methyl Ester

Argon gas was bubbled for 15 min through a solution of the preceding intermediate (2.04 g, 10.0 mmol, 1 equiv) in 2 M aqueous sodium carbonate (20 mL), and DMF (150 mL). The mixture was then treated with tris(dibenzylidieneacetone)dipalladium (0) (0.46 g, 0.50 mmol, 0.05 equiv), and triphenylarsine (0.61 g, 2.0 mmol, 0.20 equiv), then heated to reflux, under argon, for 12 h. The mixture was taken up in ethyl acetate (500 mL) and water (150 mL), then filtered through celite. The organic layer was washed with brine (3 x 50 mL), then evaporated. Purification of the residue by silica gel chromatography yielded 2.05 g (81%) of product. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.22 (dd, 1H, J = 3.8. 2.6), 7.50-7.59 (m, 4H), 7.88 (dd, 1H, J = 3.9, 2.7), 7.89-8.16 (m, 2H), 8.17-8.22 (m, 1H), 9.37 (s, 1H). This material was taken up in 1:1 1,4-dioxane-water (30 mL), and treated with lithium hydroxide hydrate (1.02 g, 24.4 mmol, 2.4 equiv), then heated to reflux for 15 min. The solution was acidified with 20% aqueous citric acid (30 mL), then extracted with ethyl acetate (75 mL). The organic layer was washed with brine (2 x 20 mL), then evaporated. The residue was taken up in CH_2Cl_2, (30 mL), and treated with oxalyl chloride (2.10 mL, 24.0 mmol, 2.4 equiv), and DMF (one drop), then heated to reflux for 30 min. Evaporation yielded 5-naphthalen-1-yl-1H-pyrrole-2-carboxylic acid chloride which was used in the subsequent procedure without additional purification.

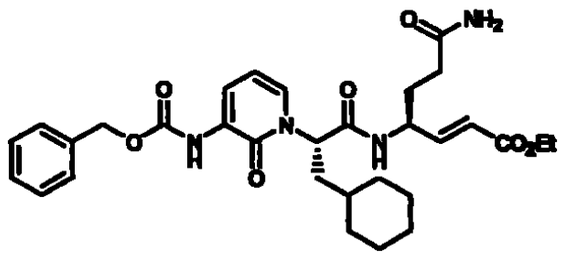
Preparation of Products 13 and 14

The preceding intermediate was converted to an inseparable 1:1 mixture of the title compounds by a process that was analogous to that described in Example 3 for the conversion of pyrrole-2-carbonyl chloride to compounds 3 and 4 and utilizing intermediate Y1 (Example 22) in lieu of Y2 where appropriate. ^{1}H NMR ($CDCl_3$) δ 1.55-2.00 (m, 6H), 2.50-3.50 (m, 7H), 4.00-4.50 (m, 3H), 4.42-5.60 (m, 1H), 5.90-8.40 (m, 15H), 10.49 (s, 0.5H), 11.54 (s, 0.5H).

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EXAMPLE 14

Preparation of Compound 15: *trans*-(2'*S*,4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)-3'-cyclohexylpropionylamino]-6-carbamoyl-hex-2-enoicAcid Ethyl Ester



Preparation of Intermediate (2*R*)-3-Cyclohexyl-2-hydroxypropionic Acid

Boc-D-Cyclohexylalanine-OH (3.00 g, 11.1 mmol, 1 equiv) was dissolved in 1,4-dioxane (10 mL), and a solution of HCl in 1,4-dioxane (4.0 M, 10 mL) was added. The reaction was stirred at 23 °C for 5 h, then the solvent was removed under reduced pressure. The residue was dissolved in 1 M H_2SO_4 (22 mL), cooled to 0 °C and 2 N $NaNO_2$ (22 mL) was added via addition funnel under argon. The reaction mixture was stirred at 0 °C for 3 h and warmed to room temperature overnight. The resulting mixture was extracted with MTBE (3 x 40 mL), dried over Na_2SO_4 and concentrated. The residue was triturated with petroleum ether, filtered and dried in the air to afford the title intermediate (0.6 g, 31%) as off-white solid. ^1H NMR (DMSO-d_6) δ 3.09-3.24 (m, 2H), 4.20-4.24 (m, 1H), 7.13-7.18 (m, 1H), 7.38-7.47 (m, 2H), 8.49 (s, br. 1H).

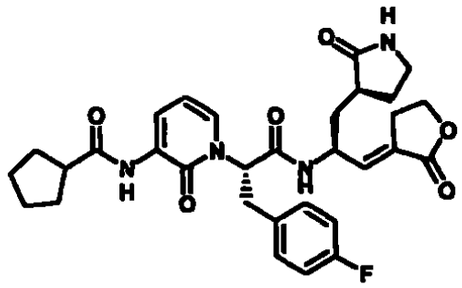
Preparation of Compound 15

Intermediate C1 (Example 5) was converted to product 15 by a process analogous to that described in Example 7 for the conversion of C1 to compound 7 utilizing (2*R*)-3-cyclohexyl-2-hydroxypropionic acid (Example 14) where appropriate: mp = 64-66 °C; IR (cm^{-1}) 3302, 2925, 1721, 1651, 1197; ^1H NMR ($CDCl_3$) δ 0.93-1.05 (m, 2H), 1.18-1.22 (m, 4H), 1.32 (t, 3H, J = 7.2), 1.66-1.75 (m, 4H), 1.82-1.91 (m, 2H), 1.94-2.06 (m, 2H), 2.10-2.17 (m, 2H), 2.90-2.92 (m, 2H), 4.23 (q, 2H, J = 7.2), 4.52-4.60 (m, 1H), 5.23 (s, 2H), 5.65 (t, 1H, J = 8.1), 5.82-5.86 (m, 1H), 5.62 (dd, 1H, J = 15.9, 1.8), 6.01-6.05 (m, 1H), 6.37 (t, 1H, J = 7.2), 6.85 (dd, 1H, J = 15.9, 5.7), 7.25-7.29 (m, 1H), 7.36-7.43 (m, 5H), 7.88 (s, br. 1H), 8.09 (d, 1H; J = 6.9); Anal. $C_{31}H_{40}N_4O_7 \cdot 1.0H_2O$: C, H, N.

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EXAMPLE 15

Preparation of Compound 16: *trans*-(2'*S*,2'''*S*,3''''*S*)-Cyclopentanecarboxylic acid(1-{2'-(4''-fluorophenyl)-1'-[2'''-(2''''-oxo-dihydrofuran-3''''-ylidene)-1'''-(2''''-oxopyrrolidin-3''''-ylmethyl)ethylcarbamoyl]ethyl}-2-oxo-1,2-dihydropyridin-3-yl)amide



Preparation of Intermediate Cyclopentanecarboxylic Acid (2-Hydroxypyridin-3-yl)amide

A sample of 10% Pd on C (0.40 g) was added to a solution of 2-hydroxy-3-nitropyridine (3.52 g, 25.0 mmol, 1 equiv) in EtOH. The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) overnight and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (100 mL), cooled to 0 °C, and cyclopentanecarbonyl chloride (25 mmol, 3.04 mL, 1 equiv) and NMM (2.75 mL, 25 mmol, 1 equiv) were added sequentially. The resulting mixture was stirred at 0 °C for 20 min, then was partitioned between water (400 mL) and 10% CH_3OH in CH_2Cl_2 (2 x 400 mL). The organic layers were dried over Na_2SO_4, concentrated, and the resulting residue recrystallized from CH_2Cl_2/hexanes to afford the title intermediate as a off-white solid (3.36 g, 65%); mp = 242-243 °C; IR (cm^{-1}) 3263, 1644, 1605, 1521, 1199; ^1H NMR (DMSO-d_6) δ 1.51-1.57 (m, 2H), 1.60-1.72 (m, 4H), 1.79-1.88 (m, 2H), 2.98-3.08 (m, 1H), 6.20 (t, 1H, J = 6.9), 7.08 (d, 1H, J = 6.6), 8.23 (d, 1H, J = 7.5), 9.02 (s, br. 1H), 11.95 (s, br. 1H); Anal. $C_{11}H_{14}N_2O_2$: C, H, N.

Preparation of Compound 16

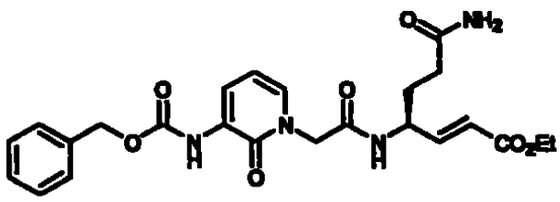
The preceding intermediate was converted to compound 16 by a process that was analogous to that described in Example 19 for the conversion of F2 to R1: mp = 135-137 °C; IR (cm^{-1}) 3288, 2954, 1754, 1682, 1511, 1219; ^1H NMR ($CDCl_3$) δ 0.84-0.93 (m, 2H), 1.55-1.66 (m, 4H), 1.82-2.02 (m, 5H), 2.27-3.22 (m, 2H), 2.70-2.89 (m, 3H), 3.09-

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3.17 (m, 1H), 3.20-3.37 (m, 2H), 3.42-3.39 (m, 1H), 5.63 (t, 1H, J = 7.2), 6.03 (s, br. 1H), 6.25-6.35 (m, 2H), 6.94 (t, 2H, J = 8.7), 7.08-7.12 (m, 2H), 7.25 (d, 1H, J = 9.0), 8.30-8.35 (m, 2H), 8.44 (d, 1H, J = 6.0); Anal. $C_{31}H_{35}FN_4O_6 \cdot 1.0H_2O$: C, H, N.

EXAMPLE 16

Preparation of Compound 17: *trans*-(4*S*)-4-[2'-(3"-Benzyloxycarbonylamino-2"-oxo-2"*H*-pyridin-1"-yl)acetylamino]-6-carbamoylhex-2-enoic Acid Ethyl Ester



Preparation of intermediate (3-benzyloxycarbonylamino-2-oxo-2*h*-pyridin-1-yl)acetic acid *tert*-butyl ester

Sodium hydride (0.070 g of a 60% suspension in mineral oil, 1.75 mmol, 1.0 equiv) was added to a solution of (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (prepared as described in Example 1) (0.415 g, 1.70 mmol, 1 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C, then *tert*-butyl bromoacetate (0.275 mL, 1.86 mmol, 1.1 equiv) was added. The reaction mixture was warmed to 23 °C for 45 min, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 100 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided the title compound (0.485 g, 85%) as an off-white solid: mp = 88-90 °C; IR (cm^{-1}) 3380, 1739, 1652, 1604; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 4.57 (s, 2H), 5.20 (s, 2H), 6.25 (t, 1H, J = 7.1), 6.87 (dd, 1H, J = 6.9, 1.7), 7.27-7.41 (m, 5H), 7.86 (s, br, 1H), 8.05 (d, br, 1H J = 6.8); Anal. $C_{19}H_{22}N_2O_5$: C, H, N.

Preparation of Intermediate (3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)acetic Acid

(3-Benzyloxycarbonylamino-2-oxo-2*H*-pyridin-1-yl)acetic acid *tert*-butyl ester (0.485 g, 1.35 mmol) was stirred in a 1:1 mixture of trifluoroacetic acid and CH_2Cl_2 at 23°C for 1 h. The volatiles were then removed under reduced pressure and the residue

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was triturated with Et_2O (40 mL). The resulting solid was filtered through a medium frit, washed with Et_2O (20 mL) and air-dried to give the title intermediate (0.315 g, 77%): mp = 171-173 °C; ^1H NMR (DMSO-d_6) δ 4.67 (s, 2H), 5.15 (s, 2H), 6.28 (t, 1H, J = 7.1), 7.29-7.43 (m, 7H), 7.85 (dd, 1H, J = 7.4, 1.7), 8.47 (s, 1H).

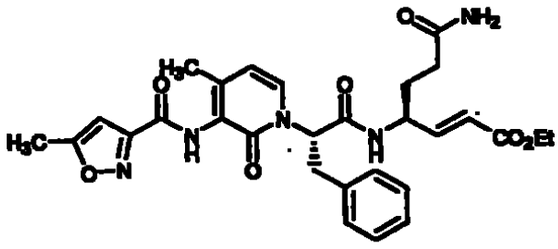
Preparation of Compound 17

The preceding intermediate was converted to compound 17 by a process analogous to that described in Example 23 for the conversion of W2 to J2: mp = 169-174 °C; IR (cm^{-1}) 3273, 1719, 1649; ^1H NMR (DMSO-d_6) δ 1.19 (t, 3H, J = 7.1), 1.64-1.85 (m, 2H), 2.10 (t, 2H, J = 7.6), 4.11 (q, 2H, J = 7.1), 4.38-4.41 (m, 1H), 4.60 (d, 1H, J = 15.5), 4.67 (d, 1H, J = 15.5), 5.15 (s, 2H), 5.92 (dd, 1H, J = 15.8, 1.3), 6.26 (t, 1H, J = 7.1), 6.76-6.83 (m, 2H), 7.09-7.42 (m, 7H), 7.84 (d, 1H, J = 7.3), 8.41-8.44 (m, 2H); Anal. $C_{24}H_{28}N_4O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 17

Preparation of Compound 18: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{4"-methyl-3"-[(5"'-methylisoxazole-3"'-carbonyl)amino]-2"-oxo-2"*H*-pyridin-1"-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester



Preparation of Intermediate 5-Methylisoxazole-3-carboxylic Acid (2'-hydroxy-4'-methylpyridin-3'-yl)amide

A sample of 10% Pd on C (0.35g) was added to a solution of 2-hydroxy-3-nitropyridine (2.03 g, 14.5 mmol, 1 equiv) in EtOH. The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) overnight and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (100 mL), cooled to 0 °C, and 5-methylisoxazole-3-carbonyl chloride (2.11g, 14.5 mmol, 1 equiv) and NMM (1.51 mL, 14.5 mmol, 1 equiv) were

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added sequentially. The resulting mixture was stirred at 0 °C for 20 min, and then was partitioned between water (400 mL) and 10% CH_3OH in CH_2Cl_2 (2 x 400 mL). The organic layers were dried over Na_2SO_4, concentrated and the resulting residue was recrystallized from CH_2Cl_2/hexanes to afford the title intermediate as an off-white solid (2.42 g, 76%): IR (cm^{-1}) 3330, 1650, 1536; ^1H NMR (DMSO-d_6) δ 3.34 (s, 3H), 6.31 (t, 1H, J = 6.6), 6.73 (s, 1H), 7.21 (d, 1H, J = 7.2), 8.29 (s, 1H, J = 7.2), 9.46 (s, br. 1H), 12.23 (s, br. 1H).

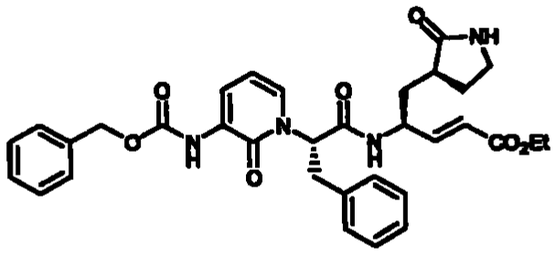
Preparation of Compound 18

The preceding intermediate was converted to Compound 18 by a process analogous to that described in Example 7 for the conversion of C1 to Compound 7 utilizing (2*R*)-2-hydroxy-3-phenylpropionic acid where appropriate: mp = 138-141 °C; IR (cm^{-1}) 3289, 1663, 1542, 1203; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.2), 1.62-1.89 (m, 2H), 1.99 (s, 3H), 2.02-2.07 (m, 1H), 2.47 (s, 3H), 3.03-3.39 (m, 5H), 4.12 (q, 2H, J = 7.2), 4.32-4.41 (m, 1H), 5.76 (dd, 1H, J = 15.6, 1.5), 5.80-5.83 (m, 1H), 6.13 (d, 1H, J = 7.5), 6.60 (s, br. 1H), 6.75 (dd, 1H, J = 15.6, 5.4), 7.15-7.24 (m, 5H), 7.76 (d, 1H, J = 7.2), 8.65 (d, 1H, J = 7.8), 9.59 (s, br. 1H); Anal. $C_{29}H_{33}N_5O_7$•1.5TFA: C, H, N.

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EXAMPLE 18

Preparation of Compound 19: *trans*-(2'*S*,3'''*S*,4*S*)-4-[2'-(3''-Benzyloxy-carbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester

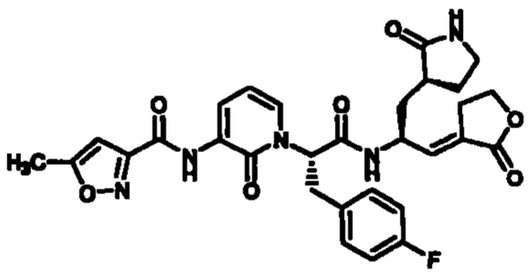


The title compound was prepared from K1 (Example 19) by a process analogous to that described in Example 19 for the conversion of K1 to R1 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid, (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 2), and commercially available (carbethoxymethylene)-

triphenylphosphorane where appropriate: IR (cm^{-1}) 3272, 1684 (br), 1590, 1514, 1273, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 1.42-1.55 (m, 1H), 1.59-1.75 (m, 1H), 2.00-2.27 (m, 3H), 3.07-3.28 (m, 3H), 3.43 (dd, 1H, J = 13.7, 7.3), 4.19 (q, 2H, J = 7.1), 4.36-4.47 (m, 1H), 5.12-5.21 (m, 2H), 5.75 (dd, 1H, J = 15.6, 1.2), 5.85-5.94 (m, 1H), 6.26 (t, 1H, J = 7.2), 6.58 (s, 1H), 6.70 (dd, 1H, J = 15.6, 5.7), 7.10-7.41 (m, 10H), 7.44-7.50 (m, 1H), 7.71 (s, 1H), 7.97 (d, 1H J = 6.2), 8.28 (d, 1H, J = 6.8); Anal. $C_{33}H_{36}N_4O_7 \cdot 0.25H_2O$: C, H, N.

EXAMPLE 19

Preparation of Compound 20: *trans*-(2"*S*,2""*S*,3""""*S*)-5-Methylisoxazole-3-carboxylic Acid (1'-{2"-(4"'-fluorophenyl)-1"-[2""-(2""'-oxodihydrofuran-3""'-ylidene)-1""'-(2""""-oxopyrrolidin-3""""-ylmethyl)ethylcarbamoyl]ethyl}-2'-oxo-1',2'-dihydropyridin-3'-yl)amide (R1)



Preparation of Intermediate (1*S*,3'*S*)-{2-(*tert*-Butyldiphenylsilanyloxy)-1-[1'-(2",4"-dimethoxybenzyl)-2'-oxopyrrolidin-3'-ylmethyl]ethyl}carbamicAcid *tert*-Butyl Ester (L1)

Intermediate K1 (4.41 g, 10.8 mmol, 1 equiv) was stirred in CH_2Cl_2 (50 mL) and the mixture was cooled to 0 °C. Triethylamine (7.52 mL, 54.0 mmol, 5 equiv), *tert*-butylchlorodiphenylsilane (5.53 mL, 21.6 mmol, 2 equiv) and 4-(dimethylamino)pyridine (0.330 g, 2.70 mmol, 0.25 equiv) were added successively. The mixture was allowed to warm to 23 °C and was stirred for 2 h. It was then diluted with MTBE (400 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography to provide the title intermediate (3.51 g, 50%) as a white foam: IR (cm^{-1}) 3319, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.42 (s, 9H), 1.44-1.65 (m, 2H), 2.05-2.17 (m, 1H), 2.23-2.35 (m, 1H), 2.44-2.56 (m, 1H), 3.14-3.21 (m, 2H), 3.55-3.68 (m, 2H), 3.69-3.81 (m, 1H),

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3.79 (s, 3H), 3.79 (s, 3H), 4.42 (s, 2H), 4.77 (d, 1H, J = 9.3), 6.41-6.46 (m, 2H), 7.09-7.13 (m, 1H), 7.34-7.46 (m, 6H), 7.61-7.67 (m, 4H); Anal. $C_{37}H_{50}N_2O_6Si$: C, H, N.

Preparation of Intermediate (1'*S*,2*R*,3"*S*)-*N*-{2'-(*tert*-Butyldiphenylsilanyloxy)-1'-[1"-(2"',4"'-dimethoxybenzyl)-2"-oxopyrrolidin-3"-ylmethyl]ethyl}-2-hydroxy-3-(4""-fluorophenyl)propionamide (M1)

Intermediate L1 from above (3.4 g, 5.26 mmol, 1 equiv) was dissolved in 1,4-dioxane (20 mL) at 23 °C. A solution of HCl in the same solvent (4.0 M, 20 mL) was added. After stirring 75 min, the volatiles were evaporated to provide a residue which was dissolved in CH_3CN (25 mL) and cooled to 0 °C. (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic acid (intermediate S1, see below, 0.968 g, 5.26 mmol, 1 equiv), 4-methylmorpholine (1.91 mL, 17.4 mmol, 3.3 equiv) and HATU (2.20 g, 5.79 mmol, 1.1 equiv) were added successively and the reaction mixture was allowed to warm to 23 °C and stirred 2.5 h. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 100 mL) and a mixture of brine and $NaHCO_3$ (1:1, 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (first in 5% CH_3OH in CH_2Cl_2, then in 3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.90 g, 51%) as a white foam: IR (cm^{-1}) 3389, 3319, 1660, 1508; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.52-1.66 (m, 2H), 2.02-2.13 (m, 2H), 2.20-2.39 (m, 2H), 2.77-2.86 (m, 1H), 3.07-3.23 (m, 3H), 3.47 (dd, 1H, J = 9.9, 5.9), 3.59 (dd, 1H, J = 9.9, 3.6), 3.77 (s, 3H); 3.78 (s, 3H), 3.99-4.11 (m, 1H), 4.22-4.29 (m, 1H), 4.31-4.41 (m, 2H), 6.36-6.45 (m, 2H), 6.81-6.89 (m, 2H), 7.05 (d, 1H, J = 8.0), 7.13-7.22 (m, 3H), 7.34-7.46 (m, 6H), 7.59-7.67 (m, 4H); Anal. $C_{41}H_{49}FN_2O_6Si \cdot 0.25H_2O$: C, H, N.

Preparation of Intermediate (1'*S*,2*R*,3"*S*)-Methanesulfonic Acid 1-{2'-(*tert*-butyldiphenylsilanyloxy)-1'-[1"-(2"',4"'-dimethoxybenzyl)-2"-oxopyrrolidin-3"-ylmethyl]ethylcarbamoyl}-2-(4""-fluorophenyl)ethyl Ester (N1)

Intermediate M1 from above (2.13 g, 2.99 mmol, 1 equiv) and iPr_2NEt (0.729 mL, 4.19 mmol, 1.4 equiv) were dissolved in CH_2C_2 (35 mL) and cooled to –10 °C. Methanesulfonyl chloride (0.277 mL, 3.58 mmol, 1.2 equiv) was added dropwise, slowly, with vigorous stirring. After 30 min, the reaction mixture was diluted with

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MTBE (500 mL), washed with a mixture of brine and 10% $KHSO_4$ (2:1, 100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate 5-Methylisoxazole-3-carboxylic Acid(2'-hydroxypyridin-3'-yl)amide (F2)

A suspension of 10% palladium on carbon (0.45 g) and 2-hydroxy-3-nitropyridine (7.00 g, 50.0 mmol, 1 equiv) in EtOH (210 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine which was used without further purification. This crude material was suspended in CH_3CN (170 mL) and cooled to 0 °C. 5-Methylisoxazole-3-carbonyl chloride (8.00 g, 55.0 mmol, 1 equiv) was added in one portion. After 25 min at 0 °C, the reaction mixture was allowed to warm to 23 °C and stirred for an additional 75 min. The thick mixture was then poured into dilute HCl (0.02 M, 150 mL) and mixed thoroughly. The undissolved solid was collected by filtration and washed with H_2O (2 x 20 mL) then dried under vacuum overnight to provide the title intermediate (7.1 g, 65%): ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 6.29 (dd, 1H, J = 7.2, 6.6), 6.69 (s, 1H), 7.19 (dd, 1H, J = 6.6, 1.8), 8.26 (dd, 1H, J = 7.2, 1.8), 9.43 (s, 1H), 12.20 (s, 1H).

Preparation of Intermediate (1'''*S*,2''*S*,3'''*S*)-5-Methylisoxazole-3-carboxylic Acid{1'-[1''-{2'''-(*tert*-butyldiphenylsilanyloxy)-1'''-[1''''-(2'''',4''''-dimethoxybenzyl)-2'''-oxopyrrolidin-3'''-ylmethyl]ethylcarbamoyl}-2''-(4''''-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (O1)

Intermediate F2 from above (1.11 g, 5.06 mmol, 1.7 equiv) was stirred in THF (14 mL). Sodium hydride (60% dispersion in mineral oil, 0.173 g, 4.32 mmol, 1.45 equiv) was added. After stirring 30 min, a solution of intermediate N1 from above (1 equiv based on M1) in THF (11 mL) was added. The resulting mixture was heated to reflux overnight, then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 100 mL) and brine and $NaHCO_3$ (3:1, 100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the desired

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intermediate O1 as a white foam (2.58 g, 95%): IR (cm^{-1}) 3331, 3284, 1666, 1596, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.45-1.71 (m, 2H), 1.94-2.32 (m, 3H), 2.52 (s, 3H), 3.07-3.19 (m, 3H), 3.42-3.52 (m, 2H), 3.67-3.74 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.99-4.10 (m, 1H), 4.30 (d, 1H, J = 14.6), 4.39 (d, 1H, J = 14.6), 5.54-5.63 (m, 1H), 6.25 (t, 1H, J = 7.3), 6.42-6.50 (m, 3H), 6.81-6.88 (m, 2H), 7.04-7.13 (m, 3H), 7.20-7.26 (m, 1H), 7.36-7.48 (m, 7H), 7.60-7.68 (m, 4H), 8.40 (dd, 1H, J = 7.3, 1.6), 9.60 (s, 1H); Anal. $C_{51}H_{56}FN_5O_8Si$: C, H, N.

Preparation of Intermediate (2"*S*,2'''*S*,3'''*S*)-5-Methylisoxazole-3-carboxylic Acid {1'-[1"-{1'''-[1''''-(2'''',4''''-dimethoxybenzyl)-2'''-oxopyrrolidin-3'''-ylmethyl]-2'''-hydroxyethylcarbamoyl}-2"-(4''''-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (P1)

Intermediate O1 from above (2.51 g, 2.75 mmol, 1 equiv) was dissolved in a mixture of CH_3CN (30 mL) and H_2O (1 mL) in a plastic tube. Hydrofluoric acid (48%, 5 mL) was added dropwise. After 1 h and 1.5 h, more hydrofluoric acid (2.5 mL and 2 mL respectively) was added. After 3.5 h total, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (250 mL), extracted with CH_2Cl_2 (3 x 400 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the title intermediate (1.84 g, 99%) as a white foam: IR (cm^{-1}) 3401 (br), 3331, 1655, 1590, 1531, 1508, 1455, 1208; ^1H NMR ($CDCl_3$) δ 1.47-1.63 (m, 2H), 1.87-1.99 (m, 1H), 2.07-2.18 (m, 1H), 2.33-2.44 (m, 1H), 2.49 (s, 3H), 3.10-3.24 (m, 3H), 3.46-3.56 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.84-3.89 (m, 1H), 3.92-4.03 (m, 1H), 4.19 (d, 1H, J = 14.5), 4.39 (d, 1H, J = 14.5), 5.54-5.61 (m, 1H), 6.22 (t, 1H, J = 7.2), 6.38-6.46 (m, 3H), 6.85-6.93 (m, 2H), 6.99-7.04 (m, 1H), 7.06-7.13 (m, 2H), 7.24 (dd, 1H, J = 7.2, 1.7), 8.33 (d, 1H, J = 7.3), 8.38 (dd, 1H, J = 7.2, 1.7), 9.54 (s, 1H); Anal. $C_{35}H_{38}FN_5O_8 \cdot 0.50H_2O$: C, H, N.

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Preparation of Intermediate *trans*-(2"*S*,2"'*S*,3""*S*)-5-Methylisoxazole-3-carboxylic Acid {1'-[1"-[1"'-[1""-(2"",4""-dimethoxybenzyl)-2""-oxopyrrolidin-3""-ylmethyl]-2"'-(2-oxocyclopentylidene)ethylcarbamoyl]-2"-(4""-fluorophenyl)ethyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (Q1)

Intermediate P1 from above (1.76 g, 2.60 mmol, 1 equiv) and commercially available Dess-Martin periodinane (1.11 g, 2.60 mmol, 1 equiv) were combined in CH_2Cl_2 (20 mL) at 23 °C and stirred 2 h. The volatiles were evaporated. The residue was suspended in toluene and concentrated to dryness (2 x 25 mL). The resulting residue was dissolved in a mixture of ethylene glycol dimethyl ether and DMF (5:1, 24 mL). 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) (0.902 g, 2.60 mmol, 1 equiv) was added and the reaction mixture was heated to 100 °C for 1.5 h. It was then allowed to cool, diluted with EtOAc (500 mL), washed with brine (200 mL, 100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed (gradient elution, 2→3% CH_3OH in CH_2Cl_2) then rechromatographed (50% EtOAc in CH_2Cl_2) to give the title intermediate (1.46 g) contaminated with triphenylphosphine oxide (approximately 35% by weight): ^1H NMR ($CDCl_3$) δ 1.47-1.62 (m, 2H), 1.87-1.98 (m, 1H), 2.21-2.31 (m, 1H), 2.38-2.52 (m, 1H), 2.50 (s, 3H), 2.81-2.93 (m, 1H), 3.10-3.33 (m, 4H), 3.50 (dd, 1H, *J* = 14.1, 7.0), 3.76 (s, 3H), 3.77 (s, 3H), 4.19 (d, 1H, *J* = 14.3), 4.29-4.52 (m, 3H), 4.38 (d, 1H, *J* = 14.3), 5.42-5.49 (m, 1H), 6.23 (t, 1H, *J* = 7.2), 6.27-6.33 (m, 1H), 6.40-6.48 (m, 3H), 6.90-6.97 (m, 2H), 7.00-7.12 (m, 3H), 7.15 (dd, 1H, *J* = 7.2, 1.6), 8.39 (dd, 1H, *J* = 7.2, 1.6), 8.83 (d, 1H, *J* = 5.7), 9.56 (s, 1H).

Preparation of Product R1 (Compound 20)

Intermediate Q1, prepared above, was dissolved in a mixture of $CHCl_3$ (30 mL) and H_2O (3 mL). DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was added and the reaction mixture was warmed in a 60 °C oil bath for 1.5 h. More DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was added and the reaction vessel was held in the 60 °C oil bath for 1.5 h more. DDQ (0.390 g, 1.72 mmol, 1.4 equiv) was again added. After stirring 2 h more, the reaction mixture was allowed to cool, diluted with CH_2Cl_2 (250 mL), and washed sequentially with a mixture of brine and 1 N HCl (2:1, 80 mL), a mixture of brine and $NaHCO_3$ (2:1, 80 mL) and brine (80 mL). The organic phase was dried over $MgSO_4$ and

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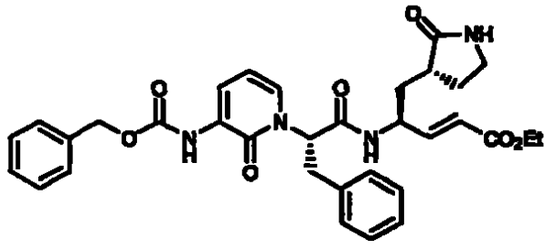
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evaporated. The residue was purified by flash column chromatography (2.5% CH_3OH in CH_2Cl_2) to provide the desired product (0.530 g, 73%) as an off-white amorphous solid: IR (cm^{-1}) 3336, 1750, 1682, 1530; ^1H NMR ($CDCl_3$) δ 1.39-1.49 (m, 1H), 1.63-1.80 (m, 1H), 2.09-2.37 (m, 3H), 2.49 (s, 3H), 2.74-2.86 (m, 1H), 3.11 (dd, 1H, *J* = 13.8, 8.5), 3.14-3.38 (m, 3H), 3.39 (dd, 1H, *J* = 13.8, 7.5), 4.30-4.46 (m, 3H), 5.72-5.79 (m, 1H), 6.29 (t, 1H, *J* = 7.2), 6.30-6.36 (m, 1H), 6.44-6.47 (m, 1H), 6.77 (s, 1H), 6.88-6.97 (m, 2H), 7.04-7.11 (m, 2H), 7.44-7.50 (m, 1H), 8.37 (dd, 1H, *J* = 7.2, 1.6), 8.66 (d, 1H, *J* = 6.2), 9.47 (s, 1H); Anal. $C_{30}H_{30}FN_5O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 20

Preparation of Compound 21: *trans*-(2'*S*,3'''*R*,4*S*)-4-[2'-(3''-Benzyloxycarbonylamino-2''-oxo-2''*H*-pyridin-1''-yl)-3'-phenylpropionylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester

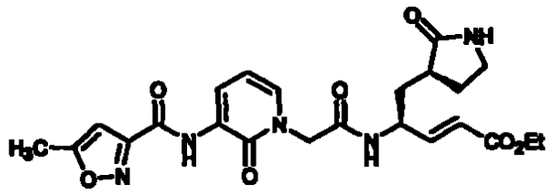


The title compound was prepared from (2*S*,3'*R*)-{1-[1'-(2'',4''-dimethoxybenzyl)-2'-oxopyrrolidin-3'-ylmethyl]-2-hydroxyethyl}carbamic acid *tert*-butyl ester (prepared as described in Dragovich, et al. *J. Med. Chem.* 1999, *42*, 1213) by a process analogous to that described in Example 19 for the conversion of K1 to R1 utilizing commercially available (2*R*)-2-hydroxy-3-phenylpropionic acid, (2-hydroxypyridin-3-yl)carbamic acid benzyl ester (Example 2), and commercially available (triphenyl-λ^5-phosphanylidene)acetic acid ethyl ester where appropriate: IR (cm^{-1}) 3483, 3272, 1684 (br), 1514, 1267, 1196; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1), 1.48-1.79 (m, 2H), 2.02-2.24 (m, 2H), 2.27-2.39 (m, 1H), 3.12 (dd, 1H, *J* = 13.7, 8.2), 3.19-3.34 (m, 2H), 3.48 (dd, 1H, *J* = 13.7, 7.8), 4.19 (q, 2H, *J* = 7.1), 4.43-4.53 (m, 1H), 5.17 (s, 2H), 5.73 (dd, 1H, *J* = 15.6, 1.3), 5.90-5.98 (m, 1H), 6.27 (t, 1H, *J* = 7.1), 6.63 (dd, 1H, *J* = 15.6, 6.0), 6.65-6.71 (m, 1H), 7.13-7.27 (m, 6H), 7.31-7.40 (m, 4H), 7.50 (dd, 1H, *J* = 7.1,

1.6), 7.75 (s, 1H), 7.97 (d, 1H, J = 6.6), 8.69 (d, 1H, J = 7.0); Anal. $C_{33}H_{36}N_4O_7$·0.50H_2O: C, H, N.

EXAMPLE 21

Preparation of Compound 22: *trans*-(4*S*,3'''*S*)-4-(2'-{3''-[(5'''-Methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}acetylamino)-5-(2'''-oxopyrrilidin-3'''-yl)pent-2-enoic Acid Ethyl Ester



Preparation of Intermediate {3-[(5'-Methylisoxazole-3'-carbonyl)amino]-2-oxo-2*H*-pyridin-1-yl}acetic Acid *tert*-Butyl Ester

To a solution of 5-methylisoxazole-3-carboxylic acid (2'-hydroxy-4'-methylpyridin-3'-yl)amide (F2, Example 19) (0.520 g, 2.37 mmol, 1 equiv) in THF (20 mL) at 0 °C was added NaH (0.095 g, 2.37 mmol, 1.0 equiv). The resulting mixture was stirred at 0 °C for 20 min, and then *t*-butyl bromoacetate (0.385 mL, 2.61 mmol, 1.1 equiv) was added. The reaction mixture was stirred and warmed to room temperature for 30 min, then was partitioned between 0.5 N HCl (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided the title intermediate (0.628 g, 79%) as a white solid: IR (cm^{-1}) 3343, 1743, 1651, 1581, 1156; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.53 (s, 3H), 4.65 (s, 2H), 6.32 (t, 1H, J = 7.2), 6.51 (s, 1H), 7.01 (dd, 1H, J = 6.9, 1.8), 8.50 (dd, 1H, J = 7.5, 1.8), 9.63 (s, br. 1H); Anal. $C_{16}H_{19}N_3O_5$: C, H, N.

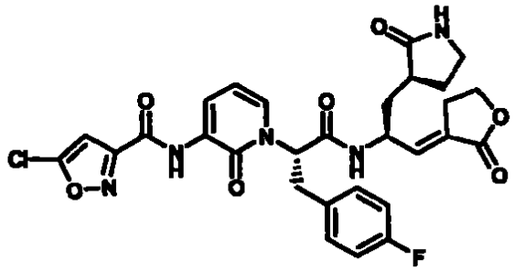
Preparation of Compound 22

The preceding intermediate was transformed into Compound 22 by a process that was analogous to that described in Example 25 for the transformation of V3 to product R3: mp = 102-106 °C; IR (cm^{-1}) 3336, 1684, 1534, 1457; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2), 1.67-1.75 (m, 1H), 1.98-2.09 (m, 1H), 2.37-2.49 (m, 1H), 2.53 (s, 3H),

2.55-2.61 (m, 1H), 3.34-3.46 (m, 2H), 3.51-3.52 (m, 1H), 4.17 (q, 2H, J = 7.2), 4.61-4.78 (m, 3H), 5.98 (dd, 1H, J = 15.6, 1.5), 6.20 (s, br. 1H), 6.35 (t, 1H, J = 7.8), 6.51 (s, 1H), 6.85 (dd, 1H, J = 15.6, 5.1), 7.17 (d, 1H, J = 7.2), 8.33 (d, 1H, J = 7.2), 8.49 (d, 1H, J = 7.5), 9.57 (s, br. 1H); Anal. $C_{23}H_{27}N_5O_7$: C, H, N.

EXAMPLE 22

Preparation of Compound 23: *trans*-(2"*S*,2""*S*,3""""*S*)-5-Chloroisoxazole-3-carboxylic Acid (1'-{2"-(4"'-fluorophenyl)-1"-[2""-(2""'-oxodihydrofuran-3""'-ylidene)-1""'-(2""""-oxopyrrolidin-3""""-ylmethyl)ethylcarbamoyl]ethyl}-2'-oxo-1',2'-dihydropyridin-3'-yl)amide (R2)



Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid (S1)

This intermediate was prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,365, filed August 24, 1999.

Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid Methyl Ester (T1)

This intermediate was prepared as described in co-pending U.S. Provisional Patent Application No. 60/150,365, filed August 24, 1999.

Preparation of Intermediate (2*R*)-3-(4-Fluorophenyl)-2-trifluoromethanesulfonyloxypropionic Acid Methyl Ester (U1)

Intermediate T1 from above (0.198 g, 1.00 mmol, 1 equiv) was dissolved in CH_2Cl_2 (6 mL) and cooled in an ice bath. 2,6-Lutidine (0.198 mL, 1.70 mmol, 1.7 equiv) and trifluoromethanesulfonic anhydride (0.269 mL, 1.60 mmol, 1.6 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (200

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mL), washed with a mixture of brine and 1 N HCl (2:1, 75 mL) and brine (75 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid Ethyl Ester

To a solution of ethyl chlorooximidoacetate (11.0 g, 72.6 mmol, 1 equiv) in 1,1-dichloroethylene (350 mL) was added Et_3N (25.3 mL, 181 mmol, 2.5 equiv) in 1,1-dichloroethylene (100 mL) via addition funnel over 30 min. The reaction mixture was stirred at room temperature for 23 h, 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. The residue was purified by flash column chromatography (10% EtOAc in hexanes) to give the title intermediate (4.49 g, 35%) as a pale yellow oil: IR (cm^{-1}) 1735, 1436, 1253; ^1H NMR ($CDCl_3$) δ 1.45 (t, 3H, J = 7.2), 4.49 (q, 2H, J = 7.2), 7.29 (s, 1H).

Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid

An aqueous solution of LiOH (2.0 M, 22.5 mL, 45.0 mmol, 2.0 equiv) was added to a solution of the preceding intermediate (3.95 g, 22.5 mmol, 1 equiv) in EtOH (80 mL) at 23 °C. The resulting mixture was stirred at room temperature for 45 min, then the volatiles were removed under reduced pressure. The residue thus obtained was partitioned between 1.0 N HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated to give the title intermediate (crude) (2.84 g, 86%) as a off-white solid which was used without further purification: ^1H NMR (DMSO-d_6) δ 7.15 (s, 1H).

Preparation of Intermediate 5-Chloroisoxazole-3-carbonyl Chloride

A solution of 5-chloroisoxazole-3-carboxylic acid (0.750 g, 4.32 mmol, 1 equiv) and thionyl chloride (9.0 mL, 120 mmol, 28 equiv) in $CHCl_3$ (21 mL) was heated to reflux for 28 h. The volatiles were evaporated to provide a residue which was dissolved in benzene (40 mL), which was subsequently evaporated to give the title intermediate as a yellow oil which was used without further purification.

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Preparation of Intermediate 5-Chloroisoxazole-3-carboxylic Acid (2'-hydroxypyridin-3'-yl)amide (F3)

A suspension of 10% palladium on carbon (0.15 g) and 2-hydroxy-3-nitropyridine (1.70 g, 12.1 mmol, 2.8 equiv) in EtOH (60 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give 2-hydroxy-3-aminopyridine (1.33 g, 99%) which was used without further purification. A portion of this material (0.524 g, 4.76 mmol, 1.1 equiv) was combined with the 5-chloroisoxazole-3-carbonyl chloride prepared above (4.32 mmol, 1 equiv based on theoretical yield) in THF (50 mL) and stirred 60 min. The volatiles were evaporated and the residue was stirred in half saturated $NaHCO_3$ (20 mL) for 30 min. The undissolved solid was collected by filtration, washed with H_2O (3 x 5 mL) and dried under vacuum overnight to provide the title intermediate (0.900 g, 87%) as a tan solid which was used without further purification. ^1H NMR (DMSO-d_6) δ 6.30 (t, 1H, J = 6.9), 7.22 (dd, 1H, J = 6.9, 1.7), 7.25 (s, 1H), 8.24 (dd, 1H, J = 6.9, 1.7), 9.47 (s, 1H), 12.22 (s, 1H).

Preparation of Intermediate (2*S*)-2-{3'-[(5"-Chloroisoxazole-3"-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}-3-(4"'-fluorophenyl)propionic Acid Methyl Ester (V1)

Intermediate F3 from above (0.280 g, 1.17 mmol, 1.17 equiv) was suspended in THF (7 mL). Sodium hydride (60% dispersion in mineral oil, 0.044 g, 1.1 mmol, 1.1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U1 from above (1.00 mmol, 1 equiv, based on T1) in THF (10 mL) was added dropwise. The resulting mixture was stirred 16 hours, then diluted with MTBE (250 mL) and washed with brine (2 x 80 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (33% EtOAc in hexanes) to provide the title intermediate (0.316 g, 75%) as a white foam: IR (cm^{-1}) 3331, 1743, 1690, 1643, 1602, 1531, 1437; ^1H NMR ($CDCl_3$) δ 3.33 (dd, 1H, J = 14.5, 10.3), 3.53 (dd, 1H, J = 14.5, 5.5), 3.78 (s, 3H), 5.36 (dd, 1H, J = 10.3, 5.5), 6.18 (t, 1H, J = 7.2), 6.67 (s, 1H), 6.82 (dd, 1H, J = 7.2, 1.7), 6.89-6.97 (m, 2H), 7.01-7.07 (m, 2H), 8.38 (dd, 1H, J = 7.2, 1.7), 9.52 (s, 1H); Anal. $C_{19}H_{15}ClFN_3O_5$: C, H, N.

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Preparation of Intermediate (2*S*)-2-{3'-[(5"-Chloroisoxazole-3"-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}-3-(4"'-fluorophenyl)propionic Acid (W1)

Intermediate V1 from above (0.445 g, 1.06 mmol, 1 equiv) was dissolved in CH_3OH (10 mL). An aqueous solution of NaOH (1.0 M, 4.2 mL, 4.2 mmol, 4 equiv) was added dropwise. The reaction mixture was stirred 2 h, then poured into a mixture of brine and 10% $KHSO_4$ (1:1, 50 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to provide the title intermediate as a yellow foam which was used without further purification.

Preparation of Intermediate *trans*-(2'*S*,3"*S*)-3-[2'-Amino-3'-(2"-oxodihydrofuran-3"-ylidene)propyl]pyrrolidin-2-one (Y1)

Intermediate X1 (prepared in a manner analogous to that described in Baldwin et al., *J. Org. Chem.* 1971, *36*, 1441) (0.413 g, 1.27 mmol, 1.2 equiv) was stirred for 45 min in a mixture of TFA (5 mL) in CH_2Cl_2 (10 mL). Then the volatiles were evaporated to provide the title intermediate which was used without purification.

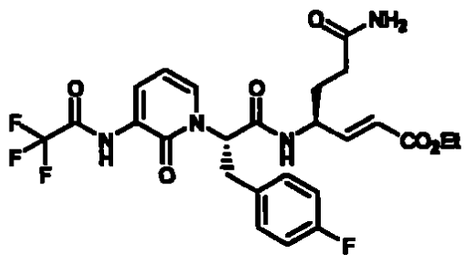
Preparation of Product R2 (Compound 23)

Intermediates W1 (1.06 mmol, 1 equiv based on V1) and Y1 (1.27 mmol, 1.2 equiv based on X1) were combined in CH_3CN (14 mL) and cooled in an ice bath. 4-Methylmorpholine (0.583 mL, 5.30 mmol, 5 equiv) and HATU (0.403 g, 1.06 mmol, 1 equiv) were added and the reaction mixture was allowed to warm to 23 °C and stirred 1.5 h. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (3:1, 80 mL), a mixture of brine and $NaHCO_3$ (3:1, 80 mL) and brine (80 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was chromatographed (5% CH_3OH in CH_2Cl_2) then rechromatographed (2.5% CH_3OH in CH_2Cl_2) to provide the desired product R2 (0.418 g, 64%) contaminated with a diastereomer (approximately 30%, presumably the 2"R epimer): ^1H NMR ($CDCl_3$) (mixture of isomers) δ 1.33-1.51 (m), 1.62-1.88 (m), 2.06-2.39 (m), 2.73-2.88 (m), 2.98-3.45 (m), 4.27-4.44 (m), 5.71-5.88 (m), 6.27-6.43 (m), 6.66 (s), 6.68 (s), 6.81 (s), 6.88-6.98 (m), 7.03-7.24 (m), 7.48 (d, J = 7.3), 7.55-7.62 (m), 8.34-8.42 (m), 8.65 (d, J = 6.2), 8.77 (d, J = 7.0), 9.41-9.48 (m).

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EXAMPLE 23

Preparation of Compound 24: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-{3'-(4"-fluorophenyl)-2'-[2"'-oxo-3"'-(2"",2"",2""-trifluoroacetylamino)-2"'*H*-pyridin-1"'-yl]propionylamino}hex-2-enoic Acid Ethyl Ester (J2)



Preparation of Intermediate (2*R*)-3-(4'-Fluorophenyl)-2-hydroxypropionic Acid Benzyl Ester (T2)

Intermediate S1 (1.00 g, 5.43 mmol, 1 equiv) was dissolved in CH_3CN (8 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.812 mL, 5.43 mmol, 1 equiv) and benzyl bromide (0.646 mL, 5.43 mmol, 1 equiv) were added successively. The resulting solution was stirred 40 h, then diluted with MTBE (250 mL) and washed with 5% $KHSO_4$ and brine (75 mL each). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (1.25 g, 84%) as a colorless oil which solidified over several days: IR (cm^{-1}) 3450, 1954, 1890, 1725, 1602; ^1H NMR ($CDCl_3$) δ 2.76-2.81 (m, 1H), 2.94 (dd, 1H, J = 14.1, 6.2), 3.08 (dd, 1H, J = 14.1, 4.6), 4.42-4.49 (m, 1H), 5.14 (d, 1H, J = 12.1), 5.21 (d, 1H, J = 12.1), 6.86-6.94 (m, 2H), 7.03-7.11 (m, 2H), 7.29-7.42 (m, 5H); Anal. $C_{16}H_{15}FO_3$: C, H.

Preparation of Intermediate (2*R*)-3-(4-Fluorophenyl)-2-trifluoromethanesulfonyloxypropionic Acid Benzyl Ester (U2)

Intermediate T2 from above (0.134 g, 0.489 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice bath. 2,6-Lutidine (0.114 mL, 0.979 mmol, 2 equiv) and trifluoromethanesulfonic anhydride (0.156 mL, 0.927 mmol, 1.9 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (150 mL), washed with a mixture of brine and 1 N HCl (2:1, 75 mL) and brine (50 mL), dried over

Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate 2,2,2-Trifluoro-*N*-(2'-hydroxypyridin-3'-yl)acetamide (F4)

TFA (4 mL) was added to a solution of intermediate F1 (0.700 g, 3.33 mmol, 1 equiv) in CH_2Cl_2 (6 mL). After stirring 30 min, the volatiles were evaporated. The residue was suspended in toluene and concentrated to dryness to provide crude 2-hydroxy-3-aminopyridine which was (without further purification) suspended in CH_2Cl_2 (14 mL) and cooled in an ice bath. 4-Methylmorpholine (1.10 mL, 10.0 mmol, 3 equiv) and trifluoroacetic anhydride (0.471 mL, 3.33 mmol, 1 equiv) were added successively. After 30 min, more 4-methylmorpholine (0.550 mL, 5 mmol, 1.5 equiv) was added. The reaction mixture was stirred an additional 1.5 h, then diluted with EtOAc (250 mL) and washed with brine, H_2O and brine (25 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.173 g, 25%) as a white amorphous solid: ^1H NMR (DMSO-d_6) δ 6.27 (t, 1H, J = 6.9), 7.32 (dd, 1H, J = 6.9, 1.8), 7.94 (dd, 1H, J = 6.9, 1.8), 10.16 (s, 1H), 12.20 (s, 1H); Anal. $C_7H_5F_3N_2O_2$: C, H, N.

Preparation of Intermediate (2*S*)-3-(4'-Fluorophenyl)-2-[2"-oxo-3"-(2"',2"',2"'-trifluoroacetylamino)-2"*H*-pyridin-1"-yl]propionic Acid Benzyl Ester (V2)

Intermediate F4 from above (0.111 g, 0.539 mmol, 1.1 equiv) was suspended in THF (3 mL). Sodium hydride (60% dispersion in mineral oil, 0.020 g, 0.50 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U2 (0.489 mmol, 1 equiv, based on T2) in THF (5 mL) was added dropwise. The resulting mixture was stirred 2 hours, then diluted with MTBE (150 mL) and washed with brine (2 x 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (0.190 g, 84%) as a thick oil: IR (cm^{-1}) 3343, 1743, 1727, 1655, 1602, 1296, 1214, 1161; ^1H NMR ($CDCl_3$) δ 3.31 (dd, 1H, J = 14.4, 10.0), 3.52 (dd, 1H, J = 14.4, 5.4), 5.21 (s, 2H), 5.39 (dd, 1H, J = 10.0, 5.4), 6.18 (t, 1H, J = 7.3), 6.85 (dd, 1H, J

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= 7.3, 1.7), 6.87-7.04 (m, 4H), 7.25-7.38 (m, 5H), 8.31 (dd, 1H, *J* = 7.3, 1.7), 9.03 (s, 1H); Anal. $C_{23}H_{18}F_4N_2O_4$: C, H, N.

Preparation of Intermediate (2*S*)-3-(4'-Fluorophenyl)-2-[2"-oxo-3"-(2"",2"",2""-trifluoroacetylamino)-2"*H*-pyridin-1"-yl]propionic Acid (W2)

A suspension of 10% palladium on carbon (0.030 g) and intermediate V2 from above (0.151 g, 0.327 mmol, 1 equiv) in EtOH (5 mL) was subjected to one atmosphere of hydrogen for 16 hours. After purging the reaction vessel with argon, the mixture was filtered through Whatman #3 paper and the filtrate was evaporated to give the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(4*S*)-4-Amino-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (AA1)

Intermediate Z1 (prepared according to Dragovich, et al., *J. Med. Chem.* 1998, *41*, 2806) (0.177 g, 0.326 mmol, 1 equiv) was stirred for 2 h in a solution of HCl in 1,4-dioxane (2.0 M, 8 mL). Then the volatiles were evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(2'*S*,4*S*)-4-{3'-(4"-Fluorophenyl)-2'-[2""-oxo-3""-(2"",2"",2""-trifluoroacetylamino)-2""*H*-pyridin-1""-yl]propionylamino}-6-(tritylcarbamoyl)hex-2-enoic Acid Ethyl Ester (I3)

Intermediates W2 and AA1 (as prepared above) were combined in CH_2Cl_2 (5 mL) and cooled in an ice bath. HOBt (0.049 g, 0.36 mmol, 1.1 equiv), iPr_2NEt (0.171 mL, 0.982 mmol, 3 equiv) and EDC (0.063 g, 0.33 mmol, 1 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C overnight, then diluted with EtOAc (200 mL) and washed with 5% $KHSO_4$ and brine (50 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (44% EtOAc in hexanes) to provide the title intermediate (0.138 g, 53%) as a white amorphous solid: ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.26-2.34 (m, 2H), 3.01-3.10 (m, 1H), 3.31-3.40 (m, 1H), 4.19 (q, 2H, *J* = 7.1), 4.46-4.56 (m, 1H), 5.42-5.49 (m, 1H), 5.63 (dd, 1H, *J* = 15.7, 1.6),

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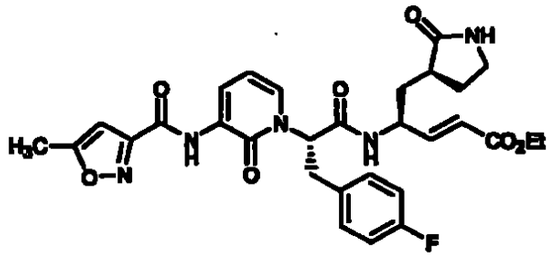
6.18 (t, 1H, J = 7.3), 6.62-6.71 (m, 2H), 6.88-6.96 (m, 2H), 7.00-7.06 (m, 2H), 7.10-7.34 (m, 17H), 8.25 (dd, 1H, J = 7.3, 1.6), 9.02 (s, 1H); Anal. $C_{44}H_{40}F_4N_4O_6$: C, H, N.

Preparation of Product J2 (Compound 24)

Intermediate I3 from above (0.112 g, 0.141 mmol, 1 equiv) and triisopropylsilane (0.086 mL, 0.420 mmol, 3 equiv) were combined in CH_2Cl_2 (4 mL). TFA (2 mL) was added. After stirring 30 min, CCl_4 (4 mL) was added and the volatiles were evaporated. The residue was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to provide the desired product (0.078 g, 100%) as a tan amorphous powder: ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 1.75-1.96 (m, 2H), 2.13-2.30 (m, 2H), 3.12 (dd, 1H, J = 13.7, 7.5), 3.46 (dd, 1H, J = 13.7, 8.5), 4.20 (d, 2H, J = 7.1), 4.45-4.55 (m, 1H), 5.63 (dd, 1H, J = 15.7, 1.6), 5.66-5.74 (m, 1H), 5.92 (s, 1H), 6.28 (s, 1H), 6.37 (t, 1H, J = 7.3), 6.67 (dd, 1H, J = 15.7, 5.7), 6.92-7.00 (m, 2H), 7.09-7.17 (m, 2H), 7.54 (dd, 1H, J = 7.3, 1.6), 7.60 (d, 1H, J = 7.5), 8.34 (dd, 1H, J = 7.3, 1.6), 9.04 (s, 1H); Anal. $C_{25}H_{26}F_4N_4O_6 \cdot 1.25H_2O$: C, H, N.

EXAMPLE 24

Preparation of Compound 25: trans-(2'*S*,3''''*S*,4*S*)-4-(3'-(4''-Fluorophenyl)-2'-{3'''-[(5''''-methylisoxazole-3''''-carbonyl)amino]-2'''-oxo-2'''*H*-pyridin-1'''-yl}propionylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester



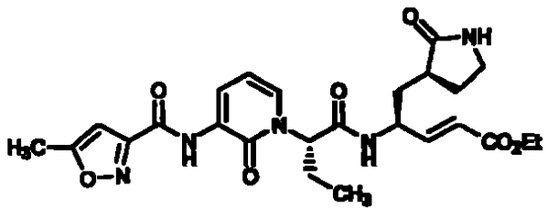
The title compound was prepared from F2 (Example 19) in a manner analogous to that described for the conversion of U2 to I3 in Example 23 utilizing intermediate Y2 (Example 25) where appropriate: IR (cm^{-1}) 3331, 1690, 1590, 1531, 1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0), 1.45-1.55 (m, 1H), 1.64-1.75 (m, 1H), 2.03-2.31 (m, 3H), 2.49 (s, 3H), 3.10 (dd, 1H, J = 13.7, 7.9), 3.20-3.46 (m, 3H), 4.20 (q, 2H, J = 7.0), 4.36-4.47 (m, 1H), 5.67 (dd, 1H, J = 15.7, 1.4), 5.85-5.92 (m, 1H), 6.29 (t, 1H, J = 7.2), 6.45

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(s, 1H), 6.70 (dd, 1H, J = 15.7, 5.7), 6.86 (s, 1H), 6.90-6.97 (m, 2H), 7.10-7.16 (m, 2H), 7.60 (dd, 1H, J = 7.2, 1.6), 8.37 (dd, 1H, J = 7.2, 1.6), 8.51 (d, 1H, J = 6.6), 9.47 (s, 1H).

EXAMPLE 25

Preparation of Compound 26: *trans*-(2'*S*,3'''*S*,4*S*)-4-(2'-{3"-[(5'''-Methyl-isoxazole-3'''-carbonyl)amino]-2"-oxo-2"*H*-pyridin-1"-yl}butyrylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester (R3)



Preparation of Intermediate (2*R*)-2-Trifluoromethanesulfonyl-oxybutyric acid *tert*-butyl ester (U3)

Commercially available T3 (0.575 g, 3.59 mmol, 1 equiv) was dissolved in CH_2Cl_2 (25 mL) and cooled in an ice bath. 2,6-Lutidine (0.836 mL, 7.18 mmol, 2 equiv) and trifluoromethanesulfonic anhydride (1.15 mL, 6.84 mmol, 1.9 equiv) were added and the reaction mixture was stirred 30 min. It was then diluted with MTBE (400 mL), washed with a mixture of brine and 1 N HCl (2:1, 100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated to provide the title intermediate which was used without further purification.

Preparation of Intermediate (2*S*)-2-{3'-[(5"-Methylisoxazole-3"-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid *tert*-Butyl Ester (V3)

Intermediate F2 from above (0.200 g, 0.912 mmol, 1.1 equiv) was suspended in THF (6 mL). Sodium hydride (60% dispersion in mineral oil, 0.0332 g, 0.830 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U3 (0.830 mmol, 1 equiv, based on T3) in THF (7 mL) was added dropwise. The resulting mixture was stirred 2 hours, then diluted with EtOAc (200 mL) and washed with brine (2 x 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (25% EtOAc in hexanes) to provide the title intermediate (0.178 g, 59%) as an oil: R_f = 0.30 (25% EtOAc in hexanes); IR (cm^{-1})

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3331, 1731, 1690, 1649, 1602, 1531; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.3), 1.45 (s, 9H), 1.83-2.01 (m, 1H), 2.17-2.31 (m, 1H), 2.50 (s, 3H), 5.44-5.51 (m, 1H), 6.32 (t, 1H, J = 7.2), 6.48 (s, 1H), 7.10 (dd, 1H, J = 7.2, 1.8), 8.45 (dd, 1H, J = 7.2, 1.8), 9.64 (s, 1H); Anal. $C_{18}H_{23}N_3O_5$: C, H, N.

Preparation of Intermediate (2*S*)-2-{3'-[(5"-Methylisoxazole-3"-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid (W3)

Intermediate V3 from above (0.143 g, 0.397 mmol, 1 equiv) was stirred for 1 h in a solution of TFA (2 mL) in CH_2Cl_2 (3 mL). The volatiles were evaporated. The residue was suspended in toluene (10 mL) and concentrated to dryness, providing the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-Amino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic Acid Ethyl Ester (Y2)

Intermediate X2, prepared according to the method disclosed in the co-pending application, U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999(0.130 g, 0.398 mmol, 1 equiv), was stirred for 30 min in a solution of TFA (2 mL) in CH_2Cl_2 (3 mL). The volatiles were evaporated. The residue was suspended in toluene (10 mL) and concentrated to dryness, providing the title intermediate which was used without further purification.

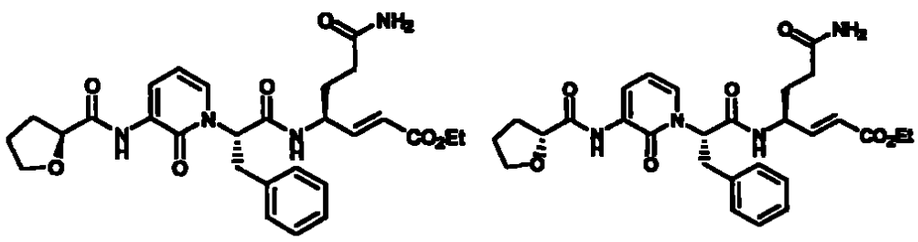
Preparation of Product R3 (Compound 26)

Intermediates W3 and Y2 (as prepared above) were combined in CH_2Cl_2 (7 mL) and cooled in an ice bath. HOBt (0.064 g, 0.47 mmol, 1.2 equiv), iPr_2NEt (0.484 mL, 2.78 mmol, 7 equiv) and EDC (0.084 g, 0.44 mmol, 1.1 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C overnight, then diluted with EtOAc (500 mL) and washed with 5% $KHSO_4$, half saturated $NaHCO_3$, and brine (100 mL each). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.119 g, 58%) as a white foam: IR (cm^{-1}) 3331, 1684, 1649, 1590, 1531; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.3), 1.29 (t, 3H, J = 7.1), 1.47-1.58 (m, 1H), 1.62-1.77 (m, 1H), 1.85-2.00 (m, 1H), 2.08-2.33 (m, 4H), 2.49 (s, 3H),

3.25-3.42 (m, 2H), 4.19 (q, 2H, J = 7.1), 4.39-4.50 (m, 1H), 5.73 (dd, 1H, J = 8.8, 6.8), 5.97 (dd, 1H, J = 15.7, 1.4), 6.34 (t, 1H, J = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, J = 15.7, 5.9), 7.18 (s, 1H), 7.59 (dd, 1H, J = 7.2, 1.8), 8.42 (dd, 1H, J = 7.2, 1.8), 8.58-8.62 (m, 1H), 9.56 (s, 1); Anal. $C_{25}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EXAMPLE 26

Preparation of a 1:1 Mixture of Compound 27: *trans*-(2'*S*,2'''*S*,4*S*)-6-Carbamoyl-4-(2'-{2''-oxo-3''-[(tetrahydrofuran-2'''-carbonyl)amino]-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester and Compound 28: *trans*-(2'*S*,2'''*R*,4*S*)-6-Carbamoyl-4-(2'-{2''-oxo-3''-[(tetrahydrofuran-2'''-carbonyl)amino]-2''*H*-pyridin-1''-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester

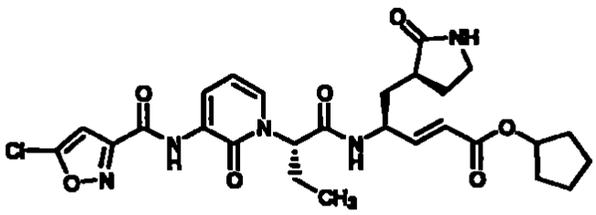


The title compounds were prepared from I1 (Example 5) by a process analogous to that described in Example 5 for the conversion of I1 to product J1 utilizing intermediate tetrahydrofuran-2-carbonyl chloride (racemic, Aldrich) where appropriate: IR (cm^{-1}) 3344, 1646, 1519, 1178; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, *J* = 7.2), 1.72-1.82 (m, 1H), 1.95-2.04 (m, 2H), 2.16-2.23 (m, 2H), 2.32-2.43 (m, 1H), 3.18-3.27 (m, 1H), 3.51-3.60 (m, 5H), 3.93-4.00 (m, 1H), 4.05-4.12 (m, 1H), 4.22 (q, 2H, *J* = 7.20, 4.46-4.55 (m, 2H), 5.54-5.69 (m, 2H), 6.34-6.41 (m, 2H), 6.68 (dd, 1H, *J* = 15.6, 5.4), 6.86-6.93 (m, 1H), 7.17-7.41 (m, 5H), 8.42-8.45 (m, 1H), 9.37 (d, 1H, *J* = 10.2); Anal. $C_{28}H_{34}N_4O_7 \cdot 1.5TFA$: C, H, N.

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EXAMPLE 27

Preparation of Compound 29: *trans*-(2'*S*,3'''*S*,4*S*)-4-(2'-{3''-[(5'''-Chloroisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrroldin-3'''-yl)pent-2-enoic Acid Cyclopentyl Ester (R4)



Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid *tert*-Butyl Ester (V4)

Intermediate F3 from above (0.781 g, 3.26 mmol, 1.1 equiv) was suspended in THF (10 mL). Sodium hydride (60% dispersion in mineral oil, 0.119 g, 2.98 mmol, 1 equiv) was added in one portion. After stirring 30 min, a solution of intermediate U3 (2.96 mmol, 1 equiv, based on T3) in THF (15 mL) was by syringe. The resulting mixture was stirred 2 hours, then diluted with EtOAc (500 mL) and washed with brine (2 x 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the title intermediate (0.834 g, 74%): R_f = 0.33 (20% EtOAc in hexanes); IR (cm^{-1}) 3334, 1732, 1694, 1650, 1603, 1537; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* = 7.4), 1.46 (s, 9H), 1.85-2.00 (m, 1H), 2.17-2.32 (m, 1H), 5.44-5.50 (m, 1H), 6.33 (t, 1H, *J* = 7.3), 6.68 (s, 1H), 7.12 (dd, 1H, *J* = 7.3, 1.7), 8.43 (dd, 1H, *J* = 7.3, 1.7), 9.61 (s, 1H); Anal. $C_{17}H_{20}ClN_3O_5$: C, H, N.

Preparation of Intermediate (2*S*)-2-{3'-[(5''-Chloroisoxazole-3''-carbonyl)amino]-2'-oxo-2'*H*-pyridin-1'-yl}butyric Acid (W4)

Intermediate V4 from above (0.544 g, 1.42 mmol, 1 equiv) was stirred for 1 h in a mixture of TFA (9 mL) and CH_2Cl_2 (9 mL). The volatiles were evaporated. The residue was suspended in CCl_4 and concentrated to dryness (2 x 10 mL), providing the title intermediate which was used without further purification.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-*tert*-Butoxycarbonylamino-5-[1'-(2",4"-dimethoxybenzyl)-2'-oxopyrrolidin-3'-yl]pent-2-enoicAcid Cyclopentyl Ester (X3)

Intermediate K1 (prepared according to Dragovich, et al., *J. Med. Chem.* 1999, *42*, 1213) (2.00 g, 4.90 mmol, 1 equiv) and commercially available Dess-Martin periodinane (2.30 g, 5.38 mmol, 1.1 equiv) were combined in CH_2Cl_2 (50 mL) and stirred 2 h. The solvent was evaporated and the residue was suspended in and then evaporated from toluene (2 x 25 mL). The resulting residue was dissolved in THF (100 mL). (Triphenyl-λ^5-phosphanylidene)acetic acid cyclopentyl ester (prepared in a manner analogous to that described in Baldwin, et al. *J. Org. Chem.* 1971, *36*, 1441) (2.28 g, 5.87 mmol, 1.2 equiv) was added. The reaction mixture was heated to reflux for 100 min, allowed to cool, diluted with EtOAc (300 mL) and washed with a mixture of brine and $NaHCO_3$ (1:1, 100 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 44→50% EtOAc in hexanes) to provide the title intermediate (1.58 g, 62%) as a foam: IR (cm^{-1}) 3307, 1708, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.50-1.93 (m, 10H), 1.97-2.08 (m, 1H), 2.21-2.33 (m, 1H), 2.48-2.60 (m, 1H), 3.17-3.23 (m, 2H), 3.80 (s, 6H), 4.26-4.40 (m, 1H), 4.41 (s, 2H), 5.18-5.24 (m, 1H), 5.26-5.33 (m, 1H), 5.92 (dd, 1H, J = 15.6, 1.6), 6.41-6.47 (m, 2H), 6.82 (dd, 1H, J = 15.6, 5.2), 7.08-7.13 (m, 1H); Anal. $C_{28}H_{40}N_2O_7 \cdot 0.75H_2O$: C, H, N.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-*tert*-Butoxycarbonylamino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic Acid Cyclopentyl Ester (X4)

Intermediate X3 from above (1.54 g, 2.98 mmol, 1 equiv) was dissolved in a mixture of H_2O (5 mL) and $CHCl_3$ (50 mL). DDQ (0.947 g, 4.17 mmol, 1.4 equiv) was added and the reaction mixture was heated in a 60 °C oil bath for 1.5 h. More DDQ (0.90 g, 3.96 mmol, 1.3 equiv) was added and heating at 60 °C was continued for 2 h more. After cooling to 23 °C, the reaction mixture was diluted with CH_2Cl_2 (600 mL) and washed with a mixture of brine and 10% $KHSO_4$ (1:1, 150 mL) and a mixture of brine and $NaHCO_3$ (2 x 200 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (gradient elution, 2→3% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.850 g, 78%) as a tan foam: IR (cm^{-1}) 3305, 1698, 1522, 1279, 1165; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.52-

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2.05 (m, 1H), 2.38-2.54 (m, 2H), 3.29-3.40 (m, 2H), 4.29-4.41 (m, 1H), 5.17-5.27 (m, 2H), 5.93 (dd, 1H, J = 15.7, 1.6), 5.96-6.40 (m, 1H), 6.82 (dd, 1H, J = 15.7, 5.3); Anal. $C_{19}H_{30}N_2O_5 \cdot 0.30H_2O$: C, H, N.

Preparation of Intermediate *trans*-(3'*S*,4*S*)-4-Amino-5-(2'-oxo-pyrrolidin-3'-yl)pent-2-enoic acid Cyclopentyl Ester (Y3)

Intermediate X4 (0.522 g, 1.42 mmol, 1 equiv) was stirred for 40 min in a solution of TFA (7 mL) in CH_2Cl_2 (10 mL). The volatiles were evaporated. The residue was suspended in CCl_4 and concentrated to dryness (2 x 20 mL), providing the title intermediate which was used without further purification.

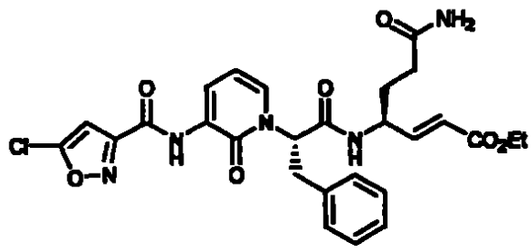
Preparation of Product R4 (Compound 29)

Intermediates W4 and Y3 (as prepared above) were combined in CH_2Cl_2 (25 mL) and cooled in an ice bath. HOBt (0.269 g, 1.99 mmol, 1.4 equiv), iPr_2NEt (1.74 mL, 9.99 mmol, 7 equiv) and EDC (0.341 g, 0.1.78 mmol, 1.25 equiv) were added sequentially. The reaction mixture was allowed to warm to 23 °C over the weekend. It was then diluted with EtOAc (500 mL) and washed with a mixture of brine and 10% $KHSO_4$ (1:1, 100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to provide the title intermediate (0.590 g, 72%) as a white foam: IR (cm^{-1}) 3295, 1690, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.3), 1.50-2.02 (m, 10H), 2.11-2.37 (m, 4H), 3.25-3.44 (m, 2H), 3.64-3.74 (m, 1H), 4.41-4.52 (m, 1H), 5.18-5.24 (m, 1H), 5.69 (dd, 1H, J = 9.0, 6.6), 5.94 (dd, 1H, J = 15.6, 1.4), 6.36 (t, 1H, J = 7.3), 6.67 (s, 1H), 6.82 (dd, 1H, J = 15.6, 5.9), 7.15 (s, 1H), 7.58 (dd, 1H, J = 7.3, 1.7), 8.42 (dd, 1H, J = 7.3, 1.7), 8.49 (m, 1H), 9.52 (s, 1H); Anal. $C_{27}H_{32}ClN_3O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 28

Preparation of Compound 30: *trans*-(2'*S*,4*S*)-6-Carbamoyl-4-(2'-{3"-[(5"'-chloroisoxazole-3"'-carbonyl)amino]-2"-oxo-2"*H*-pyridin-1"-yl}-3'-phenylpropionylamino)hex-2-enoic Acid Ethyl Ester



Preparation of Intermediate (1'*S*,4"*S*)-5-Chloroisoxazole-3-carboxylic Acid {1'-[1"-Benzyl-4"-(*tert*-butyldimethylsilanyloxymethyl)-2"-oxo-6"-(tritylcarbamoyl)hexyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide

To solution of 5-chloroisoxazole-3-carboxylic acid (Example 22, 0.253 g, 1.71 mmol, 2.0 equiv) in $CHCl_3$ (21 mL) was added $SOCl_2$ (9 mL). The reaction mixture was heated to reflux for 26 h. The volatiles were removed under reduced pressure to give crude 5-chloroisoxazole-3-carbonyl chloride.

A sample of 10% Pd on C (0.070 g) was added to a solution of (1'*S*,4"*S*)-5-chloroisoxazole-3-carboxylic acid {1'-[1"-Benzyl-4"-(*tert*-butyldimethylsilanyloxy-methyl)-2"-oxo-6"-(tritylcarbamoyl)hexyl]-2'-oxo-1',2'-dihydropyridin-3'-yl}amide (Example 1, 0.74 g, 0.855 mmol, 1 equiv) in EtOAc (15 mL). The reaction mixture was stirred at room temperature under H_2 atmosphere (balloon) for 4 h, and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in THF (15 mL), cooled to 0 °C, and 5-chloroisoxazole-3-carbonyl chloride (1.71 mmol, 2.0 equiv) and NMM (0.188 mL, 1.71 mmol, 2.0 equiv) were added sequentially. The resulting mixture was stirred at 0 °C for 1 h, then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (35% EtOAc in hexanes) to afford the title intermediate (0.666 g, 90%): IR (cm^{-1}) 3332, 1684, 1531; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.60-1.71 (m, 1H), 1.80-1.83 (m, 1H), 2.12-2.16 (m, 2H), 3.16-3.23 (m, 1H), 3.36-3.41 (m, 1H), 3.47-3.55 (m, 2H), 3.81-3.90 (m, 1H), 5.64-5.70 (m, 1H), 6.26 (t, 1H, J = 7.2), 6.47 (d, 1H, J = 8.7), 6.70 (s,

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1H), 7.02 (s, br. 1H), 7.17-7.33 (m, 20H), 7.37 (d, 1H, J = 7.2), 8.40 (d, J = 7.8), 9.56 (s, br. 1H).

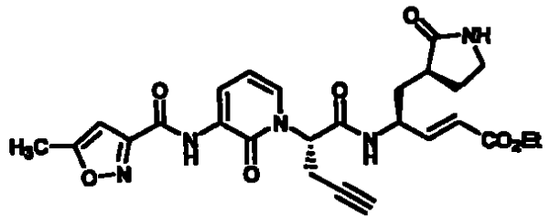
Preparation of Compound 30

The preceding intermediate was converted into compound 30 by a process that was analogous to that described in Example 7 for the conversion of intermediate C1 to compound 7: mp = 163-165 °C; IR (cm^{-1}) 3335, 1648, 1533, 1179; ^1H NMR ($CDCl_3$) δ 0.34 (t, 3H, J = 7.2), 1.76-1.86 (m, 1H), 1.94-2.00 (m, 1H), 2.23 (t, 2H, J = 6.9), 3.20-3.27 (m, 1H), 3.35-3.42 (m, 2H), 3.51-3.58 (m, 1H), 4.22 (q, 2H, J = 7.2), 4.52-4.57 (m, 1H), 5.69 (dd, 1H, J = 15.6, 1.5), 6.70 (s, br. 1H), 6.14 (s, br. 1H), 6.32 (s, br. 1H), 6.39 (t, 1H, J = 7.2), 6.69 (dd, 1H, J = 15.6, 5.4), 7.21-7.33 (m, 4H), 7.47 (d, 1H, J = 7.2), 8.44 (d, 1H, J = 7.5), 9.47 (s, br. 1H); Anal. $C_{27}H_{28}ClN_5O_7 \cdot 0.6H_2O$: C, H, N.

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EXAMPLE 29

Preparation of Compound 31: *trans*-(2'*S*,3'''*S*,4*S*)-4-(2'-{3''-[(5'''-Methyl-isoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}pent-4'-ynoyl-amino)-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid Ethyl Ester

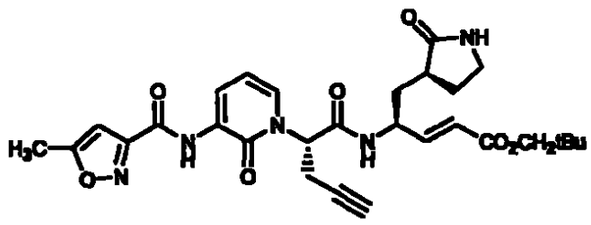


The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and Y2 and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3295, 1684, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.1), 1.52-1.62 (m, 1H), 1.64-1.80 (m, 1H), 2.04 (t, 1H, J = 2.6), 2.08-2.38 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, J = 17.0, 8.4, 2.6), 3.01 (ddd, 1H, J = 17.0, 6.8, 2.6), 3.22-3.39 (m, 2H), 4.18 (q, 2H, J = 7.1), 4.44-4.55 (m, 1H), 5.71-5.78 (m, 1H), 6.03 (dd, 1H, J = 15.6, 1.5), 6.32 (t, 1H, J = 7.2), 6.46 (s, 1H), 6.85 (dd, 1H, J = 15.6, 5.4), 6.89 (s, 1H), 7.49 (dd, 1H,

J = 7.2, 1.7), 8.41 (dd, 1H, J = 7.2, 1.7), 8.68 (d, 1H, J = 6.8), 9.52 (s, 1H); Anal. $C_{26}H_{29}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EXAMPLE 30

Preparation of Compound 32: *trans*-(2'*S*,3'''*S*,4*S*)-4-(2'-{3''-[(5'''-Methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}-pent-4'-ynoylamino)-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic acid 2,2-Dimethylpropyl Ester

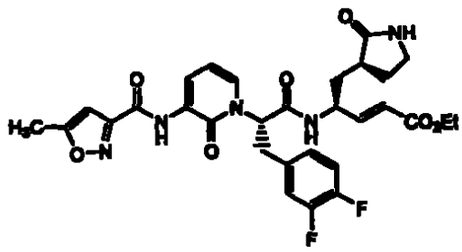


The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and trans-(3'*S*,4*S*)4-*tert*-butoxycarbonylamino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic acid 2,2-dimethylpropyl ester (prepared from K1 in a manner similar to that described for the preparation of X4 in Example 27) and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3295, 1690, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.54-1.80 (m, 2H), 2.05 (t, 1H, J = 2.6), 2.10-2.39 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, J = 17.0, 8.2, 2.6), 3.01 (ddd, 1H, J = 17.0, 6.8, 2.6), 3.22-3.38 (m, 2H), 3.82 (s, 2H), 4.45-4.56 (m, 1H), 5.72-5.79 (m, 1H), 6.06 (dd, 1H, J = 15.7, 1.5), 6.33 (t, 1H, J = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, J = 15.7, 5.4), 6.93 (s, 1H), 7.51 (dd, 1H, J = 7.2, 1.7), 8.41 (dd, 1H, J = 7.2, 1.7), 8.69 (d, 1H, J = 6.6), 9.52 (s, 1H); Anal. $C_{29}H_{35}N_5O_7 \cdot 0.25H_2O$: C, H, N.

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EXAMPLE 31

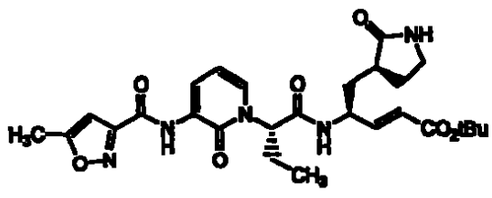
Preparation of Compound 33: *trans*-(2'*S*,3''''*S*,4*S*)-4-(3'-(3'',4''-Difluorophenyl)-2'-{3'''-[(5''''-methylisoxazole-3''''-carbonyl)amino]-2'''-oxo-2'''*H*-pyridin-1'''-yl}propionylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester



The title compound was prepared by a method analogous to that described in Example 19 for the preparation of specific intermediate R1 utilizing (2*R*)-3-(3',4'-difluorophenyl)-2-hydroxypropionic acid (synthesized from (2*R*)-2-*tert*-butoxycarbonylamino-3-(3',4'-difluorophenyl)propionic acid in analogy to the preparation of intermediate S1 described in Example 22) and triethylphosphonoacetate where appropriate: IR (cm^{-1}) 3331, 1690, 1649, 1596, 1531, 1455, 1278; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.1), 1.44-1.54 (m, 1H), 1.63-1.78 (m, 1H), 2.08-2.29 (m, 3H), 2.49 (d, 3H, *J* = 0.9), 3.05 (dd, 1H, *J* = 13.6, 7.5), 3.20-3.42 (m, 3H), 4.19 (dq, 2H, *J* = 7.1, 1.7), 4.34-4.45 (m, 1H), 5.64 (dd, 1H, *J* = 15.7, 1.4), 6.00 (t, 1H, *J* = 7.8), 6.32 (t, 1H, *J* = 7.3), 6.45 (s, 1H), 6.71 (dd, 1H, *J* = 15.7, 5.6), 6.86-6.91 (m, 1H), 6.98-7.08 (m, 2H), 7.15 (s, 1H), 7.68 (dd, 1H, *J* = 7.3, 1.7), 8.39 (dd, 1H, *J* = 7.3, 1.7), 8.65 (d, 1H, *J* = 6.8), 9.46 (s, 1H); Anal. $C_{30}H_{31}F_2N_5O_7$: C, H, N.

EXAMPLE 32

Preparation of Compound 34: *trans*-(2'*S*,3''''*S*,4*S*)-4-(2'-{3''-[(5''''-Methylisoxazole-3''''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid *tert*-Butyl Ester

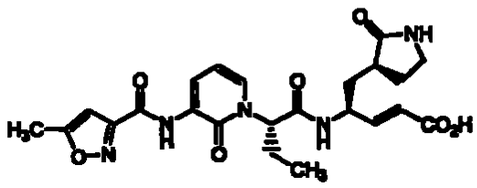


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The title compound was prepared by a method analogous to that described for the synthesis of compound R3 in Example 25: IR (cm^{-1}) 3331, 3295, 1690, 1649, 1590, 1531, 1455, 1155; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.3), 1.40-1.60 (m, 1H), 1.49 (s, 9H), 1.62-1.78 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.36 (m, 4H), 2.50 (s, 3H), 3.26-3.43 (m, 2H), 4.39-4.50 (m, 1H), 5.78 (dd, 1H, J = 8.9, 6.7), 5.89 (dd, 1H, J = 15.7, 1.3), 6.35 (t, 1H, J = 7.3), 6.47 (s, 1H), 6.76 (dd, 1H, J = 15.7, 5.9), 7.33 (s, 1H), 7.64 (dd, 1H, J = 7.3, 1.8), 8.43 (dd, 1H, J = 7.3, 1.8), 8.59 (d, 1H, J = 6.8), 9.57 (s, 1H); Anal. $C_{27}H_{35}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EXAMPLE 33

Preparation of Compound 35: *trans*-(2'*S*,3'''*S*,4*S*)-4-(2'-{3''-[(5'''-Methylisoxazole-3'''-carbonyl)amino]-2''-oxo-2''*H*-pyridin-1''-yl}butyrylamino)-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid

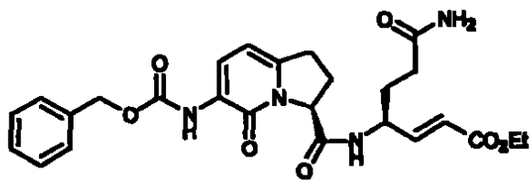


The title compound was prepared from compound 34 by acidic deprotection of the *tert*-butyl ester moiety present in that compound (following standard literature procedures): IR (cm^{-1}) 3319, 1678, 1643, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.2), 1.61-1.99 (m, 3H), 2.08-2.32 (m, 3H), 2.40-2.54 (m, 1H), 2.49 (s, 3H), 3.25-3.41 (m, 2H), 4.58-4.69 (m, 1H), 5.56-5.64 (m, 1H), 5.98 (d, 1H, J = 15.6), 6.21 (br, 1H), 6.37 (t, 1H, J = 7.3), 6.47 (s, 1H), 6.96 (dd, 1H, J = 15.6, 6.6), 7.50 (dd, 1H, J = 7.3, 1.6), 7.52 (s, 1H), 8.26 (d, 1H, J = 7.7), 8.44 (dd, 1H, J = 7.3, 1.6), 8.62 (s, 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.75H_2O$: C, H, N.

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EXAMPLE 34

Preparation of Compound 36: *trans*-(3'*S*,4*S*)-4-[(6'-Benzyloxycarbonylamino-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl)amino]-6-carbamoylhex-2-enoicAcid Ethyl Ester



Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinonitrile (a1)

n-Butyllithium (100 mL of a 1.6 M solution in hexanes, 160 mmol, 2.5 equiv) was added via cannula over 10 min to a solution of diisopropylamine (22.4 mL, 160 mmol, 2.5 equiv) in THF (600 mL) at -78 °C. The resulting pale yellow solution was stirred at –78 °C for 5 min, then was warmed to 0 °C for an additional 5 min. 2-Hydroxy-6-methylnicotinonitrile (8) (8.58 g, 64.0 mmol, 1 equiv) was added as a solid in small portions over 15 min and the deep orange *solution* thus obtained was stirred for 1 h at 0 °C. Allyl bromide (8.31 mL, 96.0 mmol, 1.5 equiv) was then added and the reaction mixture was warmed to 23 °C, maintained at that temperature for 30 min, and was partitioned between 1.0 M HCl (300 mL) and EtOAc (2 x 250 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The resulting orange solid was triturated with boiling Et_2O (100 mL) and subsequently cooled to 23 °C, then was filtered through a medium frit, washed with Et_2O (2 x 50 mL) and air-dried to give a1 (6.42 g, 58%) as a tan solid: mp = 122-125 °C; IR (KBr pellet, cm^{-1}) 2223, 1654; ^1H NMR (DMSO-d_6) δ 2.32-2.37 (m, 2H), 2.62 (t, 2H, J = 7.6), 4.96-5.06 (m, 2H), 5.69-5.83 (m, 1H), 6.23 (d, 1H, J = 7.3), 8.03 (d, 1H, J = 7.3), 12.55 (s, br, 1H); Anal. $C_{10}H_{10}N_2O$·0.10H_2O: C, H, N.

Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinamide (b1)

Hydrogen peroxide (30 wt. % solution in water, 45 mL) was added to a solution of a1 (12.13 g, 70.2 mmol) in a mixture of EtOH (150 mL) and 10% aqueous NaOH (280 mL) at 23 °C. The reaction mixture was heated to 50 °C for 18 h, then was cooled to 23 °C and the volatiles were removed under reduced pressure. The residue was acidified

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with 12 M HCl to pH 2-3, and the resulting precipitate was filtered, washed with water (2 x 50 mL), and air-dried to afford b1 as a yellow solid (13.48 g, 100%): mp = 195-198 °C; IR (cm^{-1}) 3329, 3134, 1688, 1642; ^1H NMR (DMSO-d_6) δ 2.31-2.38 (m, 2H), 2.64 (t, 2H, J = 7.6), 4.96-5.05 (m, 2H), 5.71-5.84 (m, 1H), 6.29 (d, 1H, J = 7.3), 7.45 (s, br, 1H), 8.21 (d, 1H, J = 7.3), 9.00 (s, br, 1H), 12.37 (s, br, 1H); Anal. $C_{10}H_{12}N_2O_2 \cdot 0.15H_2O$: C, H, N.

Preparation of Intermediate 6-But-3-enyl-2-hydroxynicotinic Acid (c1)

A solution of b1 (12.38 g, 70.1 mmol) in 10% aqueous KOH (350 mL) was heated to reflux for 20 h and subsequently cooled to room temperature. The reaction mixture was acidified with 12 M HCl to pH 2-3, and the resulting precipitate was filtered, washed with water (2 x 50 mL), and dried under vacuum to afford c1 as a yellow solid (12.46 g, 92%): mp = 151-155 °C; IR (cm^{-1}) 2905 (br), 1736, 1652; ^1H NMR (DMSO-d_6) δ 2.34-2.29 (m, 2H), 2.73 (t, 2H, J = 7.6), 4.96-5.07 (m, 2H), 5.72-5.85 (m, 1H), 6.56 (d, 1H, J = 7.5), 8.28 (d, 1H, J = 7.5), 13.26 (s, br, 1H), 14.64 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparation of Intermediate (6-But-3-enyl-2-hydroxypyridin-3-yl)carbamic Acid Benzyl Ester (d1)

Triethylamine (13.9 mL, 99.7 mmol, 2.0 equiv) and diphenylphosphoryl azide (16.1 mL, 74.7 mmol, 1.5 equiv) were added sequentially to a suspension of c1 (9.63 g, 49.8 mmol, 1 equiv) in 1,4-dioxane (450 mL) at 23 °C. The resulting solution was heated to reflux for 7.5 h, then benzyl alcohol (10.3 mL, 99.5 mmol, 2.0 equiv) was added and reflux was continued for an additional 16 h. The dark brown reaction mixture was cooled to 23 °C and the volatiles were removed under reduced pressure. The resulting dark brown oil was partitioned between water (300 mL) and EtOAc (2 x 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The solid thus obtained was triturated with Et_2O (150 mL) and was filtered through a medium frit, washed with Et_2O (2 x 50 mL) and air-dried to give d1 (7.34 g, 49%) as an off-white powder: mp = 179-180 °C; IR (cm^{-1}) 3386, 1727, 1645; ^1H NMR ($CDCl_3$) δ 2.39-2.46 (m, 2H), 2.65 (t, 2H, J = 7.5), 4.97-5.07 (m, 2H), 5.21 (s, 2H), 5.73-5.87 (m,

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1H), 6.10 (d, 1H, J = 7.5), 7.32-7.44 (m, 5H), 7.68 (s, br, 1H), 8.06 (s, br, 1H), 12.74 (s, br, 1H); Anal. $C_{17}H_{18}N_2O_3$: C, H, N.

Preparation of Intermediate (6-But-3-enyl-2-methoxypyridin-3-yl)carbamic Acid Benzyl Ester (e1)

Trimethyloxonium tetrafluoroborate (2.0 g, 13.5 mmol, 1.2 equiv) and 2,6-di-*tert*-butylpyridine (1.52 mL, 6.76 mmol, 0.6 equiv) were added to a solution of d1 (3.36 g, 11.26 mmol, 1 equiv) in CH_2Cl_2 (80 mL) at 23 °C. The reaction mixture was stirred at that temperature for 65 h, then was partitioned between water (2 x 50 mL) and CH_2Cl_2 (2 x 200 mL) and combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (5% EtOAc in hexanes) to afford e1 (3.19 g, 91%) as colorless oil: IR (cm^{-1}) 3432, 1733; ^1H NMR ($CDCl_3$) δ 2.42-2.49 (m, 2H), 2.73 (t, 2H, J = 7.6), 3.96 (s, 3H), 4.94-5.07 (m, 2H), 5.20 (s, 2H), 5.80-5.94 (m, 1H), 6.71 (d, 1H, J = 7.9), 7.11 (s, br, 1H), 7.32-7.43 (m, 5H), 8.16 (s, br, 1H); Anal. $C_{18}H_{20}N_2O_3$: C, H, N.

Preparation of Intermediate (3'*R*)-[6-(3',4'-Dihydroxybutyl)-2-methoxypyridin-3-yl]carbamic Acid Benzyl Ester (f1)

To a mixture of 1:1 *t*-BuOH and water (300 mL) at 0 °C was added $(DHQD)_2AQN$ (0.148 g, 0.164 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (16.2 g, 49.2 mmol, 3 equiv), K_2CO_3 (6.8 g, 49.2 mmol, 3 equiv), potassium osmate dihydrate (0.024 g, 0.066 mmol, 0.004 equiv), and then e1 in t-BuOH (25 mL), sequentially. The resulting mixture was stirred at 0 ° C for 20 h, then warmed to room temperature and Na_2SO_3 (30 g) was added carefully. The mixture was stirred at room temperature for 2 h, then the volatiles were removed under reduced pressure. The residue was partitioned between water (200 mL) and EtOAc (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to afford f1 (5.57 g, 98%) as pale yellow oil: IR (cm^{-1}) 3427 (br), 1731; ^1H NMR ($CDCl_3$) δ 1.76-1.87 (m, 2H), 2.07-2.11 (m, 1H), 2.80-2.89 (m, 2H), 3.46-3.53 (m, 1H), 3.60-3.67 (m, 1H), 3.71-3.77 (m, 1H), 3.96 (s, 3H), 4.64 (d, 1H, J = 3.2), 5.21 (s, 2H), 6.76 (d, 1H, J = 7.8), 7.12 (s, br, 1H), 7.34-7.43 (m, 5H), 8.22 (s, br, 1H); Anal. $C_{18}H_{22}N_2O_5$: C, H, N.

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Preparation of Intermediate (3'*R*)-{6-[4'-(*tert*-Butyl-dimethyl-silanyloxy)-3'-hydroxybutyl]-2-methoxypyridin-3-yl}carbamic Acid Benzyl Ester (g1)

Triethylamine (1.55 mL, 11.1 mmol, 2.5 equiv), *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol, 1.6 equiv), and 4-dimethylaminopyridine (0.025 g, 0.20 mmol, 0.045 equiv) were added sequentially to a solution of f1 (1.54 g, 4.45 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 23 °C. The reaction mixture was stirred for 19 h at 23 °C, then was 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 (20% EtOAc in hexanes) provided g1 (1.69 g, 82%) as a colorless oil: IR (cm^{-1}) 3436, 1734; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.72-1.94 (m, 2H), 2.72-2.88 m, 2H), 3.26 (d, 1H, J = 3.1), 3.50 (dd, 1H, J = 9.8, 6.9), 3.58-3.63 (m, 1H), 3.65-3.70 (m, 1H), 3.95 (s, 3H), 5.20 (s, 2H), 6.75 (d, 1H, J = 8.1), 7.11 (s, br, 1H), 7.33-7.43 (m, 5H), 8.20 (s, br, 1H); Anal. $C_{24}H_{36}N_2O_5Si$: C, H, N.

Preparation of Intermediate (3*S*)-(3-Hydroxymethyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)-Carbamic Acid Benzyl Ester (h1)

2,6-Lutidine (2.43 mL, 20.84 mmol, 4.0 equiv) and trifluoromethanesulfonic anhydride (1.31 mL, 7.82 mmol, 1.5 equiv) were added sequentially to a solution of g1 (2.4 g, 5.21 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at –78 °C. The colorless reaction mixture was stirred at –78 °C for 45 min, warmed to 23 °C for an additional 15 min, then was partitioned between 0.5 M HCl (150 mL) and CH_2Cl_2 (2 x 150 mL). The organic layer was dried over Na_2SO_4 and was concentrated. The residue thus obtained was dissolved in THF (120 mL) at 23 °C and tetrabutylammonium fluoride (15.63 mL of a 1.0 *M* solution in THF, 15.63 mmol, 3.0 equiv) was added. The reaction mixture was stirred at that temperature for 1 h, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The residue thus obtained was purified by flash column chromatography (80% EtOAc in hexanes) to give h1 (0.953 g, 58%) as a colorless oil: IR (cm^{-1}) 3379 (br), 1727, 1649; ^1H NMR ($CDCl_3$) δ 1.86-1.97 (m, 1H), 2.29-2.41 (m, 1H), 2.90-3.15 (m, 2H), 3.80-3.93 (m, 2H), 4.78-4.86 (m, 1H), 5.11-5.15 (m, 1H), 5.20 (s, 2H), 6.20 (d,

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1H, J = 7.5), 7.30-7.41 (m, 5H), 7.75 (s, br, 1H), 8.07 (d, 1H, J = 7.5); Anal. $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

Preparation of Intermediate (3*S*)-6-Benzyloxycarbonylamino-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i1)

Dimethylsulfoxide (0.522 mL, 7.36 mmol, 2.6 equiv) was added dropwise to a solution of oxalyl chloride (0.321 mL, 3.68 mmol, 1.3 equiv) in CH_2Cl_2 (80 mL) at –78 °C. The reaction mixture was stirred for 20 min at that temperature, then a solution of h1 (0.890 g, 2.83 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added via cannula. After stirring an additional 20 min at –78 °C, triethylamine (1.97 mL, 14.15 mmol, 5.0 equiv) was added dropwise. The reaction mixture was maintained at –78 °C for 1.5 h, then acetic acid (15.57 mmol, 0.891 mL, 5.5 equiv) was added. The reaction mixture was warmed to 0 °C for 5 min, then was washed with water (50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford the crude aldehyde product as off-white foam. This material was utilized without further purification.

A solution of $NaClO_2$ (2.88 g, 25.47 mmol, 9.0 equiv) and NaH_2PO_4 (2.73 g, 19.81 mmol, 7.0 equiv) in water (60 mL) was added dropwise to a solution of the proceeding crude aldehyde (2.83 mmol, 1 equiv) in a mixture of *t*BuOH (60 mL) and 2-methyl-2-butene (10 mL) over 15 min at 23 °C. The resulting mixture was stirred at room temperature for 1 h, then, the volatiles were removed under reduced pressure. The residue thus obtained was partitioned between 0.5 M HCl (150 mL) and 10% CH_3OH in CH_2Cl_2 (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The resulting residue was purified by flash column chromatography (10% CH_3OH in CH_2Cl_2) to give i1 (0.346 g, 37%) as off-white solid: mp = 204-206 °C; IR (cm^{-1}) 3298, 1722, 1564, 1208; ^1H NMR (DMSO-d_6) δ 2.17-2.55 (m, 2H), 2.45-2.59 (m, 2H), 4.98 (dd, 1H, J = 9.6, 2.7), 5.16 (s, 2H), 6.23 (d, 1H, J = 7.5), 7.34-7.45 (m, 5H), 7.83 (d, 1H, J = 7.5), 8.34 (s, 1H); Anal. $C_{17}H_{16}N_2O_5$: C, H, N.

Preparation of Product k1 (Compound 36)

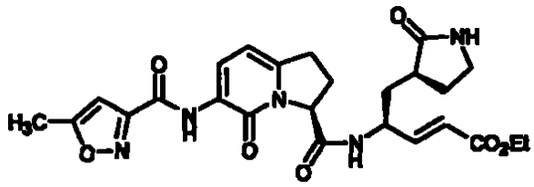
Intermediate i1 was transformed into compound 36 (via coupling with intermediate AA1) by a process that was analogous to that described in Example 23 for

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the transformation of W2 to product J2: ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.1), 1.64-1.84 (m, 2H), 2.01-2.16 (m, 2H), 2.41-2.50 (m, 1H), 3.01-3.06 (m, 2H), 4.11 (q, 2H, J = 7.1), 4.41 (m, br, 1H), 5.01 (dd, 1H, J = 9.2, 2.7), 5.14 (s, 2H), 5.87 (dd, 1H, J = 15.8, 1.4), 6.20 (d, 1H, J = 7.6), 6.75 (s, br, 1H), 6.82 (dd, 1H, J = 15.8, 5.0), 7.09-7.42 (m; 7H), 7.81 (d, 1H, J = 7.6), 8.38 (s, 1H), 8.55 (d, 1H, J = 8.4).

EXAMPLE 35

Preparation of Compound 37: *trans*-(3'*S*,3'''*S*,4*S*)-4-({6'-[(5''-Methylisoxazole-3''-carbonyl)amino]-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl}amino)-5-(2'''-oxopyrrolidin-3'''-yl)-pent-2-enoic Acid Ethyl Ester



Preparation of Intermediate (3''*R*)-(5-Methylisoxazole-3-carboxylic Acid {6'-[4''-(*tert*-butyldimethylsilanyloxy)-3''-hydroxybutyl]-2'-methoxypyridin-3'-yl}amide (g2)

A suspension of intermediate g1 (prepared as described in Example 34) (4.21 g, 9.14 mmol, 1 equiv) and Pd on C (10%, 0.375 g) in EtOAc (120 mL) was stirred under an H_2 atmosphere (balloon) at 23 °C for 1 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (120 mL), cooled to 0 °C, and NMM (1.00 mL, 9.10 mmol, 1.0 equiv) and 5-methylisoxazole-3-carbonyl chloride (1.33 g, 9.14 mmol, 1.0 equiv) were added sequentially. The reaction mixture was stirred at 0 °C for 1 h, then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Trituration of the residue with a 1:3 mixture of Et_2O and hexanes (130 mL) provided a white solid which was collected by filtration, washed with hexanes (25 mL), and air-dried (2.61 g, 66%): mp = 100-102 °C; IR (cm^{-1}) 3390, 1696, 1593, 1536; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.78-1.95 (m, 2H), 2.52 (s, 3H), 2.78-2.90 (m, 2H), 3.45-3.53 (m, 2H), 3.60-3.74 (m, 2H), 4.03 (s, 3H), 6.51 (s, 1H), 6.79 (d, 1H, J = 7.9), 8.55 (d, 1H, J = 7.9), 8.95 (s, 1H); Anal. $C_{21}H_{33}N_3O_5Si$: C, H, N.

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Preparation of Intermediates (3*S*)-6-[(5'-Methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i2) and (3*S*)-8-Chloro-6-[(5'-methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (i3)

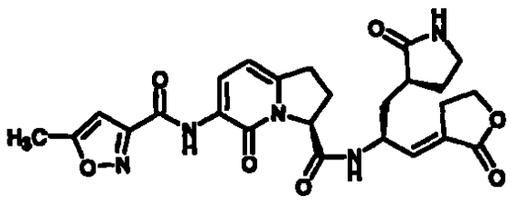
The preceding intermediate (g2) was transformed into a 1:4 mixture of intermediates i2 and i3 by a process that was analogous to that described in Example 34 for the transformation of g1 to i1: (i2) IR (cm^{-1}) 3343, 2977 (br), 1741, 1688, 1648; ^1H NMR ($CDCl_3$) δ 2.28-2.74 (m, 2H), 2.50 (s, 3H), 3.04-3.32 (m, 2H), 5.31 (d, 1H, J = 7.9), 6.36 (d, 1H, J = 7.7), 6.48 (s, 1H), 8.58 (d, 1H, J = 7.7), 9.40 (s, 1H); (i3) IR (cm^{-1}) 2240, 1652, 1532, 1260; ^1H NMR (DMSO-d_6) δ 1.53-1.63 (m, 2H), 3.11-3.20 (m, 2H), 5.14 (dd, 1H, J = 6.9, 2.7), 6.75 (s, 1H), 8.32 (s, 1H), 9.41 (s, br. 1H).

Preparation of Product 11 (Compound 37)

Intermediate i2 was transformed into compound 37 (via coupling with intermediate Y2) by a process that was analogous to that described in Example 25 for the transformation of W3 to product R3: IR (cm^{-1}) 3336, 1684, 1651, 1596, 1536; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1), 1.63-1.89 (m, 2H), 2.04-2.15 (m, 1H), 2.38-2.64 (m, 3H), 2.50 (s, 3H), 2.98-3.06 (m, 1H), 3.26-3.42 (m, 4H), 4.19 (q, 2H, J = 7.1), 4.63-4.65 (m, 1H), 5.15 (dd, 1H, J = 8.3, 2.7), 5.97-6.05 (m, 2H), 6.21 (d, 1H, J = 7.3), 6.48 (s, 1H), 6.89 (dd, 1H, J = 15.6, 5.5), 8.44-8.52 (m, 2H), 9.40 (s, 1H); Anal. $C_{25}H_{29}N_5O_7$·0.6TFA: C, H, N.

EXAMPLE 36

Preparation of Compound 38: *trans*-(2"*S*,3*S*,3'"*S*)-6-[(5'-Methylisoxazole-3'-carbonyl)amino]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid [2"-(2'"-oxodihydrofuran-3'"-ylidene)-1"-(2'"-oxopyrrolidin-3'"-ylmethyl)ethyl]amide

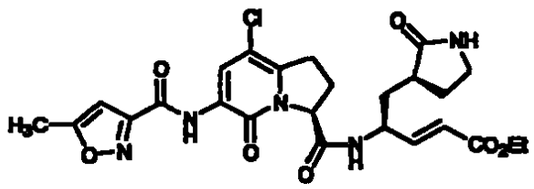


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The title compound was prepared from intermediate i2 (via coupling with intermediate Y1) by a process that was analogous to that described in Example 22 for the transformation of W1 to product R2: IR (cm^{-1}) 3336, 1752, 1686, 1651, 1594, 1535; ^1H NMR ($CDCl_3$) δ 1.59-1.68 (m, 1H), 1.77-1.81 (m, 1H), 2.09-1.81 (m, 1H), 2.37-2.45 (m, 2H), 2.50 (s, 3H), 2.58-2.66 (m, 1H), 2.91-3.05 (m, 2H), 3.23-3.44 (m, 4H), 4.39 (t, 2H, J = 7.2), 4.60-4.67 (m, 1H), 5.10-5.13 (m, 1H), 6.09 (s, 1H), 6.21 (d, 1H, J = 7.9), 6.41-6.48 (m, 2H), 8.45-8.50 (m, 2H), 8.77 (d, 1H, J = 6.2), 9.39 (s, 1H).

EXAMPLE 37

Preparation of Compound 39: *trans*-(3'*S*,3'''*S*,4*S*)-4-({8'-Chloro-6'-[(5''-methylisoxazole-3''-carbonyl)amino]-5'-oxo-1',2',3',5'-tetrahydroindolizine-3'-carbonyl}amino)-5-(2'''-oxopyrrolidin-3'''-yl)-pent-2-enoic Acid Ethyl Ester



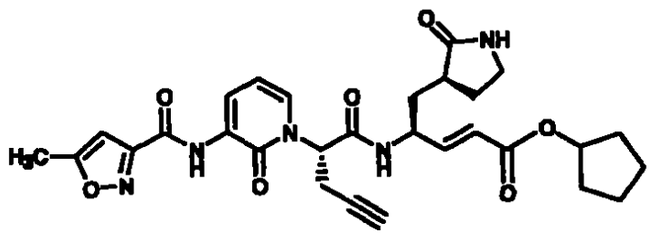
The title compound was prepared from intermediate i3 (via coupling with intermediate Y2) by a process that was analogous to that described in Example 25 for the transformation of W3 to product R3: IR (cm^{-1}) 3334, 1683, 1532; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.2), 1.66-1.89 (m, 4H), 2.33-2.50 (m, 1H), 2.53 (s, 3H), 2.67-2.72 (m, 1H), 3.04-3.20 (m, 2H), 3.27-3.48 (m, 2H), 4.21 (q, 2H, J = 7.2), 4.62-4.64 (m, 1H), 5.16-5.20 (m, 1H), 5.94 (s, br. 1H), 5.99 (dd, 1H, J = 15.6, 1.5), 6.51 (s, 1H), 6.89 (dd, 1H, J = 15.6, 5.7), 8.52 (s, 1H), 8.56 (s, br. 1H), 9.41 (s, br. 1H); Anal. $C_{25}H_{28}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

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EXAMPLE 38

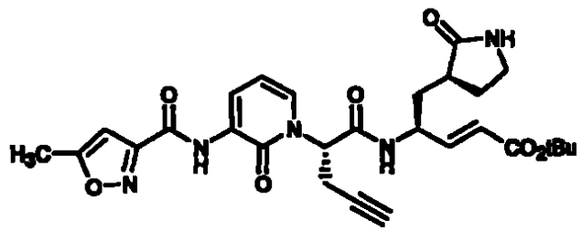
Compound 40: *trans*-(2'*S*,3''''*S*,4*S*)-4-[2'-(3''-{[1'''-(5''''-Methylisoxazol-3''''-yl)methanoyl]amino}-2'''-oxo-2'''*H*-pyridin-1'''-yl)pent-4''-ynoylamino]-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Cyclopentyl Ester



The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and Y3 and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3302, 1690, 1649, 1632; ^1H NMR ($CDCl_3$) δ 1.62-1.80 (m, 7H), 1.87-1.92 (m, 2H), 2.01-2.12 (m, 2H), 2.26-2.40 (m, 2H), 2.53 (s, 3H), 2.95-3.12 (m, 2H), 3.26-3.36 (m, 2H), 4.50-4.53 (m, 1H), 5.20-5.25 (m, 1H), 5.54-5.60 (m, 1H), 6.01 (dd, 1H, *J* = 15.6, 1.5), 6.31 (t, 2H, *J* = 7.2), 6.40 (s, br, 1H), 6.49 (s, 1H), 6.83 (dd, 1H, *J* = 15.6, 5.4), 7.43 (dd, 1H, *J* = 6.9, 1.8), 8.44 (dd, 1H, *J* = 6.9, 1.5), 8.58 (d, 1H, *J* = 6.6), 9.56 (s, 1H); Anal. ($C_{29}H_{33}N_5O_7 \cdot 0.75H_2O$) C, H, N.

EXAMPLE 39

Preparation of Compound 41: *trans*-(2'*S*,3''''*S*,4*S*)-4-[2'-(3''-{[1'''-(5''''-Methylisoxazol-3''''-yl)methanoyl]amino}-2'''-oxo-2'''*H*-pyridin-1'''-yl)pent-4''-ynoylamino]-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid *tert*-Butyl Ester



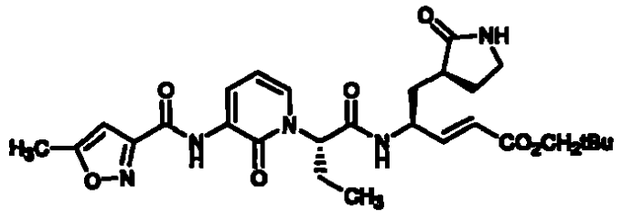
The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-

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fluorophenylalanine) to product R2 utilizing intermediates F2, K1, and (triphenyl-λ^5-phosphanylidene)-acetic acid *tert*-butyl ester and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: mp = 195 °C, dec.; IR (cm^{-1}) 3295, 1690, 1649; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.50-1.79 (m, 2H), 2.04 (t, 1H, J = 2.6), 2.05-2.37 (m, 3H), 2.49 (s, 3H), 2.92 (ddd, 1H, J = 17.0, 8.6, 2.6), 3.02 (ddd, 1H, J = 17.0, 6.7, 2.6), 3.20-3.37 (m, 2H), 4.41-4.52 (m, 1H), 5.65-5.73 (m, 1H), 5.94 (dd, 1H, J = 15.6, 1.4), 6.33 (t, 1H, J = 7.3), 6.46 (s, 1 H), 6.70 (s, 1 H), 6.73 (dd, 1 H, J = 15.6, 5.3), 7.48 (dd, 1 H, J = 7.3, 1.7), 8.41 (dd, 1 H, J = 7.3, 1.7), 8.62 (d, 1 H, J = 6.6), 9.53 (s, 1H); Anal. ($C_{28}H_{33}N_5O_7$) C, H, N.

EXAMPLE 40

Preparation of Compound 42: *trans*-(2'*S*,3'''*S*,4*S*)-4-[2'-(3''-{[1'''-(5'''-Methylisoxazol-3'''-yl)methanoyl]amino}-2''-oxo-2''*H*-pyridin-1''-yl)butanoylamino]-5-(2'''-oxopyrrolidin-3'''-yl)pent-2-enoic Acid 2,2-Dimethylpropyl Ester

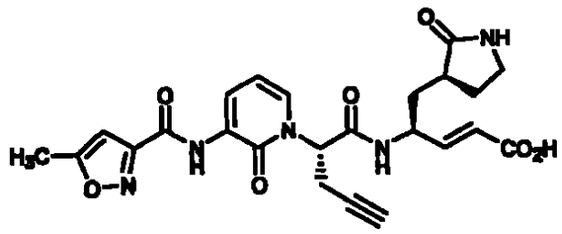


The title compound was prepared by a method analogous to that described in Example 25 for the preparation of specific intermediate R3 utilizing trans-(3'*S*,4*S*)4-*tert*-butoxycarbonylamino-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic acid 2,2-dimethylpropyl ester (prepared from K1 in a manner similar to that described for the preparation of X4 in Example 27) where appropriate: IR (cm^{-1}) 3331, 3295, 1690, 1649; ^1H NMR ($CDCl_3$) δ 0.87-0.99 (m, 12H), 1.51-1.61 (m, 1H), 1.64-1.79 (m, 1H), 1.83-2.00 (m, 1H), 2.10-2.37 (m, 4H), 2.49 (s, 3H), 3.26-3.43 (m, 2H), 3.83 (s, 2H), 4.43-4.54 (m, 1H), 5.71 (dd, 1H, J = 8.7, 6.9), 6.00 (dd, 1H, J = 15.7, 1.3), 6.35 (t, 1H, J = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, J = 15.7, 5.9), 7.39 (s, 1H), 7.58 (dd, 1H, J = 7.2, 1.7), 8.42 (dd, 1H, J = 7.2, 1.7), 8.53 (d, 1H, J = 7.0), 9.55 (s, 1H); Anal. ($C_{28}H_{37}N_5O_7 \cdot 0.5H_2O$) C, H, N.

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EXAMPLE 41

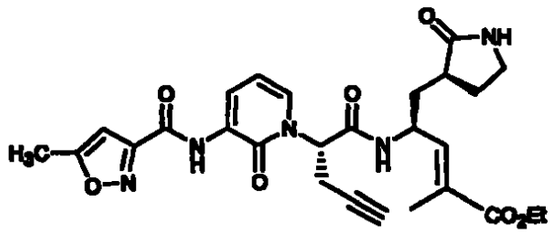
Preparation of Compound 43: ***trans*****-(2'*S*,3''''*S*,4*S*)-4-[2'-(3''-{[1'''-(5''''-Methylisoxazol-3''''-yl)methanoyl]amino}-2'''-oxo-2'''*H*-pyridin-1'''-yl)pent-4''-ynoylamino]-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid**



The title compound was prepared from compound 41 by acidic deprotection of the *tert*-butyl ester moiety present in that compound (following standard literature procedures): R_f = 0.37 (10% CH_3OH in $CHCl_3$); IR (cm^{-1}) 3295, 2950 (br), 1696, 1649; ^1H NMR ($CDCl_3$) δ 1.62-1.85 (m, 2H), 2.05-2.16 (m, 2H), 2.24-2.36 (m, 1H), 2.43-2.56 (m, 1H), 2.52 (s, 3H), 2.92-3.11 (m, 2H), 3.30-3.42 (m, 2H), 4.60-4.71 (m, 1H), 5.65-5.73 (m, 1H), 6.03 (d, 1H, *J* = 15.6), 6.37 (t, 1H, *J* = 7.2), 6.50 (s, 1H), 6.94 (dd, 1H, *J* = 15.6, 6.0), 7.24 (s, 1H), 7.47 (dd, 1H, *J* = 7.2, 1.3), 8.31 (d, 1H, *J* = 7.5), 8.45 (dd, 1H, *J* = 7.2, 1.3), 9.53 (s, 1H); Anal. ($C_{24}H_{25}N_5O_7 \cdot 0.5H_2O$) C, H, N.

EXAMPLE 42

Compound 44: ***trans*****-(2'*S*,3''''*S*,4*S*)-2-Methyl-4-[2'-(3''-{[1'''-(5''''-methylisoxazol-3''''-yl)methanoyl]amino}-2'''-oxo-2'''*H*-pyridin-1'''-yl)pent-4''-ynoylamino]-5-(2''''-oxopyrrolidin-3''''-yl)pent-2-enoic Acid Ethyl Ester**



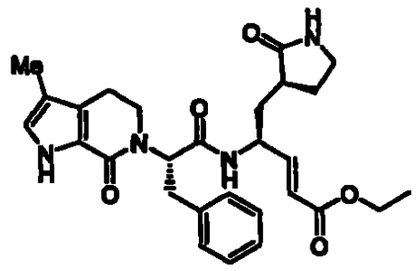
The title compound was prepared from D-propargylalanine by a process analogous to that described in Example 22 for the conversion of D-(4-fluorophenylalanine) to product R2 utilizing intermediates F2 and trans-(3'*S*,4*S*)-4-*tert*-

butoxycarbonylamino-2-methyl-5-(2'-oxopyrrolidin-3'-yl)pent-2-enoic acid ethyl ester (prepared from K1 in a manner similar to that described for the preparation of X4 in Example 27) and an alternate deprotection of the intermediate corresponding to V1 (LiI in pyridine) where appropriate: IR (cm^{-1}) 3307, 1690, 1649; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1), 1.36-1.47 (m, 1H), 1.65-1.80 (m, 1H), 1.95-2.00 (m, 4H), 2.14-2.40 (m, 3H), 2.50 (s, 3H), 2.87-3.03 (m, 2H), 3.23-3.38 (m, 2H), 4.18 (q, 2H, J = 7.1), 4.56-4.68 (m, 1H), 5.63-5.72 (m, 1H), 6.34 (t, 1H, J = 7.3), 6.47 (s, 1H), 6.52-6.58 (m, 1H), 6.81 (s, 1H), 7.46 (dd, 1H, J = 7.3, 1.6), 8.42 (dd, 1H, J = 7.3, 1.6), 8.65 (d, 1H, J = 6.4), 9.54 (s, 1H).

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EXAMPLE 43

Preparation of Compound 45: 4S-[2S-(3-Methyl-7-oxo-1,4,5,7-tetrahydro-pyrrolo[2,3-c]pyridin-6-yl)3-phenyl-propionylamino]-5-(2-oxo-pyrrolidin-3-yl)pent-2(trans)-enoic acid ethyl ester.



3-(2-Hydroxy-ethyl)-5-iodo-4-methyl-1H-pyrrole-2-carboxylic acid tert-butyl ester (0.34 mmol, 114 mg) in DMSO (2 mL) was treated with o-iodoxybenzoic acid (IBX, 0.51 mmol, 148 mg), then held at room temperature for 3h. The mixture was diluted with ethyl acetate (50 mL), washed with brine (10 mL), then concentrated under reduced pressure to provide 84 mg (75%) of 5-iodo-4-methyl-3-(2-oxo-ethyl)-1H-pyrrole-2-carboxylic acid tert-butyl ester. ^1H NMR ($CDCl_3$) d 9.63 (1H, s), 8.91 (1H, br s), 4.09 (2H, s), 2.62 (3H, s), 1.52 (9H, s).

5-Iodo-4-methyl-3-(2-oxo-ethyl)-1H-pyrrole-2-carboxylic acid tert-butyl ester (0.25 mmol, 84 mg) in MeOH (2 mL) was treated with phenylalanine methyl ester (0.25 mmol, 45 mg), then treated with sodium cyanoborohydride (0.25 mmol, 16 mg). The mixture was held at room temperature for 3h, then concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave 80 mg (46%) of 5-iodo-3-

[2S-(1-methoxycarbonyl-2-phenyl-ethylamino)-ethyl]-4-methyl-1H-pyrrole-2-carboxylic acid tert-butyl ester. ^{1}H NMR ($CDCl_3$) d 8.81 (1H, br s), 7.30-7.13 (5H, m), 3.61 (3H, s), 3.55 (1H, t, J = 6.8), 2.94 (2H, d, J = 6.3), 2.90-2.78 (2H, m), 2.76-2.70 (1H, m), 2.62-2.56 (1H, m), 1.94 (3H, s), 1.51 (9H, s).

5-Iodo-3-[2S-(1-methoxycarbonyl-2-phenyl-ethylamino)-ethyl]-4-methyl-1H-pyrrole-2-carboxylic acid tert-butyl ester (0.37 mmol, 0.18 g) in dioxane (2 mL) at 0°C was treated with HCl (0.37 mmol, 1 mL of 4M in dioxane). The mixture was held at 0°C for 15 minutes, then concentrated under reduced pressure. The residue was diluted with DMF (3 mL), then treated with HOBT (0.37 mmol, 50 mg), DCC (0.37 mmol, 77 mg), and K_2CO_3 (0.74 mmol, 0.10 g). The mixture was stirred at room temperature for 30 minutes, then diluted with ethyl acetate (50 mL), washed with brine (10 mL), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 21 mg (13%) of 2S-(3-methyl-7-oxo-1,4,5,7-tetrahydro-pyrrolo[2,3-c]pyridin-6-yl)-3-phenyl propionic acid methyl ester. It was noticed that this material had inadvertently de-iodinated. ^{1}H NMR ($CDCl_3$) d 9.28 (1H, br s), 7.31-7.18 (5H, m), 6.64 (1H, s), 5.33 (1H, dd, J = 10.4, 5.6), 3.79-3.74 (1H, m), 3.75 (3H, s), 3.57-3.42 (4H, m), 3.14 (1H, dd, J = 14.5, 10.4), 2.59-2.49 (2H, m), 2.00 (3H, s). MS (FAB) 311 (MH^+).

2S-(3-methyl-7-oxo-1,4,5,7-tetrahydro-pyrrolo[2,3-c]pyridin-6-yl)-3-phenyl propionic acid methyl ester (0.07 mmol, 21 mg) in 1:1 dioxane-water (3 mL) was treated with lithium hydroxide (0.2 mmol, 5 mg), then heated to reflux for 30 minutes. The solution was acidified with saturated aqueous citric acid (3 mL), then extracted with ethyl acetate (15 mL), washed with brine (5 mL), and concentrated under reduced pressure to provide 15 mg (75%) of 2S-(3-methyl-7-oxo-1,4,5,7-tetrahydro-pyrrolo[2,3-c]pyridin-6-yl)-3-phenyl propionic acid. This material (15 mg, 0.05 mmol) was coupled to 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester (11 mg, 0.05 mmol) in DMF (1 mL) by treatment with diisopropylethyl amine (0.02 mL, 0.01 mmol) and HATU (19 mg, 0.05 mmol) at room temperature for 2 h. The resulting solution was washed with brine (10 mL), and extracted with EtOAc (30 mL). The organics were concentrated under reduced pressure and the residue purified by preparative reverse phase chromatography (CH_3CN-H_2O) to provide 10 mg (40 %) of 4S-[2S-(3-methyl-7-oxo-1,4,5,7-tetrahydro-pyrrolo[2,3-c]pyridin-6-yl)-3-phenyl-propionylamino]-5-(2-oxo-

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pyrrolidin-3-yl)pent-2(trans)-enoic acid ethyl ester. ^{1}H NMR ($CDCl_3$) d 10.21 (1H, br s), 7.54 (1H, d, J = 7.7), 7.26-7.11 (4H, m), 6.80 (1H, d, J = 15.6), 6.62 (1H, br s), 6.23 (1H, br s), 5.82 (1H, dd, J = 15.5, 5.4), 5.28 (1H, t, J = 8.0), 4.68-4.50 (1H, m), 4.19 (2H, q, J = 7.1), 3.67-2.96 (6H, m), 2.56-2.51 (3H, m), 2.21-2.09 (2H, m), 1.96 (3H, s), 1.75-1.64 (1H, m), 1.53-1.43 (3H, m), 1.29 (3H, t, J = 7.1). HRMS (FAB) 639.1577 (MCs^+, calcd. 639.1584).

Results of tests conducted using exemplary 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), vol. 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 1 μM 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 the table below. The tabulated data in the column designated $k_{obs}/[I]$ were measured from progress curves in enzyme start experiments.

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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). Test results for the HRV assay are shown in the table below.

Anticoxsackievirus Cell Culture Assay:

Coxsackievirus types A-21 (CAV-21) and B3 (CVB3) 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 the compounds of this invention to protect cells against either CAV-21 or CVB3 infection was measured by the XTT dye reduction

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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 CVB3 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 (CVB3) 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}.

Anti-Echoviral and Anti-Enteroviral Cell Culture Assays

Echovirus type 11 (ECHO 11) was 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 the compounds of this invention to protect cells against ECHO 11 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 ECHO 11 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 1×10^4 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}. Activity of the compounds against enterovirus type 70 (EV 70) may be

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measured by the same assay as described above in this section. Enterovirus type 70 (EV 70) may be obtained from the American Type Culture Collection ATCC (Rockville, MD).

Results obtained for the compounds of the invention may be compared to results obtained in the same manner for 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 the table below. The designation "ND" indicates that a value was not determined for that compound, and the designation "NA" means not applicable.

TABLE

Compd. #	Virus Serotype	$k_{obs}/[I]$ $(M^{-1}s^{-1})^b$	EC_{50} (μM)	CC_{50} (μM)	TI
1+2 (1:1)	HRV-14[a]	36,900	0.179	50.1	280
	HRV-1A	ND	0.825	74.1	90
	HRV-10	ND	0.145	60.3	416
1	HRV-14	114,000	0.033	50.1	1518
	CAV-21[c]	ND	1.48	>10	>7
	ECHO-11[d]	ND	0.16	>10	>63
	CVB3[e]	ND	0.539	>10	>19
	ENT-70[f]	ND	0.012	>10	>833
3	HRV-14	2,900	1.27	>10	>8
4	HRV-14	574	ND	ND	ND
5	HRV-14	329,000	0.016	>10	>625
	CAV-21	ND	1.39	>10	>7
	ECHO-11	ND	0.054	>10	>185
	CVB3	ND	0.577	>10	>17
	ENT-70	ND	0.018	>10	>556
6	HRV-14	37,400	0.034	>10	>294
	CAV-21	ND	4.68	>10	>2
	ECHO-11	ND	0.346	>10	>29
	CVB3	ND	2.50	>10	>4
	ENT-70	ND	0.061	>10	>164
7	HRV-14	81,000	0.014	>10	>714
8	HRV-14	7,660	0.888	>10	>11
9	HRV-14	5,040	0.518	>10	>19
10	HRV-14	113,600	0.104	>10	>96
	HRV-1A	ND	1.182	>10	>9
	HRV-10	ND	1.406	>10	>7
11	HRV-14	193,000	<0.0032	>10	>3125

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	12	HRV-14	25,800	0.075	>10	>133
	13+14 (1:1)	HRV-14	31,000	ND	ND	ND
	15	HRV-14	6,500	0.178	>10	>56
	16	HRV-14	74,000	0.325	>10	>31
5	17	HRV-14	348	>10	>10	ND
	18	HRV-14	116,000	0.125	>10	>80
	19	HRV-14	380,000	0.003	>1	>333
	20	HRV-14	600,000	0.015	>10	>667
	21	HRV-14	6,340	0.469	>10	>21
10	22	HRV-14	18,500	1.0	>10	>10
	23	HRV-14	385,000	0.064	>10	>156
	24	HRV-14	8,800	ND	ND	ND
	25	HRV-14	1,250,000	0.002	>10	>5000
		HRV-1A	ND	0.015	>10	>667
15		HRV-10	ND	0.004	>10	>2500
		HRV-2	ND	0.004	>10	>2500
		HRV-16	ND	0.005	>10	>2000
		HRV-3	ND	0.004	>10	>2500
		HRV-25	ND	0.022	>10	>454
20		HRV-9	ND	0.01	>10	>1000
		HRV-39	ND	0.009	>10	>1111
		HRV-87	ND	0.008	>10	>1250
	26	HRV-14	170,000	0.055	>10	>182
		HRV-1A	ND	0.014	>10	>714
25		HRV-10	ND	0.027	>10	>370
		HRV-2	ND	0.016	>10	>625
		HRV-16	ND	0.050	>10	>200
		HRV-3	ND	0.029	>10	>344
		HRV-25	ND	0.102	>10	>98
30		HRV-9	ND	0.045	>10	>222
		HRV-39	ND	0.047	>10	>212
		HRV-87	ND	0.021	>10	>476
		CAV-21	ND	0.121	>10	>82
		ECHO-11	ND	0.036	>10	>277
35		CVB3	ND	0.016	>10	>625
		CVB2[g]	ND	0.055	>10	>182
		CVB5[h]	ND	0.018	>10	>556
		ECHO-6[i]	ND	0.017	>10	>588
		ECHO-9[j]	ND	0.015	>10	>666
40	27+28 (1:1)	HRV-14	3,750	1.78	>10	>7
	29	HRV-14	148,000	0.079	>10	>126
		HRV-1A	ND	0.046	>10	>217
		HRV-10	ND	0.046	>10	>217
	30	HRV-14	133,500	0.024	>10	>416
45	31	HRV-14	223,400	0.022	>10	>454
		HRV-1A	ND	0.036	>10	>277
		HRV-10	ND	0.048	>10	>208
		HRV-2	ND	0.013	>10	>769

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		HRV-16	ND	0.038	>10	>263
		HRV-3	ND	0.021	>10	>476
		HRV-25	ND	0.087	>10	>114
		HRV-9	ND	0.044	>10	>227
5		HRV-39	ND	0.043	>10	>232
		HRV-87	ND	0.021	>10	>476
		CAV-21	ND	0.161	>10	>62
		ECHO-11	ND	0.013	>10	>769
		CVB3	ND	0.024	>10	>416
10		CVB2	ND	0.057	>10	>175
		CVB5	ND	0.047	>10	>212
		ECHO-6	ND	0.021	>10	>476
		ECHO-9	ND	0.012	>10	>833
	32	HRV-14	127,500	0.126	>10	>79
15		HRV-1A	ND	0.179	>10	>55
		HRV-10	ND	0.156	>10	>64
		HRV-2	ND	0.105	>10	>95
		HRV-16	ND	0.184	>10	>54
		HRV-3	ND	0.059	>10	>169
20		HRV-25	ND	0.547	>10	>18
		HRV-9	ND	0.500	>10	>20
		HRV-39	ND	0.410	>10	>24
		HRV-87	ND	0.033	>10	>303
	33	HRV-14	1,800,000	0.001	>10	>10000
25		HRV-2	ND	0.003	>10	>3333
		HRV-16	ND	0.006	>10	>1666
		HRV-3	ND	0.003	>10	>3333
		HRV-25	ND	0.028	>10	>357
		HRV-9	ND	0.015	>10	>666
30		HRV-39	ND	0.004	>10	>2500
		HRV-87	ND	0.005	>10	>2000
		CAV-21	ND	0.004	>10	>2500
		ECHO-11	ND	0.016	>10	>625
		CVB3	ND	0.003	>10	>3333
35		CVB2	ND	0.015	>10	>666
		CVB5	ND	0.025	>10	>400
		ECHO-6	ND	0.015	>10	>666
		ECHO-9	ND	0.003	>10	>3333
	34	HRV-14	45,100	0.122	>10	>81
40		HRV-2	ND	0.154	>10	>64
		HRV-16	ND	0.543	>10	>18
		HRV-3	ND	0.061	>10	>163
		HRV-25	ND	0.923	>10	>10
		HRV-9	ND	0.593	>10	>16
45		HRV-39	ND	0.441	>10	>22
		HRV-87	ND	0.033	>10	>303
	35	HRV-14	220	>10	>10	NA
	36	HRV-14	4,540	9.0	>100	>11

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	37	HRV-14	177,000	0.162	>10	>62
		HRV-1A	ND	0.108	>10	>93
		HRV-10	ND	0.041	>10	>244
		HRV-2	ND	0.037	>10	>270
5		HRV-16	ND	0.072	>10	>138
		HRV-3	ND	0.043	>10	>232
		HRV-25	ND	0.162	>10	>61
		HRV-9	ND	0.121	>10	>82
		HRV-39	ND	0.016	>10	>625
10		HRV-87	ND	0.058	>10	>172
	38	HRV-14	0.08[k]	16.8	>100	>6
	39	HRV-14	200,000	0.040	>10	>250
		HRV-1A	ND	0.042	>10	>238
		HRV-10	ND	0.088	>10	>113
15		HRV-2	ND	0.016	>10	>625
		HRV-16	ND	0.057	>10	>175
		HRV-3	ND	0.039	>10	>256
		HRV-25	ND	0.107	>10	>93
		HRV-9	ND	0.048	>10	>208
20		HRV-39	ND	0.048	>10	>208
		HRV-87	ND	0.017	>10	>588
	40	HRV-14	186,000	0.027	>10	>370
		HRV-2	ND	0.052	>10	>192
		HRV-16	ND	0.177	>10	>56
25		HRV-3	ND	0.056	>10	>178
		HRV-25	ND	0.490	>10	>20
		HRV-9	ND	0.219	>10	>46
		HRV-39	ND	0.163	>10	>61
		HRV-87	ND	0.083	>10	>120
30	41	HRV-14	60,500	0.062	>10	>161
		HRV-2	ND	0.155	>10	>64
		HRV-16	ND	0.416	>10	>24
		HRV-3	ND	0.054	>10	>185
		HRV-25	ND	0.829	>10	>12
35		HRV-9	ND	0.562	>10	>17
		HRV-39	ND	0.445	>10	>22
		HRV-87	ND	0.060	>10	>166
		CAV-21	ND	0.593	>10	>17
		ECHO-11	ND	0.186	>10	>54
40		CVB3	ND	0.117	>10	>85
		CVB2	ND	0.213	>10	>47
		CVB5	ND	0.199	>10	>50
		ECHO-6	ND	0.147	>10	>68
		ECHO-9	ND	0.106	>10	>94
45	42	HRV-14	38,200	0.168	>10	>59
		HRV-2	ND	0.161	>10	>62
		HRV-16	ND	0.402	>10	>24
		HRV-3	ND	0.152	>10	>65

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	HRV-25	ND	0.611	>10	>16
	HRV-9	ND	0.521	>10	>19
	HRV-39	ND	0.158	>10	>63
	HRV-87	ND	ND	>10	ND
43	HRV-14	382	>10	>10	NA
44	HRV-14	12,500	ND	ND	ND
45	HRV-14	673	ND	ND	ND
WIN 51711	HRV-14	ND	0.78	>60	>77
WIN 52084	HRV-14	ND	0.07	>10	>143
WIN 54954	HRV-14	ND	2.13	>63	>30
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
Pirodavir	HRV-14	ND	0.03	>10	>300
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
	EV-11	ND	3.7	>10	>3
	ENT-70	ND	0.06	>10	>167
Pleconaril	HRV-14	ND	0.01	>10	>1000
	CAV-21	ND	0.09	>10	>107
	CVB3	ND	>10	>10	NA
	ECHO-11	ND	0.16	>10	>62

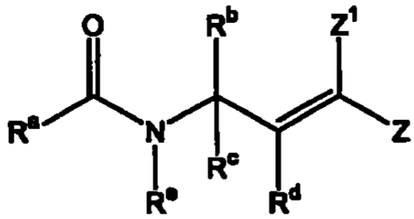
[a]HRV = human rhinovirus of designated serotype
[b]3C protease inhibition activity
[c]CAV-21 = coxsackievirus A21
[d]ECHO-11 = echovirus 11
[e]CVB3 = coxsackievirus B3
[f]ENT-70 = enterovirus 70
[g]CVB2 = coxsackievirus B2
[h]CVB5 = coxsackievirus B5
[i]ECHO-6 = echovirus 6
[j]ECHO-9 = echovirus 9
[k]K_i value, μM

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.

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WE CLAIM:

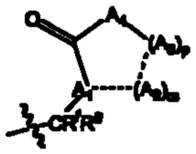
1. A compound having the formula:



wherein:

R^a is substituted or unsubstituted heterocycloalkyl or heterocycloalkylalkyl;

R^b is a substituent having the formula:



wherein:

R^f and R^g are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, or O; where each R^h, R^i and R^j is independently H or lower alkyl;

each A_3 present is independently $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, or O; where each R^h, R^i and R^j is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^h)$, $C(R^h)(R^i)$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^h)(R^i)$, $C(R^h)(R^i)(R^j)$, and $O(R^i)$, where each R^h, R^i and R^j is independently H or lower alkyl, each R^k is H, alkyl, aryl, or acyl, and each R^l is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0);

R^c is H, halogen or a substituted or unsubstituted lower alkyl group;

R^d is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

R^e is H or a substituted or unsubstituted alkylgroup; and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^a$, $-CO_2R^a$, -CN, $-C(O)NR^eR^e$, $-C(O)NR^eOR^e$, $-C(S)R^a$, $-C(S)NR^eR^e$, $-NO_2$, $-SOR^e$, $-SO_2R^a$, $-SO_2NR^eR^e$, $-SO_2(NR^e)(OR^e)$, $-SONR^a$, $-SO_3R^a$, $-PO(OR^e)_2$, $-PO(OR^e)(OR^e)$, $-PO(NR^eR^e)(OR^f)$, $-PO(NR^eR^e)(NR^fR^g)$, $-C(O)NR^eNR^eR^f$, $-C(S)NR^eNR^eR^f$, wherein R^a, R^e, R^f and R^g are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^a, R^e, R^f and R^g, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

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,

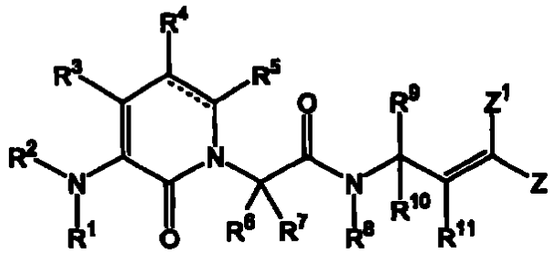
or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof.

2. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1, wherein R^b is substituted or unsubstituted heterocycloalkylalkyl.

3. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 1, wherein the alkyl moiety of the substituted or unsubstituted heterocycloalkylalkyl group is a substituted or unsubstituted saturated alkyl moiety.

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4. A compound having the formula:



wherein:

R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group;

R^3 is H or a suitable substituent; or

R^1 together with R^2 form a suitable nitrogen protecting group; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is H or a suitable substituent;

the dotted line represents an optional bond;

R^5 is H or a suitable substituent;

R^6 is H or a substituted or unsubstituted alkyl group; or

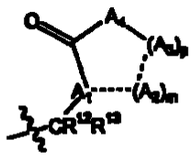
R^5 together with R^6 form a heterocycloalkyl group, which may be optionally substituted;

R^7 and R^{10} are independently H, halogen or a substituted or unsubstituted lower alkyl group;

R^8 is H or a substituted or unsubstituted lower alkyl group;

R^{11} is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

R^9 is a substituent having the formula:



wherein:

R^{12} and R^{13} are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, and $O(R^{18})$, where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, each R^{17} is H, alkyl, aryl, or acyl, and each R^{18} is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0); and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

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

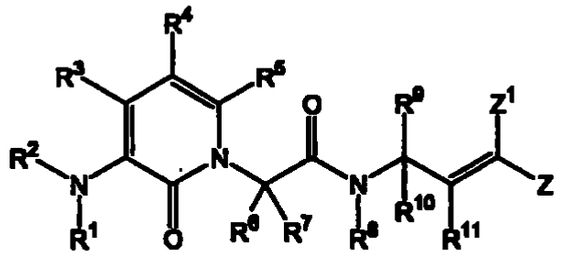
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cannot form the cycloalkyl or heterocycloalkyl group,

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

5. A compound having the formula:



wherein:

R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group;

R^3 is H or a suitable substituent; or

R^1 together with R^2 form a suitable nitrogen protecting group; or

R^2 together with R^3 form a heterocycloalkyl group or heteroaryl group, which may be optionally substituted;

R^4 is H or a suitable substituent;

R^5 is H or a suitable substituent;

R^6 is H or a substituted or unsubstituted alkyl group; or

R^5 together with R^6 form a heterocycloalkyl group, which may be optionally substituted;

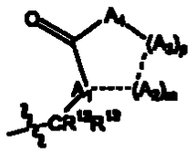
R^7 and R^{10} are independently H, halogen or a substituted or unsubstituted lower alkyl group;

R^8 is H or a substituted or unsubstituted lower alkyl group;

R^{11} is H, halogen, hydroxyl, a substituted or unsubstituted alkyl, alkoxy or alkylthio group;

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R^9 is a substituent having the formula:



wherein:

R^{12} and R^{13} are independently H or lower alkyl;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

A_2 is $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

each A_3 present is independently $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, or O; where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{17})$, $C(R^{14})(R^{15})$, or O; and when p is 0 (i.e., A_3 is not present), A_4 is $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, and $O(R^{18})$, where each R^{14}, R^{15} and R^{16} is independently H or lower alkyl, each R^{17} is H, alkyl, aryl, or acyl, and each R^{18} is H, alkyl, or aryl;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1, $(A_2)_m$, $(A_3)_p$, A_4, and C=O, where each dotted line in the ring depicts a single bond when A_2 is present (i.e., m = 1) and a hydrogen atom when A_2 is absent (i.e., m = 0); and

Z and Z^1 are independently H, F, a unsubstituted or substituted alkyl group, cycloalkyl group, heterocycloalkyl group, aryl group or heteroaryl group, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(O)NR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, wherein R^{19}, R^{20}, R^{21} and R^{22} are independently H, substituted or unsubstituted alkyl group, cycloalkyl group, aryl group, heterocycloalkyl group, an acyl group or a thioacyl group, wherein any two of the R^{19}, R^{20}, R^{21} and R^{22}, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

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,

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

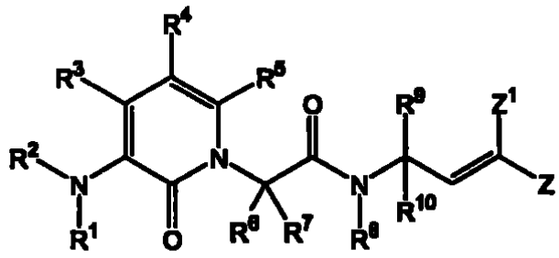
6. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4, wherein R^1, R^7, R^8 and R^{10} are each H.

7. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 wherein when R^3, R^4 and R^5 are independently H or a suitable substituent, wherein said suitable substituent is independently selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, keto, thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio

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and heteroarylthio, wherein any of the alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents are optionally substituted.

8. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



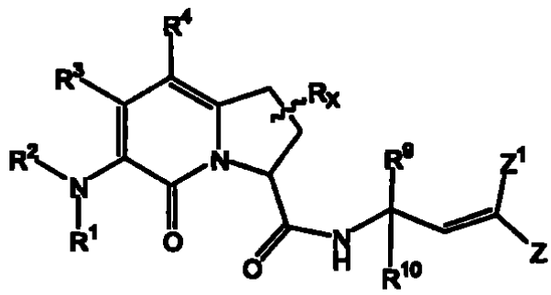
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl moieties of the above groups is substituted or unsubstituted;

R^6 is H or a substituted or unsubstituted alkyl group;

and R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, Z and Z^1 are as defined in claim 4.

9. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



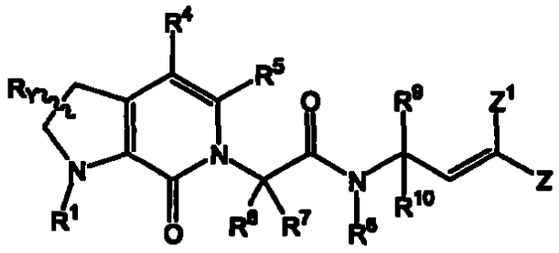
wherein:

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, an aryloxycarbonyl group or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl moieties of the above groups is substituted or unsubstituted;

R_x represents H or one or more suitable substituents;

and R^1, R^3, R^4, R^9, R^{10}, Z and Z^1 are as defined in claim 4.

10. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

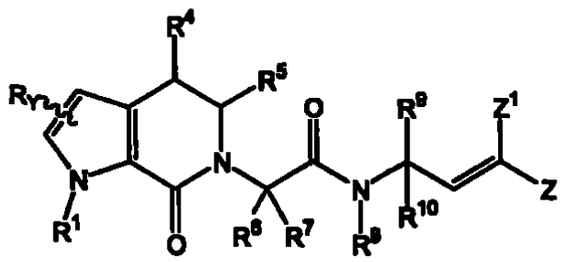
R^6 is H or a substituted or unsubstituted alkyl group;

R_y represents H or one or more suitable substituents;

and R^1, R^4, R^5, R^9, Z and Z^1 are as defined in claim 4.

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11. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



wherein:

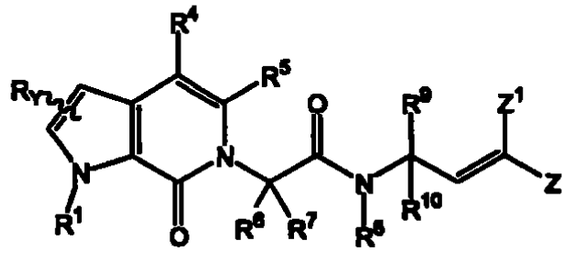
R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R_Y represents H or one or more suitable substituents;

R^4 and R^5 are independently H or a suitable substituent described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined in claim 4.

12. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 4 having the formula:



wherein:

R^7, R^8 and R^{10} are independently H or a substituted or unsubstituted lower alkyl group;

R_Y represents H or one or more suitable substituents;

R^4 and R^5 are independently H or a suitable substituent described above; and

R^1, R^6, R^9, Z and Z^1, and the variables contained therein, are as defined in claim 4.

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13. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 4, 5, 8 or 9, wherein R^2 is selected from a substituted or unsubstituted alkyloxycarbonyl group, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocycloalkylcarbonyl or heteroarylcarbonyl group.

14. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 13, wherein R^2 is a heteroarylcarbonyl group, wherein the heteroaryl moiety is a five-membered heterocycle having from one to three heteroatoms selected from O, N, and S.

15. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 14, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is a five-membered heterocycle having at least one nitrogen heteroatom and at least one oxygen heteroatom.

16. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 15, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is unsubstituted or substituted 1,2-oxazolyl, 1,3-oxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, or 1,2,5-oxadiazolyl.

17. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 16, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is selected from unsubstituted and monomethyl-substituted 1,2,4-oxadiazolyl.

18. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 16, wherein R^2 is heteroarylcarbonyl, where the heteroaryl moiety is selected from 3-isoxazolyl and 5-isoxazolyl, each unsubstituted or substituted with one or two substituents selected from methyl groups and halogens.

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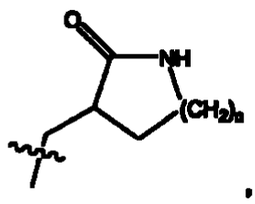
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19. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 4, 5, 8 , 10, 11 or 12, wherein R^6 is H or a substituted or unsubstituted lower alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl group, a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety.

20. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 19, wherein R^6 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl, or substituted or unsubstituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy and halogen.

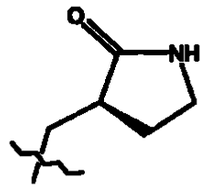
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21. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 4, 5, 8, 9, 10 , 11 or 12 wherein R^9 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alkyl; $-CH_2NHC(O)CH_3$; and

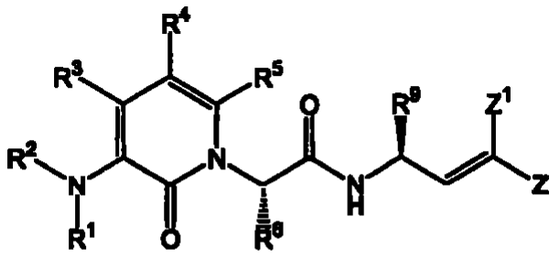


, where n is 1 or 2.

22. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 21, wherein R^9 is

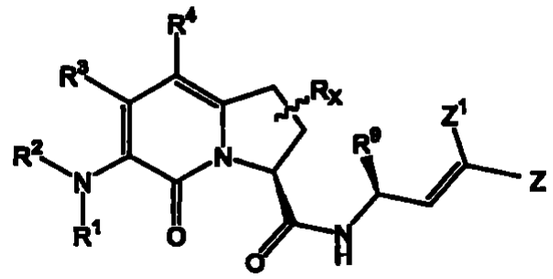


23. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 8, having the formula:



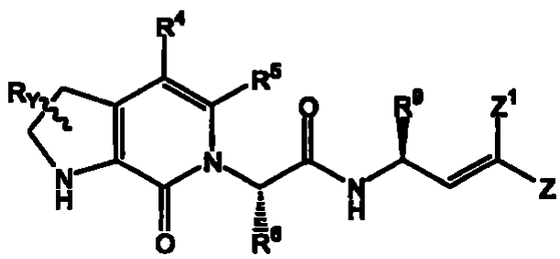
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z and Z^1 are as defined in claim 8.

24. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 9, having the formula:



wherein R^1, R^2, R^3, R^4, R^9, R_x, Z and Z^1 are as defined in claim 9.

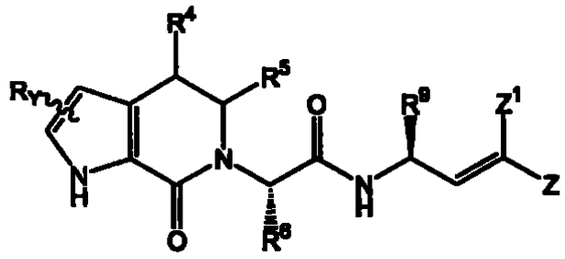
25. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 10 having the formula:



wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as defined in claim 10.

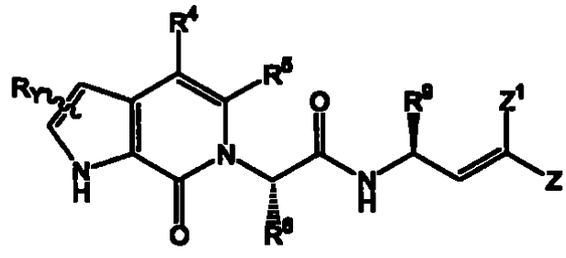
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26. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 11 having the formula:



wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as defined in claim 11.

27. A compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 12 having the formula:



wherein R^4, R^5, R^6, R^9, R_y, Z and Z^1 are as defined in claim 12.

28. The compound according to claims 4 or 5 having antipicornaviral activity corresponding to an EC_{50} less than or equal to 100 μM in an H1-HeLa cell culture assay.

29. A pharmaceutical composition comprising:

a therapeutically effective amount of at least one antipicornaviral agent selected from compounds, prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable solvates defined in claims 4 or 5; and

a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

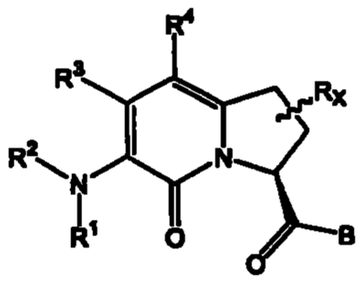
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30. A method of treating a mammalian disease condition mediated by picornaviral protease activity, comprising administering to a mammal in need thereof a therapeutically effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in claims 4 or 5.

31. 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 acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in claims 4 or 5.

32. The method as defined in claim 31, wherein the picornaviral 3C protease is a rhinoviral protease.

33. A compound having the formula:



wherein:

R^3 and R^4 are independently H or a suitable substituent;

R_X represents H or one or more suitable substituents;

B is H, $-OR^{24}$, where R^{24} is a suitable protecting group for a carboxyl moiety; and

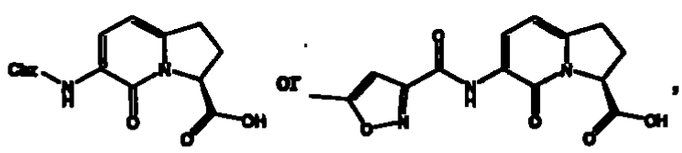
R^1 is H, a substituted or unsubstituted lower alkyl group or a suitable nitrogen protecting group;

R^2 is an alkylcarbonyl group, an arylcarbonyl group, a cycloalkylcarbonyl group, a heterocycloalkylcarbonyl group, a heteroarylcarbonyl group, or an alkyloxycarbonyl group, wherein each of the alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl moieties in the above groups may be substituted or unsubstituted, or a suitable nitrogen protecting group; or

R^1 together with R^2 form a suitable nitrogen protecting group;

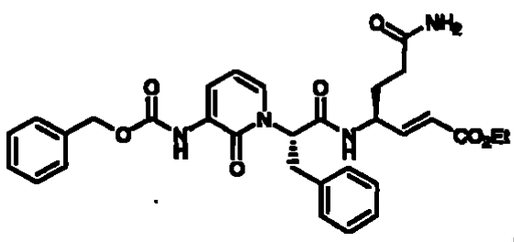
or a pharmaceutically acceptable salt thereof.

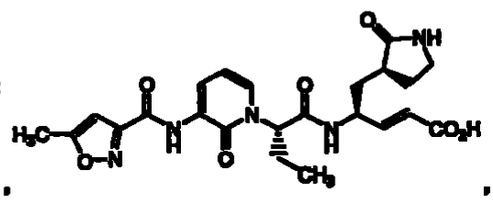
34. The compound according to claim 33 having the formula:

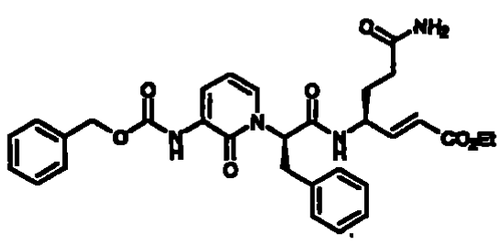


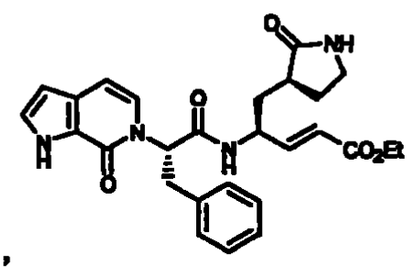
or a pharmaceutically acceptable salt thereof.

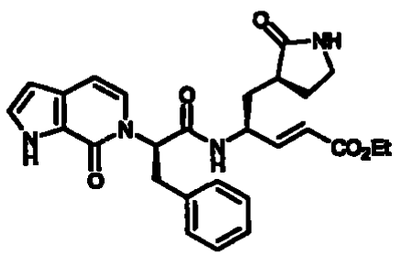
35. A compound selected from:

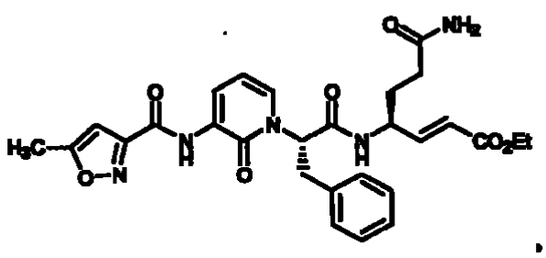




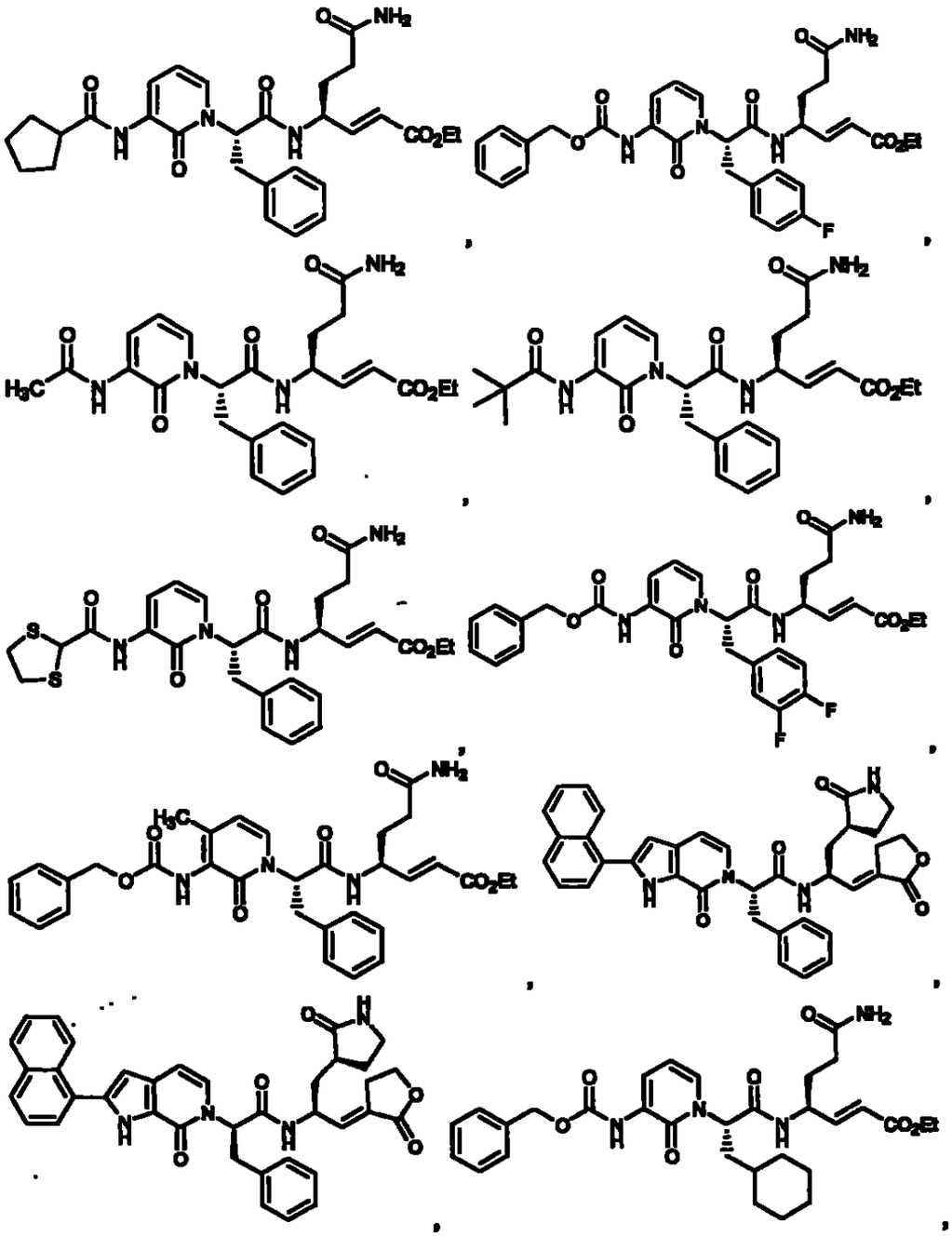






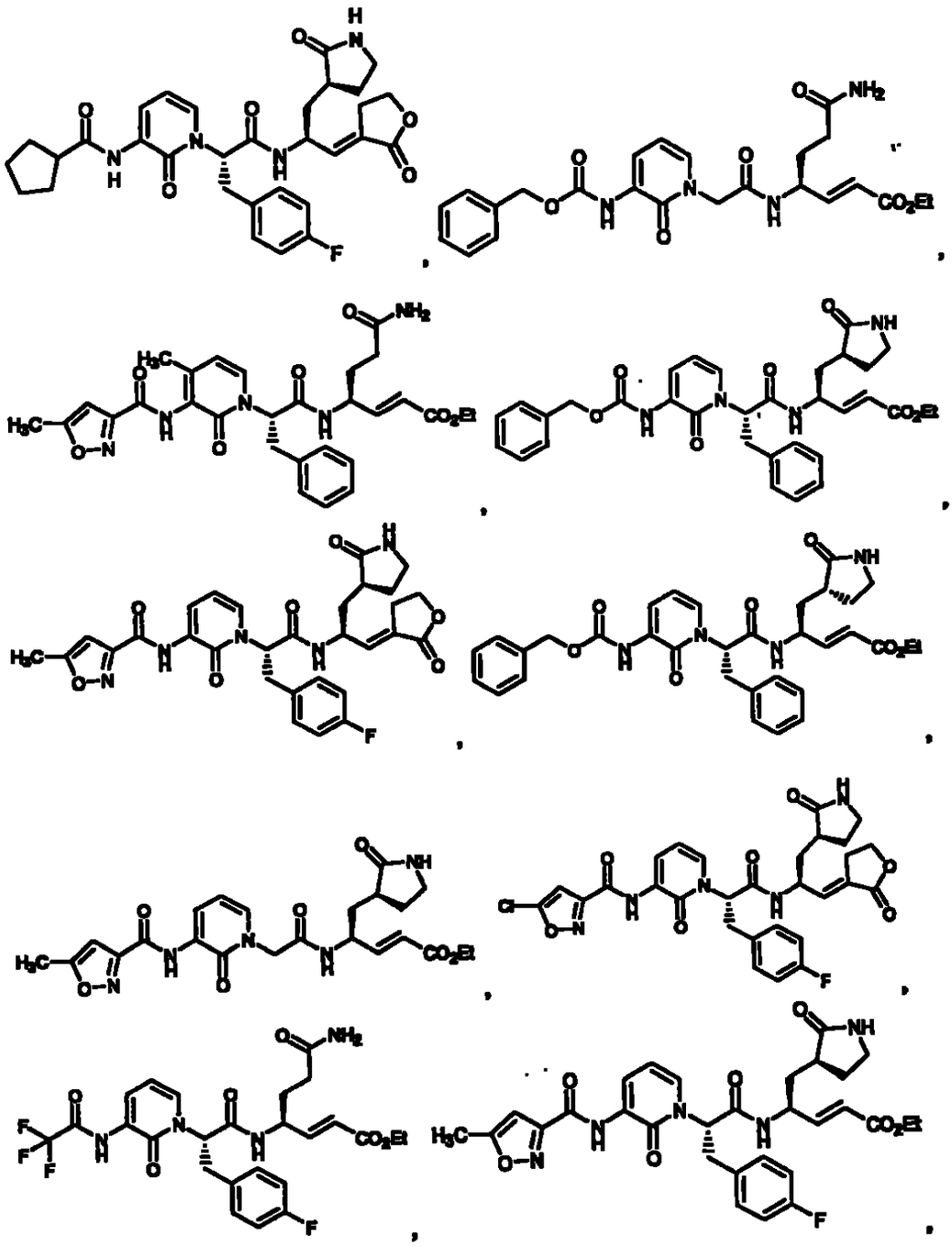


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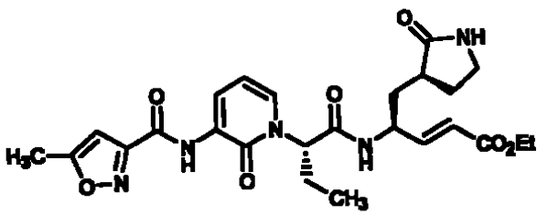


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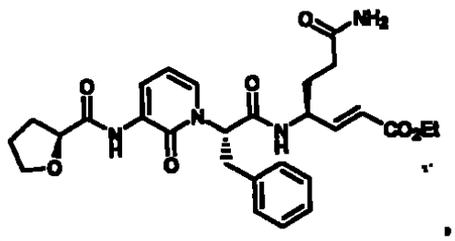
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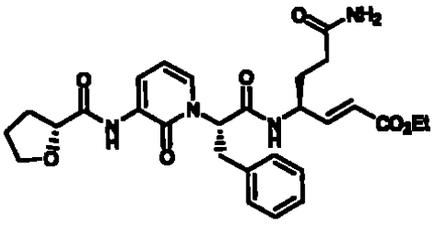
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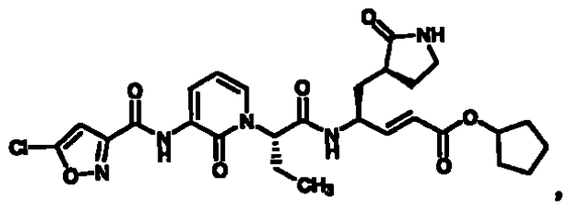
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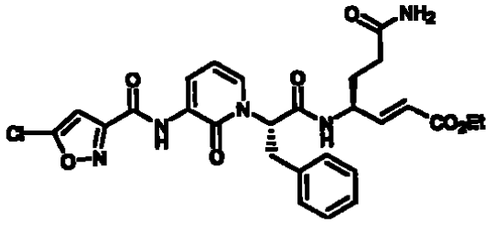
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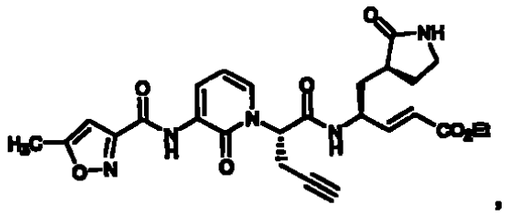
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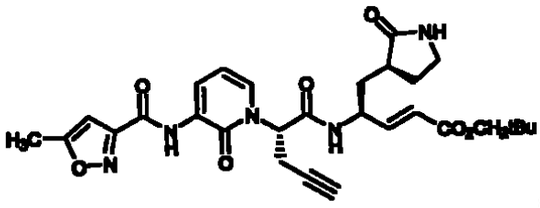
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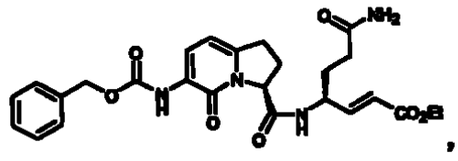
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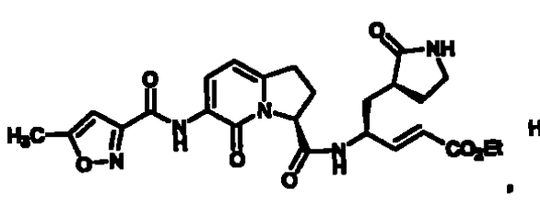
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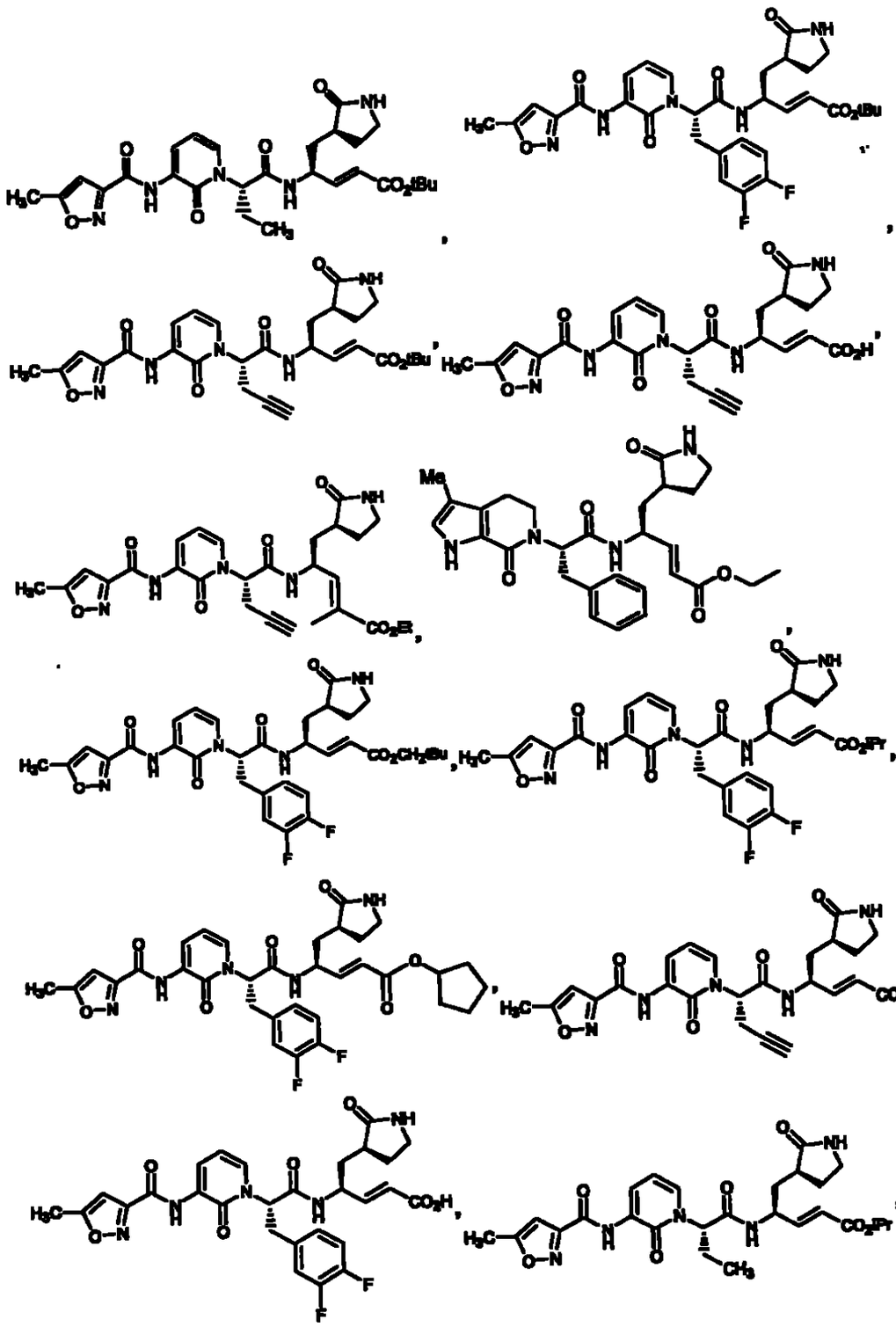
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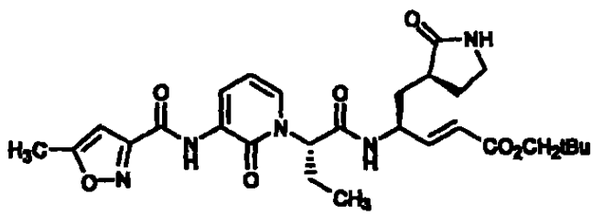
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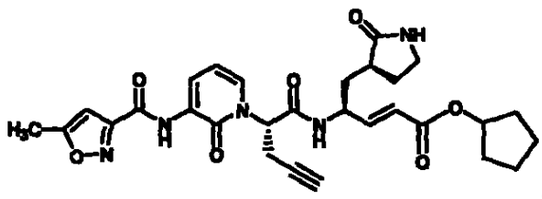


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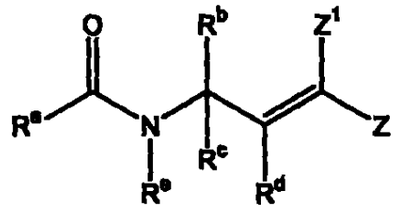
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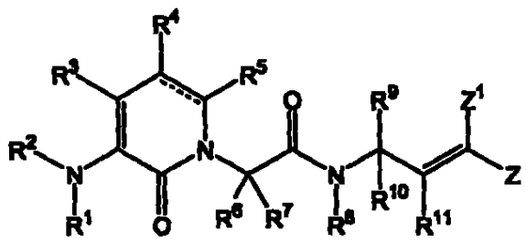
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ABSTRACT OF THE DISCLOSURE

Compounds of the formula:



where the formula variables are as defined herein, are disclosed that advantageously inhibit or block the biological activity of the picornaviral 3C protease. Also disclosed are compounds of the formula:



where the formula variables are as defined herein that advantageously inhibit or block the biological activity of the picornaviral 3C protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with one or more picornaviruses, such as rhinovirus 3C proteases. Intermediates and synthetic methods for preparing such compounds are also described.

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(TRADUCCIÓN DEL INGLES AL ESPAÑOL)

LOS ESTADOS UNIDOS DE AMERICA
A TODOS A QUIENES ESTAS PRESENTES LLEGAREN:
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas Comerciales de los Estados Unidos

Octubre 17 del año 2000

ESTE ES PARA CERTIFICAR QUE ANEXA A LA PRESENTE ESTÀ UNA FIEL COPIA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS COMERCIALES DE LOS ESTADOS UNIDOS DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE LOGRA LOS REQUERIMIENTOS PARA QUE LE SEA OTORGADA UNA FECHA DE PRESENTACIÓN BAJO 35 USC 111.

SOLICITUD NUMERO: 60/192,052
FECHA DE PRESENTACIÓN: Marzo 24 del año 2000.

Por Autorización del
COMISIONADO DE PATENTES Y MARCAS COMERCIALES

W. Montgomey (Firmado)
W. MONTGOMERY
Funcionario de Certificaciones

SELLO EN RELIEVE.

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23 - 27 - 00

HOJA DE CUBIERTA DE SOLICITUD PROVISIONAL

Esta es una solicitud para presentación de una SOLICITUD PROVISIONAL bajo 37 CFR 1.53(c).

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EXPEDIENTE NUMERO	2521.194-01PVL	Escriba a máquina un signo más (+) dentro de esta cajilla	+

INVENTOR(s)/SOLICITANTE(s)			
APELLIDO	PRIMER NOMBRE	SEGUNDO NOMBRE	RESIDENCIA (CIUDAD Y YA SEA ESTADO O PAIS EXTRANJERO)
DRAGOVICH	Peter	S.	Encinitas, California
PRINS	Thomas	J.	Cardiff, California
ZHOU	Ru		Carlsbad, California
JONSON, JR	Theodore	O.	San Diego California

TITULO DE LA INVENCIÓN (280 caracteres máximo)

C MPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS US S FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

DIRECCIÓN DE LA CORRESPONDENCIA

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Teléfono No. (212) 218-2100

PARTES DE LA SOLICITUD INCLUIDA (Cheque todo lo pertinente)

☐ Especificación Número de Páginas 181 . ☐ Cesión enteramente pequeña

☐ Dibujo(s) Número de Cubierta _____ ☐Otros (Especifique)_____.

MÉTODO DE PAGO (chequee uno)

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☐ Un cheque o giro está incluido para cubrir los honorarios de presentación provisional ☐ El comisionado está por medio del presente autorizado para cargar cualesquiera deficiencias en el pago de los honorarios de presentación y cualesquiera créditos de sobrepago a la Cuenta de Depósito Número: 06-1205	CANTIDAD DE HONORARIO DE PRESENTACIÓN PROVISIONAL ($)	$150.00

La invención fue hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos.

☐ No.

☐ Si, el nombre de la agencia del Gobierno de los E.U. y el número del contrato del Gobierno son:_____

_____

Respetuosamente sometido
FIRMA Kathryn L. Sieburth (Firmado)
NOMBRE IMPRESO o ESCRITO A MAQUINA Kathryn L. Sieburth

FECHA
Marzo 24 del año 2000
REGISTRO NO. 40,072
(si es apropiado)

☐ Inventores adicionales están siendo nombrados en hojas numeradas separadamente adjuntas con ésta.

UNICA PRESENTACIÓN DE SOLICITUD PROVISIONAL

"Correo Expreso" número de etiqueta de envio por correo
EL582469851US
Fecha de Depósito Marzo 24 del año 2000

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Por medio del presente certifico que este papel de honorario está siendo depositado con el Servicio Postal de los Estados Unidos "Oficina Postal de Correo Expreso para el Destinatario" servicio bajo 37 CFR 1.10 en la fecha arriba indicada y está dirigido al Comisionado de Patentes y Marcas Comerciales, Washington, D.C. 20231

Kathryn Sieburg
(Nombre impreso o escrito a máquina de la Persona que envía por correo el papel u honorario)

Firma ilegible (Firmado)
(Firma de la persona que envía el papel u honorario por correo)

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2621.194-01PVL

SOLICITUD DE PATENTE PROVISIONAL DE LOS ESTADOS UNIDOS

TITULO

COMPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

Inventores: Peter Scott Dragovich
Thomas Prins
Ru Zhou
Ted Johnson

Agouron Pharmaceuticals, Inc.

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Una Compañía de Warner-Lambert
10350 North Torrey Pines Road
La Jolla, California 92037

"Correo Expreso" número de etiqueta de envío por correo
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Fecha de Depósito Marzo 24 del año 2000
Por medio del presente certifico que este papel de honorario está siendo depositado con el Servicio Postal de los Estados Unidos "Oficina Postal de Correo Expreso para el Destinatario" servicio bajo 37 CFR 1.10 en la fecha arriba indicada y está dirigido al Comisionado de Patentes y Marcas Comerciales, Washington, D.C. 20231

Kathryn Sieburg
(Nombre impreso o escrito a máquina de la Persona que envía por correo el papel u honorario)

Firma Ilegible (Firmado)
(Firma de la persona que envía el papel u honorario por correo)

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TITULO

COMPUESTOS Y COMPOSICIONES ANTIPICORNAVIRALES, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SUS SÍNTESIS

ANTECEDENTES DE LA INVENCIÓN

Campo de la Invención

La invención se refiere a compuestos peptidomiméticos que contienen piridona que ventajosamente inhiben la actividad enzimática de las proteasas picornavirales 3C, especialmente proteasas de rinovirus 3C (RVPs), y aquel crecimiento viral retardado en el cultivo de célula. La invención también se refiere al uso de esos compuestos en composiciones farmacéuticas, métodos

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de tratamiento de infecciones rinovirales que usan esos compuestos y composiciones, y procesos para la síntesis de esos compuestos y compuestos útiles en la síntesis de éstos.

Antecedentes Relacionados del Arte

Los picornaviruses son una familia de viruses que contienen RNA acordonados positivos no envueltos menúdos que infectan a humanos y otros animales. Esos viruses incluyen los rinoviruses humanos, poliviruses humanos, coxsacquieviruses humanos, ecoviruses humanos, enteroviruses humano y bovino, viruses encefalomiocarditis, virus de meningitis, viruses del pié y la boca, virus de hepatitis A, y otros. Los rinoviruses humanos son una causa mayor del resfriado común. Hasta la fecha, no hay terapias efectivas en el mercado que curen el resfriado común, solamente tratamientos que alivian los síntomas.

Las infecciones picornavirales pueden ser tratadas inhibiendo las enzimas picornavirales proteolíticas 3C. Esas enzimas son requeridas para la nutrición natural de los picornaviruses. Ellos son responsables por la segmentación autocatalítica de poliproteína grande, genómica en las proteínas virales esenciales. Los miembros de la familia de proteasa 3C son proteasas de cisteína, donde el grupo sulfidrilo más a menudo segmenta la unión de amida de glicina-glutamina. La inhibición de proteasas 3C se cree que bloquea la segmentació proteolítica de la poliproteína virtal, la cual a su turno puede retardar la maduración e inhibición del procesamiento de esta proteasa de cisteína con moléculas selectivas pequeñas que son específicamente reconocidas representarían un acercamiento importante y útil para tratar y curar infecciones virales de esta naturaleza y, en particular, el resfriado común.

Algunos inhibidores de moléculas pequeñas de la actividad enzimática de las proteasas picornavirales 3C (es decir, compuestos antipicornavirales) han sido recientemente

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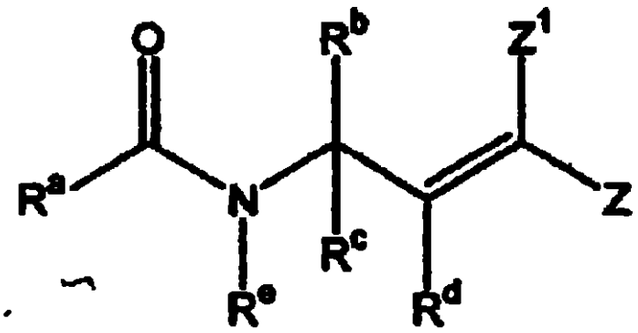
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descubiertos. Ver por ejemplo: Patente de los E.U. No. 5,856,530; Patente de los E.U. No. 5,962,487; Solicitud de Patente de los E.U. No. 08/991,282, presentada en Diciembre 16 de 1997, por Dragovich y otros; y Solicitud de Patente de los E.U. No. 09/301,977, presentada en Abril 29 de 1999, por Dragovich y otros. Ver también: Dragovich y otros, "Diseño Estructura Basado, Síntesis, y Evaluación Biológica de Inhibidores de Proteasa de 3C de Rinovirus Humano Irreversible...., "J. Med. Chem. (1999), Vol. 42, No. 7, 1203-1212, 1213-1224; y Dragovich y otros, "Síntesis de Fase Sólida de Inhibidores de Proteasa 3C de Rinovirus Humano Irreversible..., "Bioorg. & Med. Chem. (1999), Vol 7, 589-598. Existe un deseo, sin embargo, para descubrir compuestos de molécula pequeña que son especialmente agentes antipicornavirales potentes.

Los inhibidores de otras proteasas de sisteína relacionados tales como catepsinos han sido descritos en, por ejemplo, la Patente de los E.U. No. 5,374,623; Patente de los E.U. No. 5,498,616; y Publicación Internacional WIPO Nos. WO 94/04172, WO 95/15749, WO 97/19231, y WO 97/49668. Todavía permanece una necesidad para inhibidores objetivos de proteasa de sisteína picornaviral 3C con propiedades farmacéuticas deseables, tales como de alta especificidad.

RESUMEN DE LA INVENCIÓN

Esta invención se refiere a compuestos útiles para inhibir la actividad de proteasa picornaviral 3C que tienen la fórmula:

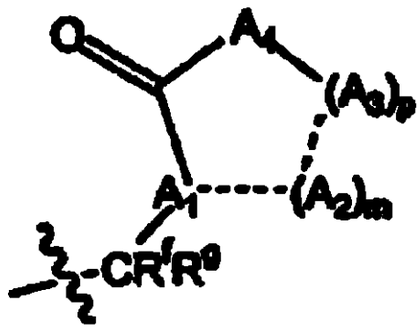


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en la cual:

R^a es heterocicloalquilalquilo o heterociclosiquilo sustituido o no sustituido;

R^b es un suetituyente que tiene la fórmula



en la cual:

R^f y R^g son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, o O; donde cada R^h, R^i y R^j es independientemente H o alquilo inferior;

cada A_3 presente esta independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^k)$, $C(R^h)(R^i)$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^k)(R^l)$, $C(R^h)(R^i)(R^j)$, y $O(R^l)$, donde cada R^h, R^i y R^j es independientemente H o alquilo inferior, cada R^k es H, alquilo, arilo, o acilo, y cada R^l es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada línea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2está ausente (es decir, m=0); y

R^c es H, halógeno o un grupo de alquilo inferior sustituido o no sustituido;

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R^d es H, halógeno, hidróxilo, un alquilo sustituido o no sustituido, grupo alcoxi o alquiltio;

R^e es H o un grupo alquilo sustituido o no sustituido; y

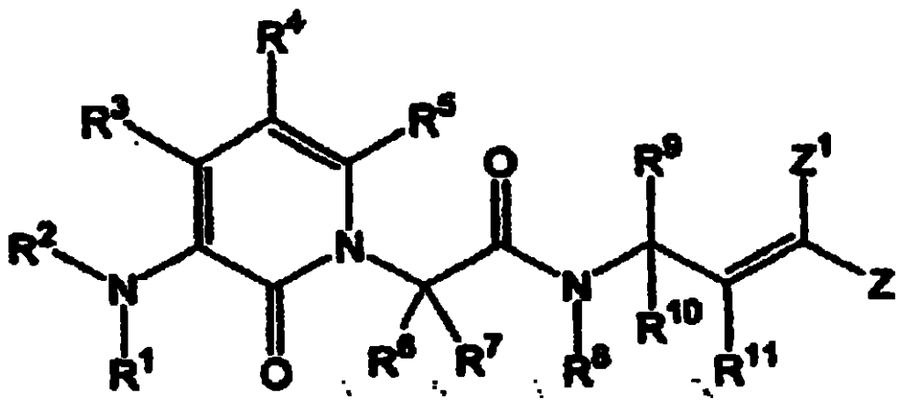
Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^n$, $-CO_2R^n$, -CN, $-C(O)NR^nR^o$, $-C(ONR^nOR^o$, $-C(S)R^n$, $-C(S)NR^nR^o$, $-NO_2$, $-SOR^o$, $-SO_2R^n$, $-SO_2NR^nR^o$, $-SO_2(NR^n)(OR^o)$, $-SONR^n$, $-SO_3R^n$, $-PO(OR^n)_2$, $-PO(OR^n)(OR^o)$, $-PO(NR^nR^o)(OR^p)$, $-PO(NR^nR^o)(NR^pR^q)$, $-C(O)NR^nNR^oR^p$, $-C(S)NR^nNR^oR^p$, en el cual R^n, R^o, R^p y R^q son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterociclilcalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^n, R^o, R^p y R^q, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

o Z y Z^1, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^1 están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo.

Preferiblemente, cuando R^a es un heterocicloalquilalquilo sustituido o no sustituido, la mitad de alquilo de ésta es una mitad alquilo saturada sustituida o no sustituida.

Especialmente, esta invención se refiere a compuestos útiles para inhibir la actividad de proteasa picornaviral 3C que tiene la Fórmula general I:

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(I)

en la cual:

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuado;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, o un grupo alcoxicarbonilo, en los cuales cada una de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo en los grupos de arriba puede ser sustituida o no sustituida, o un grupo adecuado de protección de nitrógeno;

R^3 es H o un sustituyente adecuable; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o grupo heteroarilo, el cual puede ser opcionalmente sustituido;

R^4 es H o un sustituyente adecuable;

la línea punteada representa una unión opcional

R^5 es H o un sustituyente adecuable;

R^6 es H o un grupo alquilo sustituido o no sustituido; o

R^5 junto con R^6 forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido;

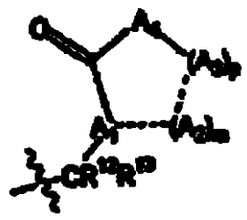
R^7 y R^{10} son independientemente H, halógeno o un grupo de alquilo más bajo sustituido o no sustituido;

R^8 es H o un grupo alquilo inferior sustituido o no sustituido;

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R^{11} es H, halógeno, hidróxilo, un grupo alquiltio o alcox, de alquilo sustituido o no sustituido;

R^9 es un sustituyente que tiene la fórmula:



En la cual,

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cada A_3 presente esta independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, y $O(R^{16})$, donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, cada R^{17} es H, alquilo, arilo, o acilo, y cada R^{18} es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada línea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2está ausente (es decir, m=0); y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, -

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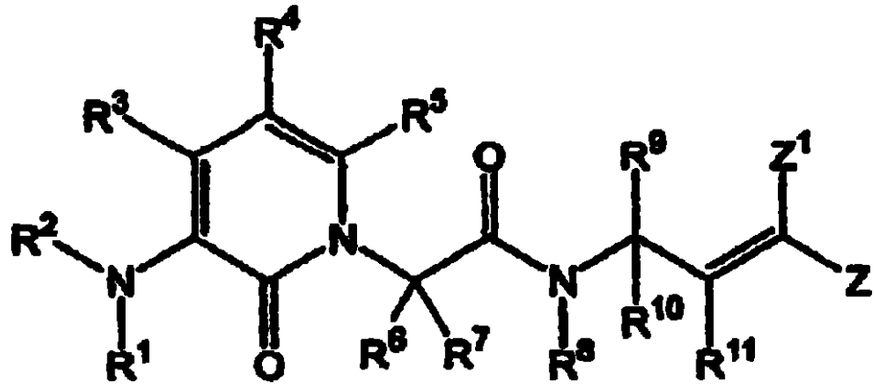
$SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterociclilcalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

o Z y Z^1, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^1 están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo.

En adición a los compuestos de la Fórmula I, los agente antipicornavirales de la invención incluyen prodrogas, metabolitos farmacéuticamente activos, y sales y solventes farmacéuticamente aceptables de tales compuestos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN Y MODALIDADES PREFERIDAS

En una incorporación, el compuesto de esta invención útil para inhibir la actividad de proteasa picornaviral 3C que tiene la fórmula I-A:



I-A

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en la cual R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Z y Z^1, y las variables contenidas en este, son como se definieron arriba, o una progroda, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvente farmacéuticamente aceptable de éste.

Preferiblemente, en los compuesto de la Fórmula I-A:

R^1, R^7, R^8, R^{10} y R^{11} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en el cual cada uno de los alquilo, arilo, cicloalquilo, mitades heteroarilo o heterocicloalquilo de los grupos de arriba pueden ser sustituido o no sustituido;

R^3 es un sustituyente apropiado; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o un grupo heteroalilo, el cual puede ser opcionalmente sustituido;

R^4 es un sustituyente apropiado;

R^5 es un sustituyente apropiado;

R^6 es un grupo alquilo no sustituido o un grupo alquilo inferior opcionalmente sustituido con un grupo cicloalquilo, un grupo heterocicloalquilo, un grupo arilo, un grupo heteroarilo, un grupo alcoxilo, un grupo ariloxi, un grupo alquiltio, un grupo ariltio, en el cual cada alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo o mitades de estos pueden ser opcionalmente sustituidos; o

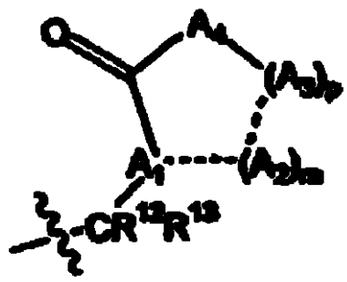
R^5 junto con R^6 forman un grupo hetrocicloalquilo membrado de cinco o seis sustituidos o no sustituidos;

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En el cual cuando R^3, R^4 y R^5 son sustituyentes apropiados, dichos sustituyentes apropiados pueden ser independientemente seleccionados de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, haloalquilo (trifluorometilo), hidróxilo, alcoxi, alquilenodioxi, arilioxi, cicloalcoxi, heterocicloalcoxi, heteroarilioxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquiloxicarbonilo, carbóxilo, carbamoilo, formilo, queto (oxo), tioqueto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilamincarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilo, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, ariltio, y heteroariltio, en el cual cualesquiera de los alquilo, arilo, cicloalquilo, heterocicloalquilo, mitades de heteroarilo presentes en los sustituyentes de arriba pueden ser además sustituido;

R^9 es un grupo aminocarbonilalquilo, un grupo aqluilcarbonilaminoalquilo, un grupo alquilaminocarbonilalquilo o un sustituyente que tiene la fórmula:

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En el cual:

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 1;

p es 1 o 2;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O;

Cada A_3 presente es independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$ o O;

A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O;

En el cual R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, y en cada R^{17} es H, alquilo, arilo, o acilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4 y C=O, donde cada línea punteada en el anillo describe una unión simple; y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19},

R^{20}, R^{21} y R^{22}, tomados junto con los átomos los cuales ellos están unidos, forman un grupo heterociclicoalquilo, el cual puede ser opcionalmente sustituido.

o Z y Z^1, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^1 están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo.

Preferiblemente, R^3, R^4 y R^5 pueden ser independientemente seleccionados de H, alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, amino, halógeno, haloalquilo (trifluorometil), hidroxilo, alcoxi, arilоxi, arilоxi, cicloalcoxi, heterocicloalcoxi, alquiloxicarbonilo, ariloxicarbonilo, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroariloxicarbonilo, heteroarilo carboniloxi, heterocicloalquiloxicarbonilo, carboxilo, alquilamino, arilamino, dialquilamino, alquilaminocarbonilo, alquilsulfonilo, o arilsulfonilo en el cual las mitades alquilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de cualquiera de los sustituyentes de arriba pueden ser opcionalmente sustituidos por uno o más de alquilo (excepto para alquilo), haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, arilоxi, mercapto, grupos alquiltio o ariltio.

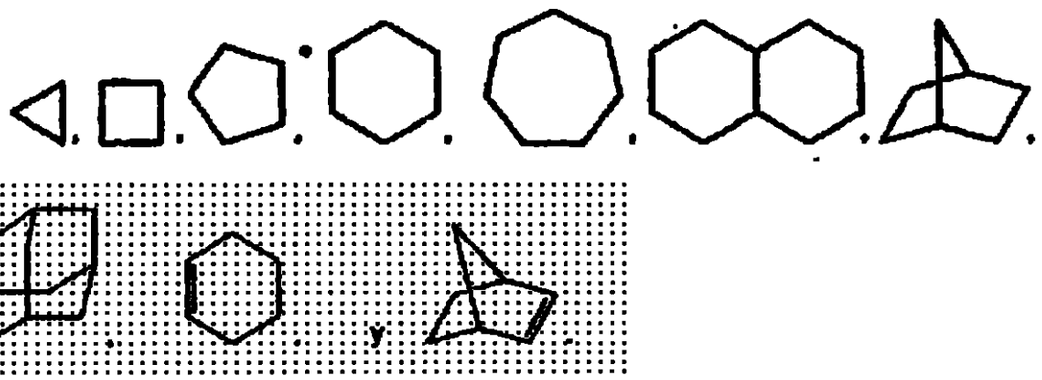
De acuerdo con una convención usada en el arte,  es usada en fórmulas estructurales aquí en el presente para describir la unión que es el punto de unión de la mitad o sustituyente para el alma o columna estructural.

Tal como es usado aquí, el termino "alquilo" representa una cadena saturada o no saturada ramificada o recta de hidrocarburo, que contiene 1 hasta 10 átomos de carbono. Ejemplarmente sustituyentes de alquilo incluyen, pero no están limitados a, metilo

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(Me), etilo, (Et), propilo, isopropilo, butilo, isobutilo, t-butilo, etenilo, propenilo, butenilo, pentanilo, etinilo, butinilo, propinilo, pentinilo, hexinilo, y el deseado. El termino "alquilo inferior" se refiere a un grupo alquilo que contiene desde 1 hasta 4 átomos de carbono.

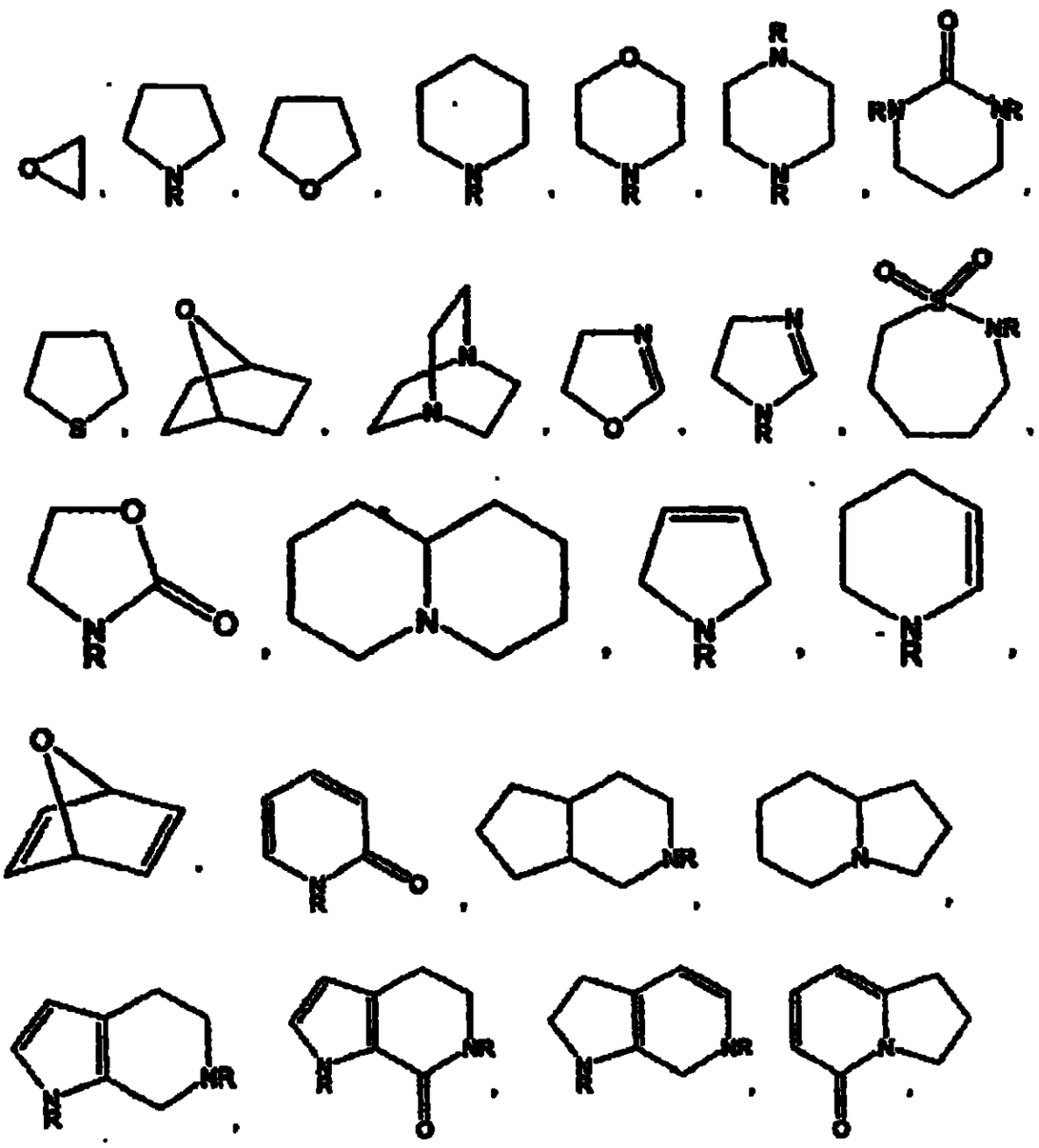
"Cicloalquilo" representa un grupo que comprende un hidrocarburo o tricicio o, bicicio, monocicio no aromático que contiene desde 3 hasta 14 átomos de carbono tal que puede ser saturado o parcialmente no saturado, anillo mono-opolicarboxilico, preferiblemente que tiene 5-14 átomos de anillo de carbono. Los cicloalquilos ejemplares incluyen anillo monocicilcos que tienen desde 3-7, preferiblemente 3-6, átomos de carbono tal como ciclopropilo, ciclobutilo, ciclopentino, ciclohexilo, cicloheptilo y similares, que pueden ser completamente saturados o parcialmente no saturados. Los ejemplos ilustrativos de grupos cicoalquilo incluyen lo siguiente:



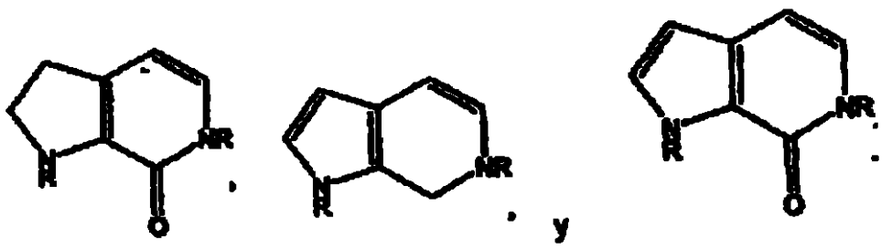
"Heterocicloalquilo" representa un grupo que comprende un radical tricicilco o, bicicilco, monocicilco monovalente, no aromático, el cual es saturado o parcialmente no saturado, que contiene 3 hasta 18 átomos de anillo y el cual incluye 1 hasta 5 heteroátomos seleccionados de nitrógeno, oxigeno y azufre, y al cual pueden ser fusionados uno o más grupos cicloalquilo, grupos arilo, o grupos heteroarilos los cuales pueden ser no sustituidos o sustituidos por uno o más de los sustituyentes descritos abajo. Los

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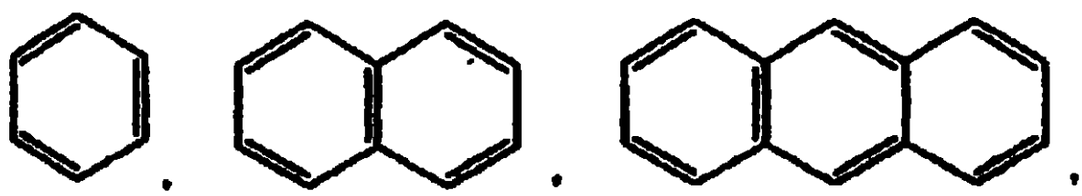
ejemplos ilustrativos de grupos heterocicloalquilos incluyen, pero no están limitados a, azetidinilo, pirrolidino, piperidilo, piperazinilo, morfolinilo, tetrahidro-2H-1,4-tiazinilo, tetrahidrofurilo, dihidrofurilo, tetrahidropiranilo, 1,3-oxatianilo, 1,3-ditianilo, azabicilo[4.3.0]nonilo, oxabicilo[2.2.1]heptilo, 1,5,9-triazaciclododecilo, y el deseado. Los ejemplos ilustrativos de grupos heterocicloalquilo incluyen las siguientes mitades:



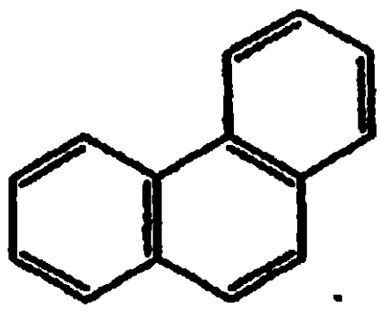
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"Arilo" representa un grupo que comprende un radical tricíclo o, bicíclico, monocíclico monovalente, aromático, que contiene de 6 hasta 18 átomos de anillo de carbono, los cuales pueden ser saturados o no saturados por uno o más de los sustituyentes descritos abajo. Los ejemplos ilustrativos de grupos arilo incluyen las siguientes mitades:



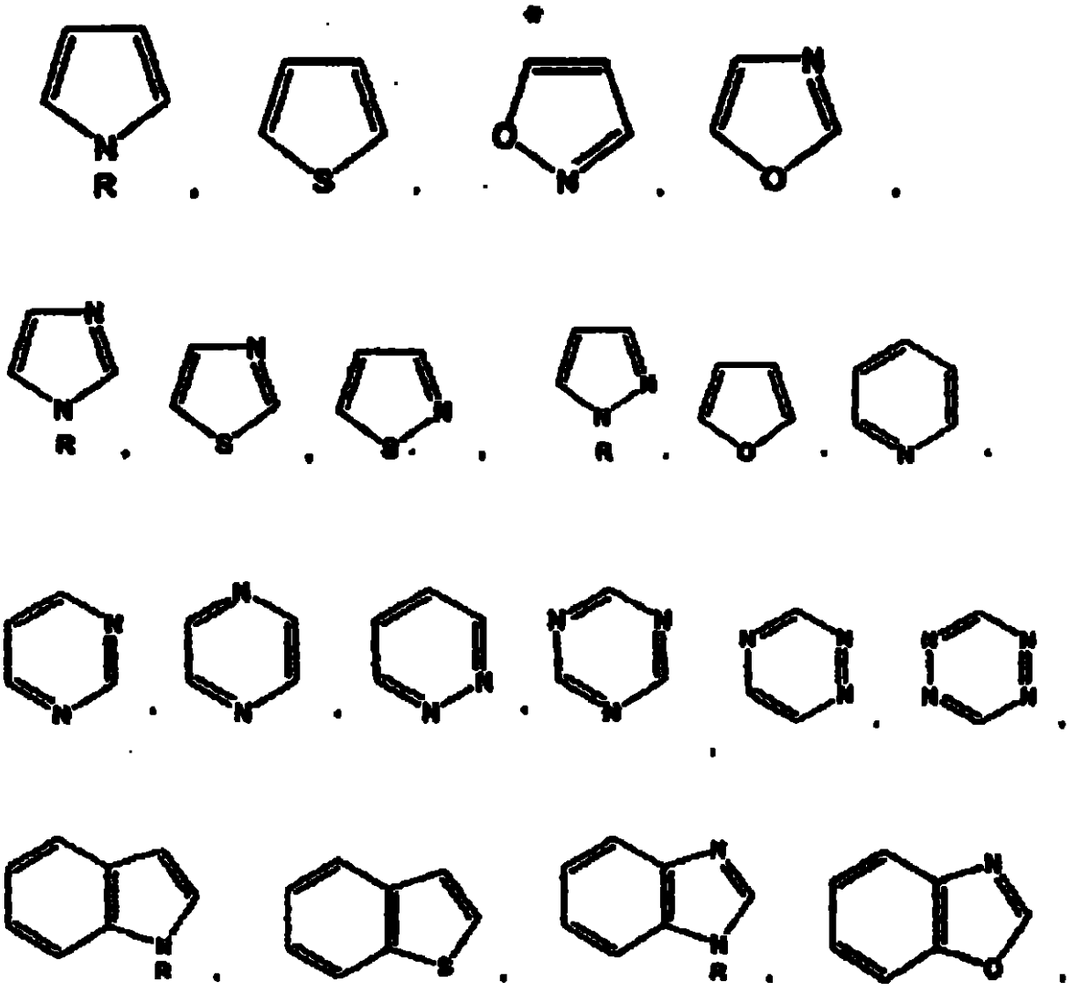
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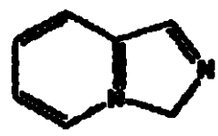
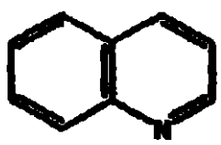
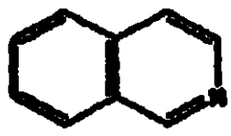
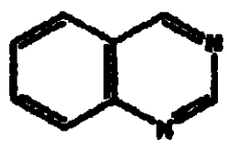
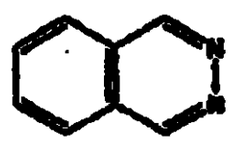
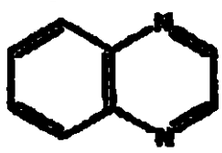
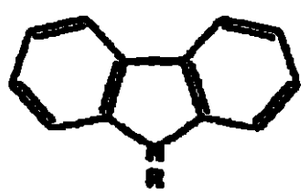
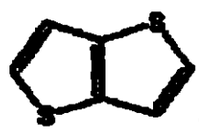
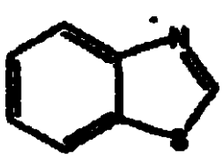
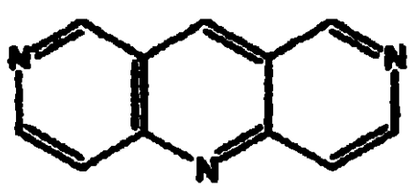
"Heteroarilo" representa un grupo que comprende un radical tricíclico o, bicíclico, monocíclico monovalente aromático, que contiene 5 hasta 18 átomos de anillos, que incluyen 1 hasta 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, el cual puede ser sustituido o no sustituido por uno o más de los sustituyentes descritos abajo. Los ejemplos ilustrativos de grupos heteroarilo incluyen, pero no están limitados a, tienilo, pirrolilo, imidazolilo, pirazolilo, furilo, isotiazolilo, furazanilo, isoxazolilo, tiazolilo, piridilo, pirazinilo, pirimidinilo, piridizinilo, triazinilo,

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benzo[b]tienilo, nafto[2,3-b]tiantrenilo, isobenzofuranilo, cloromenilo, xantenilo, fenoxatienilo, indolizinilo, isoindolilo, indolilo, indazolilo, purinilo, isoquinolilo, quinolilo, ftalazinilo, naftiridinilo, quinoxalinilo, quinzolinilo, benzotiazolilo, benzimidazolilo, tetrahidroquinolinilo, cinnolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fentatridinilo, acridinilo, perimidinilo, fenantrolinilo, fenazinilo, isotiazolilo, fenotiazinilo, y fenoxazinilo. Además ejemplos de grupos heteroarilo incluyen las siguientes mitades:



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Los "sustituyentes adecuables" Ejemplares que pueden estar presentes en cualquier de los grupos de arriba alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo están descritos en la presente e incluyen alquilo (excepto para alquilo), arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, hidróxilo, alcoxi, alquilenodioxi, arilioxi, cicloalcoxi, heterocicloalcoxi, heteroarilioxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalcoxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquiloxicarbonilo, carboxilo, carbamoilo, formilo, queto (oxo), tioqueto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo,

alquilsulfenilo, arilsulfenilo, alquilcarboniliamino, cicloalquil carboniliamino, arilcarboniliamino, heterocicloalquilcarboniliamino, heteroarilcarboniliamino, alquiltiocarboniliamino, cicloalquil tiocarboniliamino, ariltiocarboniliamino, heterocicloalquil tiocarboniliamino, heteroariltiocarboniliamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfoniliamino, arilsulfoniliamino, mercapto, alquiltio, ariltio, heteroariltio, en los cuales cualquiera de las mitades de alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los sustituyentes de arriba pueden ser además sustituidos. Los "sustituyentes adecuables" preferidos incluyen alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halógeno, hidroxilo, alcoxi, alquilenodioxi, ariloxi, cicloalcoxi, heteroariloxi, y carboxilo. Las mitades de alquilo, alquileno, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de cualquiera de los sustituyentes de arriba pueden ser opcionalmente sustituidas por uno o más de grupos alquilo (excepto para alquilo), haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidróxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltioo grupos ariltio.

Si los sustituyentes por sí mismo no son compatibles con los métodos sintéticos de esta invención, el sustituyente puede ser protegido con un grupo de protección adecuable que es estable para las condiciones de reacción usadas en esos métodos. El grupo de protector pueden ser removido a un punto adecuable en la secuencia de reacción del método para proporcionar un compuesto intermedio deseado u objetivo. Los grupos de protección adecubles y los métodos para proteger y desproteger diferentes sustituyentes usando tales grupos de protección adecuados son bien conocidos por aquellos versados en el arte; los ejemplos de los cuales pueden ser encontrados en T. Greene y P. Wuts, Grupos de Protección en Síntesis Química (3^{era} ed.), John Wiley & Sons, NY (1999), los cuales están incorporados aquí en adelante por referencia en su totalidad. En algunos casos, un sustituyente puede ser especificamente seleccionado para ser reactivo bajo las condiciones de reacción usadas en los métodos de esta invención.

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Bajo estas circunstancias, las condiciones de reacción convierten al seleccionado sustituyente en otro sustituyente que es ya sea útil en un compuesto intermediario en los métodos de ésta invención o es un sustituyente deseado en un compuesto objetivo.

En los compuestos de esta invención, R^1 y R^2, independientemente o tomados juntos, pueden ser un grupo protector de nitrógeno adecuable. Tal como está indicado arriba, los grupos protectores de nitrógeno son bien conocidos en el arte y cualquier grupo de protección de nitrógeno que es útil en los métodos de preparación de los compuestos de esta invención o puede ser útil en los compuestos antipicornavirales de esta invención pueden ser usados. Los grupos protectores de nitrógeno ejemplares incluyen alquilo, alquilo sustituido, carbamato, urea, amida, imida, enamina, sulfenilo, sulfonilo, nitro, nitroso, óxido, fosfinilo, fosforilo, cililo, organometálico, ácido borínico y grupos de ácido borónico. Los ejemplos de cada uno de esos grupos, métodos para proteger mitades de nitrógeno usando esos grupos y métodos para remover esos grupos de mitades de nitrógeno están revelados en T. Greene y P. Wuts, Supra. Preferiblemente, cuando R^1 y/o R^2 son independientemente grupos protectores de nitrógeno adecuados, Los sustituyentes adecuables R^1 y R^2 incluyen, pero no están limitados a grupos de carbamato tales como alquiloxicarbonilo (por ejemplo, Boc:t-butiloxicarbonilo) y ariloxicarbonilo (por ejemplo, Cbz:benziloxicarbonilo, o FMOC:fluoreno-9-metiloxicarbonilo), alcoxicarbonilos (por ejemplo, metoxicarbonilo), alquilo o arilcarbonilo, alquilo sustituido, especialmente arilalquilo (por ejemplo, tritilo (trifenilmetilo), benzilo y benzilo sustituido), y similares. Cuando R^1 y R^2 tomados juntos son un grupo de protección de nitrógeno adecuado, los sustituyentes adecuados R^1/R^2 incluyen ftalimido y una estabase (1,2-bis (dialquil))etileno).

Los términos "halógeno" y "halo" representan sustituyentes cloro, fluoro, bromo o yodo. "Heterocicio" está destinado para significar un grupo heteroarilo o heterocicloalquilo. "Acilo" está

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destinado para significar un radical –C(O)-R, donde R es un alquilo sustituido o no sustituido, cicloalquilo, arilo, heterocicloalquilo o grupo heteroarilo. "Aciloxi" está destinado para significar un radical –OC(O)-R, donde R es un grupo sustituido o no sustituido de alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo. "Tioacilo" está destinado para significar un radical –C(S)-R, donde R es un grupo heteroarilo o heterocicloalquilo, arilo, cicloalquilo, alquilo sustituido o no sustituido. "Sulfonilo" está destinado para significar un birradical $-SO_2-$. "Sulfenilo" está destinado para significar un birradical –SO-. "Sulfo" está destinado para significar un radical $-SO_2H$. "Hidroxi" está destinado para significar el radical –OH. "Amina" o "amino" está destinado para significar el radical $-NH_2$. "Alquilamino" está destinado para significar el radical $-NHR_a$, donde R_a es un grupo alquilo. "Dialquilamino" está destinado para significar el radical $-NR_aR_b$, donde R_a y R_b son cada una independientemente un grupo alquilo, y está destinado para incluir grupos heterocicloalquilo, en los cuales R_a y R_b, tomados juntos, forman un anillo hetyerocíclico que incluye el nitrógeno amina. "Alcoxi" está destinado para significar el radical $-OR_a$, donde R_a es un grupo alquilo. Los grupos alcoxi ejemplares incluyen metoxi, etoxi, propoxi, y similares. Los grupos "alcoxi inferior" tienen mitades de alquilo que tienen desde 1 hasta 4 carbonos. "Alcoxicarbonilo" está destinado para significar el radical $-C(O)OR_a$, donde R_a es un grupo alquilo. "Alquilsulfonilo" está destinado para significar el radical $-SO_2R_a$, donde R_a es un grupo alquilo. "Alquilenodioxi" está destinado para significar el radical divalente $-OR_aO-$ el cual está unido a átomo adyacentes (por ejemplo, átomos adyacentes sobre un anillo fenilo o naftilo), en el cual R_a es un grupo alquilo inferior. "Alquilaminocarbonilo" está destinado para significar el radical $-C(O)NHR_a$, donde R_a es un grupo alquilo. "Dialquilaminocarbonilo" está destinado para significar el radical $-C(O)NR_aR_b$, donde R_a y R_b son cada uno independientemente un grupo alquilo. "Mercapto" está destinado para significar el radical –SH. "Alquiltio" esta destinado para significar el radical $-SR_a$, donde R_a es un grupo alquilo. "Carboxi"

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está destinado para significar el radical -C(O)OH. "Keto" u "oxo" está destinado para significar el radical =O. "Tioketo" está destinado para significar el radical =S. "Carbamoilo" está destinado para significar el radical $-C(O)NH_2$. "Cicloalquilalquilo" está destinado para significar el radical -alquil-cicloalquilo, donde alquilo y cicloalquilo son definidos como arriba, y está representado por el arreglo de unión presente en los grupos $-CH_2$-ciclohexano o $-CH_2$-ciclohexeno. "Arilalquilo" está destinado para significar el radical -alquilarilo, donde alquilo y arilo son definidos como arriba, y está representados por el arreglo de unión presente en un grupo bencilo. "Aminocarbonilalquilo" está destinado para significar el radical -alquilC(O)NH_2 y está representado por el arreglo de unión presente en el grupo $-CH_2CH_2C(O)NH_2$. "Alquilaminocarbonilalquilo" está destinado para significar el radical -alquilC(O)NHR_a, donde R_a es un grupo alquilo y está representado por el arreglo de unión presente en el grupo $-CH_2CH_2C(O)NHCH_3$. "Alquilcarbonilaminoalquilo" está destinado para significar el radical -alquilNHC(O)-alquilo y está representado por el arreglo de unión presente en el grupo $-CH_2NHC(O)CH_3$. "Dialquilaminocarbonilalquilo" está destinado para significar el radical -alquilC(O)NR_aR_b, donde R_a y R_b son cada uno independientemente un grupo alquilo. "Arilioxi" está destinado para significar el radical $-OR_c$, donde R_c es un grupo arilo. "Heteroarilioxi" esta destinado para significar el radical $-OR_d$, donde R_d es un grupo heteroarilo. "Arilitio" esta destinado para significar el radical $-SR_c$, donde R_c es un grupo arilo. "Heteroarilitio" está destinado para significar el radical $-SR_d$, donde R_d es un grupo heteroarilo.

Si un compuesto de la invención es una base, una sal deseada puede ser preparada por cualquier método adecuado conocido en el arte, que incluye el tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromihídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares, o con un ácido orgánico, tal como ácido acético, ácido maléico, ácido succínico,

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ácido mandélico, ácido fumárico, ácido maiónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, ácido piranosidilo, tal como ácido glucurónico o ácido galacturónico, ácido alfa hidroxi, tal como ácido cítrico o ácido tartárico, ácido amino, tal como ácido aspártico o ácido glutámico, ácido aromático, tal como ácido benzóico o ácido cinnámico, ácido sulfónico, tal como ácido p-toluenosulfónico o ácido etanosulfónico, o similares.

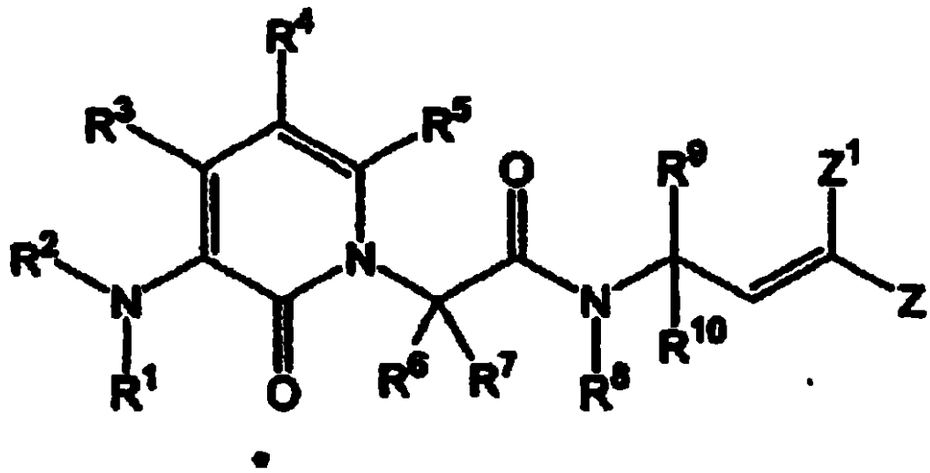
Si un compuesto de la invención es un ácido, una sal deseada puede ser preparada por cualquier método adecuable conocido en el arte, incluyendo tratamiento del ácido libre con una base inorgánico u orgánica, tal como una amina (primaria, secundaria, o terciaria); un metal alcali o un hidróxido de metal de tierra alcalina; o similares. Los ejemplos ilustrativos de sales adecuables incluyen sales orgánicas derivadas de aminoácidos tales como glicina y arginina; amoniaco; primario, secundario, y aminas terciarias; y aminas cíclicas, tales como piperidina, morfolina, y piperacina; así como también sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, zinc, aluminio, y litio.

Los compuestos de la invención pueden existir como estereoisómeros simples y/o diastereómeros, racematos, y/o mezclas de enanciómeros y/o diastereómeros. Todos tales estereoisómeros simples, diastereómeros, racematos, y mezclas de éstos están destinados para estar comprendidos dentro del amplio alcance de la presente invención. Donde la estereoquímica de los carbonos quirales presentes en las estructuras químicas ilustradas aquí en la presente no está especificada, la estructura química está destinada para abarcar compuestos que contienen ya sea estereoisómeros de cada carbono quiral. Preferiblemente, sin embargo, Los compuestos de la invención son usados en forma ópticamente pura. Cuando son usados describen un compuesto particular, el término "ópticamente puro" es usado aquí en la presente para que el compuesto sea sustancialmente enanciomércamente o diastereomércamente puro. Los compuestos

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que son sustancialmente enantioméricos puros contienen por lo menos 90% de un isómero simple y preferiblemente contienen por lo menos 95% de un isómero simple. Los compuestos que son sustancialmente diastereoméricos puros contienen por lo menos 90% de un isómero simple de cada centro de carbono quiral presente en el diastereómero, y preferiblemente contiene por lo menos 95% de un isómero simple de cada carbono quiral. Más preferiblemente, los compuestos ópticamente activos en esta invención contienen por lo menos 97.5% de un isómero simple y más preferiblemente contienen por lo menos 99% de un isómero simple. Los compuestos identificados aquí como estereoisómeros simples están destinados para describir compuestos que están presentes en una forma que contiene por lo menos 90% de un isómero simple. El término "racémico" o "mezcla racémica" se refiere a una mezcla de iguales cantidades de compuestos enantioméricos, los cuales abarcan mezclas de enantiómeros y mezclas de diastereómeros enantioméricos.

Otra modalidad de ésta invención comprende los compuestos descritos por la Fórmula I-a (tal como están representados por la Fórmula I, en la cual la línea punteada representa una unión):



I-a

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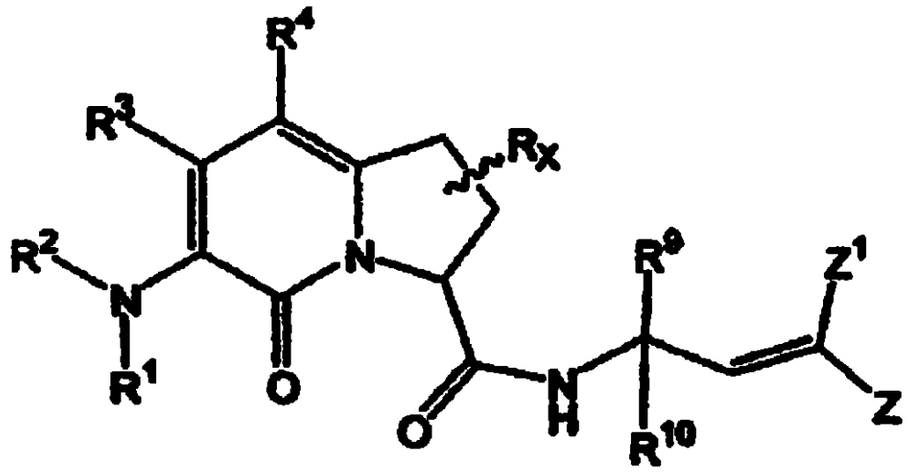
en el cual

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de la mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo de los grupos de arriba pueden ser sustituidos o no sustituidos.

R^3, R^4, R^5 son independientemente H o sustituyentes adecuables descritos arriba, y

R^1, R^6, R^7, R^8, R^9, R^{10}, Z y Z^1, y las variables contenidas en estos, son como sean definido arriba.

Todavia otra modalidad comprende los compuestos descritos por la Fórmula I-b:



I-b

en el cual:

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de la mitades de los

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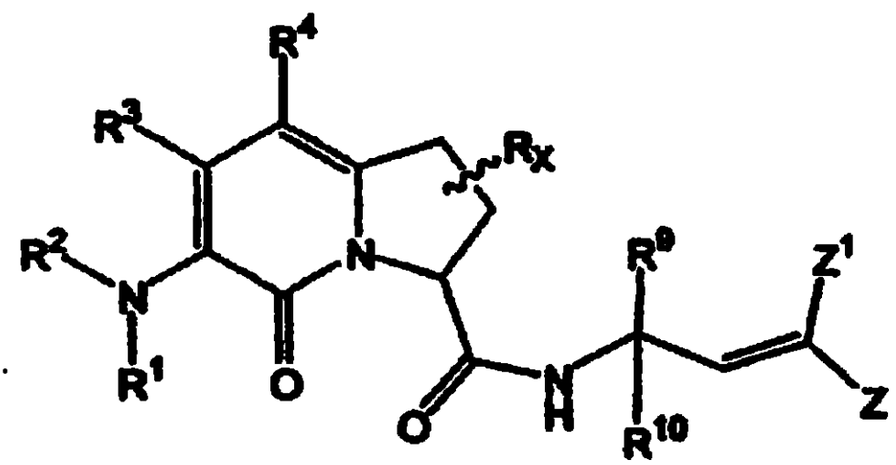
alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo de los grupos de arriba pueden ser sustituidos o no sustituidos.

R_X representa H o uno o más sustituyentes adecuables;

R^3 y R^4 son independientemente H o un sustituyente adecuable descrito arriba; y

R^1, R^9, R^{10}, Z y Z^1, y las variables contenidos en éstos, son como sean definido

Además otra modalidad de la invención comprende los compuestos descritos por la Fórmula I-c:



I-b

en la cual:

R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

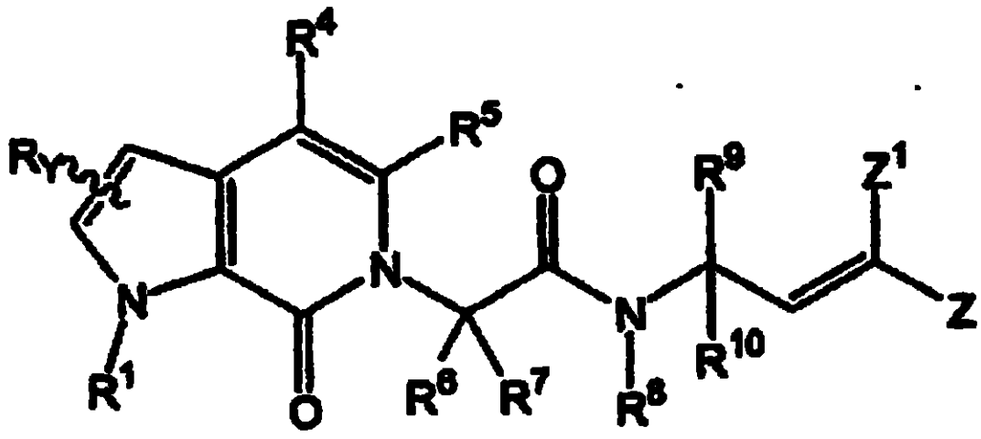
R_Y representa H o uno o más sustituyentes adecuables;

R^4 y R^5 son independientemente H o un sustituyente adecuable descrito arriba; y

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R^1, R^8, R^9, Z y Z^1, y las variables contenidas en éstos, son como se han definido arriba.

Otra modalidad de esta invención comprende los compuestos descritos por la Fórmula I-d:



I-d

en la cual:

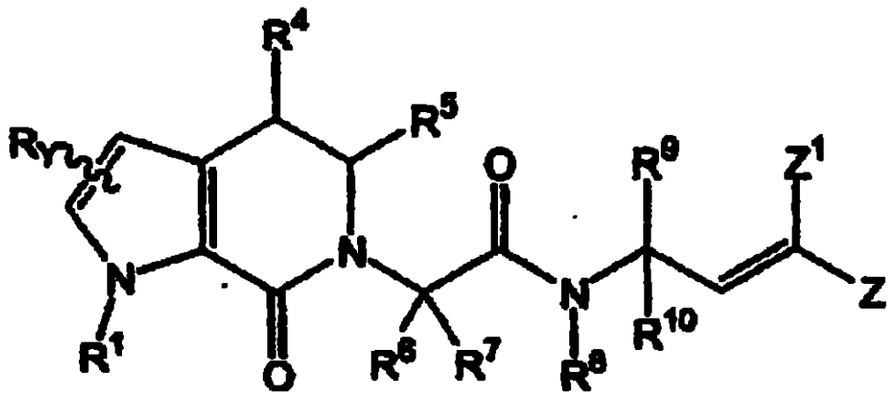
R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R_y representa H o uno o más sustituyentes adecuables;

R^4 y R^5 son independientemente H o un sustituyente adecuable descrito arriba; y

R^1, R^8, R^9, Z y Z^1, y las variables contenidas en éstos, son como se han definido arriba.

Todavía otra modalidad de esta invención comprende los compuestos descritos por la Fórmula I-e (como está representada por la Fórmula I, en la cual la línea punteada no representa una unión):



I-c

en la cual:

R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R_y representa H o uno o más sustituyentes adecuables;

R^4 y R^5 son independientemente H o un sustituyente adecuable descrito arriba; y

R^1, R^6, R^9, Z y Z^1, y las variables contenidas en éstos, son como se han definido arriba.

En modalidades preferidas las Fórmulas I-a y I-b, R^2 está seleccionado de un grupo alquiloxicarbonilo sustituido o no sustituido, alquilcarbonilo, cicloalquilcarbonilo, arilcarbonilo, heterocicloalquilcarbonilo o grupos heteroarilenocarbonilo. Preferiblemente cuando R^2 es un grupo alquiloxicarbonilo sustituido, R^2 es un grupo arilalquiloxicarbonilo sustituido o no sustituido. Los grupos ejemplares R^2 incluyen, pero no están limitados a benziloxicarbonilo, metilcarbonilo, t-butilcarbonilo, trifluorometilcarbonilo, ciclopentilcarbonilo, tetrahidrofurán-2-carbonilo, 1,3-ditiolano-2-carbonilo y similares. Preferiblemente, R^2 es un grupo heteroarilcarbonilo o arilcarbonilo, benziloxicarbonilo sustituido o no sustituido. Aún más preferiblemente, R^2 es un grupo

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heteroarilcarbonilo o benziloxicarbonilo sustituido o no sustituido, en el cual la mitad heteroarilo es un heterociclo de cinco-miembros que tiene desde uno hasta tres heteroátomos seleccionados de O, N, y S, más preferiblemente un heterociclo de cinco-miembros que tiene por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxigeno (por ejemplo, 1,2-oxazolilo sustituido o no sustituido (es decir, isoxazolilo), 1,3-oxazolilo (es decir, oxazolilo), u oxadiazolilo (1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo). Cuando la mitad heteroarilo es oxadiazolilo, 1,2,4-oxadiazolilo sustituido-monometilo y no sustituido son preferidos. En modalidades especialmente preferidas, la mitad heteroarilo es 3-isoxazolilo o 5-isoxazolilo, ya sea sustituido o no sustituido con uno o dos grupos metilo y/o halógenos (C, Cl, Br o I), con cloro o fluoro siendo preferidos. Por consiguiente, el grupo heteroarilcarbonilo en las modalidades especialmente preferidas es un grupo sustituido o no sustituido 3-carbonil-1,2-oxazolilo (es decir, 3-carbonil-isoxazolilo) o un grupo 5-carbonil-1,2-oxazolilo (es decir, 5-carbonil-isoxazolilo).

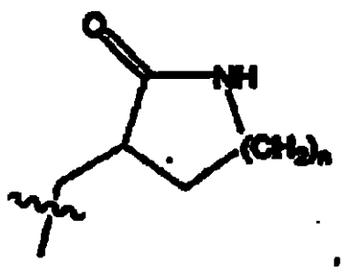
En especialmente modalidades preferidas de las Fórmulas I-a, I-c y I-e, R^6 es H o un grupo alquilo no sustituido o un grupo alquilo inferior opcionalmente sustituido, en los cuales esos grupos están comprendidos de un grupo de hidrocarburo saturado de cadena-ramificada o recta-, un grupo de hidrocarburo saturado sustituido de cadena-ramificada o recta-, o grupo comprendido de una mitad de hidrocarburo saturada de cadena-ramificada o recta- y una mitad de hidrocarburo no saturado. En cada caso, el punto de unión de R^6 es por vía de una mitad de hidrocarburo saturado. Cuando R^6 es un grupo de hidrocarburo saturado sustituido, el grupo de hidrocarburo saturado puede ser opcionalmente sustituido con un grupo cicloalquilo, un grupo heterocicloalquilo, un grupo arilo, un grupo heteroarilo, un grupo alcoxi, un grupo arilioxi, un grupo alquiltio, un grupo ariltio, en los cuales cada alquilo, cicloalquilo, arilo, heterocicloalquilo o mitad heteroarilo de éstos pueden ser opcionalmente sustituida. Cuando R^6 está comprendida de una

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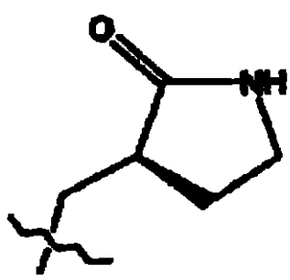
mitad de hidrocarburo saturado y una mitad de hidrocarburo no saturado, la mitad de hidrocarburo saturado puede ser unida a una mitad de hidrocarburo no saturado que contiene uno o más uniones dobles o uniones triples, las posiciones terminales de las cuales pueden ser sustituidas por los sustituyentes descritos arriba, o pueden contener mitades de hidrocarburo saturado de cadena-ramificada o recta- adicionales. Preferiblemente la mitad de hidrocarburo no saturado contiene una unión doble o una unión triple, o posición(es) terminal de la cual puede opcionalmente contener una mitad de hidrocarburo saturado de cadena-ramificada o recta-. Preferiblemente, si la mitad de hidrocarburo no saturada contiene una doble unión, ambas posiciones terminales de la unión doble contienen una mitad de hidrocarburo saturado de cadena-ramificada o recta-. En modalidades especialmente preferidas, R^6 es H o un alquilo inferior sustituido o no sustituido, arilalquilo, heteroarilalquilo, grupo cicloalquilo, o un grupo comprendido de una mitad de hidrocarburo saturada de cadena-recta y una mitad de hidrocarburo no saturado. Preferiblemente, R^6 es H, metilo, metilo sustituido, etilo, n-propilo, n-butilo, sec-butilo, 2-propin-1-ilo, 3-metil-3-buten-1-ilo, metilciclohexilo, metiltienilo sustituido o no sustituido o benzilo sustituido o no sustituido, en los cuales la mitad fenilo de benzilo sustituido es sustituido por uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino o halógeno y la mitad tienilo del –metiltienilo sustituido es sustituido por uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino o halógeno. Cuando R^6 es metilo sustituido, la mitad de metilo (metileno) puede ser sustituida con un grupo alcoxi, un grupo ariloxi, un grupo alquiltio o un grupo ariltio. Más preferiblemente, R^6 es H, etilo, 2-propin-1-ilo, -metilciclohexilo, o bencilo sustituido o no sustituido, en los cuales la mitad de fenilo del bencilo sustituido es sustituido por uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior y halógeno.

765

En modalidades especialmente preferidas de las Fórmulas I-a, I-b, I-c, I-d y I-e, R^9 es seleccionada de $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$-alquilo; $-CH_2NHC(O)CH_3$; y



, donde n es 1 o 2. Más preferiblemente,

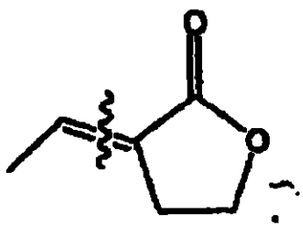


R^9 es .

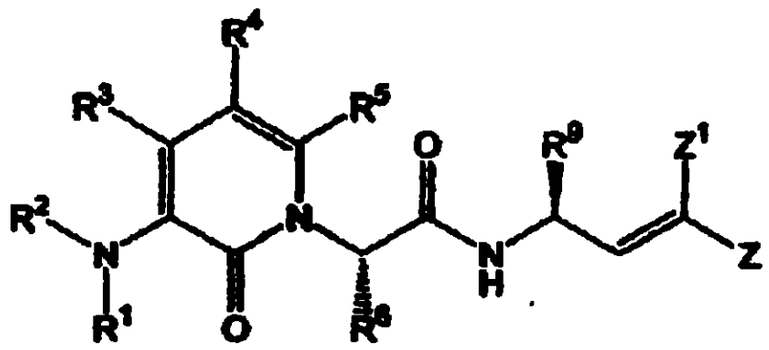
Preferiblemente, en los compuestos de las Fórmulas I-a, I-b, I-c, I-d y I-e, Z y Z^1 son independientemente H, alquilo sustituido o no sustituido, $-CO_2R^{18}$, o tomados juntos con el átomo al cual ellos están unidos, forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido. Más preferiblemente, Z y Z^1 son independientemente seleccionados de H, $-CO_2H$, alquilo sustituido o no sustituido inferior, $-CO_2$alquilo, $-CO_2$-cicloalquilo o tomados juntos con el átomo al cual ellos están unidos forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido. El grupo heterocicloalquilo puede opcionalmente contener O, N, S y/o P y puede ser sustituido por uno o más de oxo (keto) o tioketo. Más preferiblemente, Z^1 es H o alquilo inferior y Z es $-CO_2H$, $-CO_2$-alquilo sustituido o no sustituido, $-C_2$-cicloalquilo o tomados juntos con el átomo al cual ellos están unidos forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido. Los grupos ejemplares Z incluyen, pero no están limitados a grupos $-CO_2$-alquilo sustituido y no sustituido los cuales incluyen grupos

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alcali de cadena ramificada y recta tales como hetoxicarbonilo, t-butoxicarbonilo, isopropopxicarbonilo (2,2-dimetilpropil)-oxicarbonilo, y similares, grupos $-CO_2$-cicloalquilo sustituido y no sustituido tal como $-CO_2$ciclopentilo o tomados juntos con Z^1 y el atomo al cual ellos están unidos forman



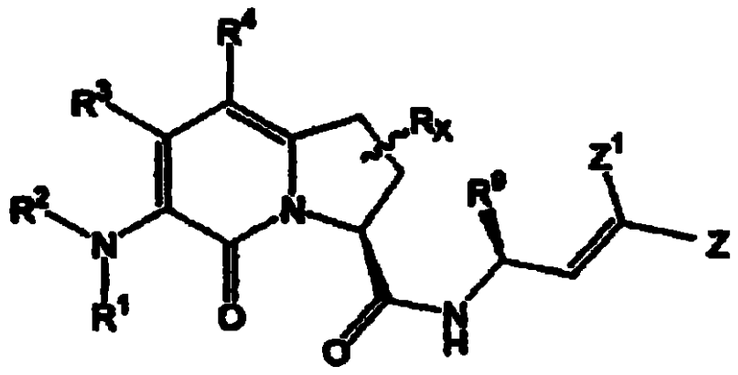
Las modalidades especialmente preferidas de esta invención comprenden compuestos de las Fórmulas I-a', I-b', I-c', I-d' y I-e' como sigue:



I-e'

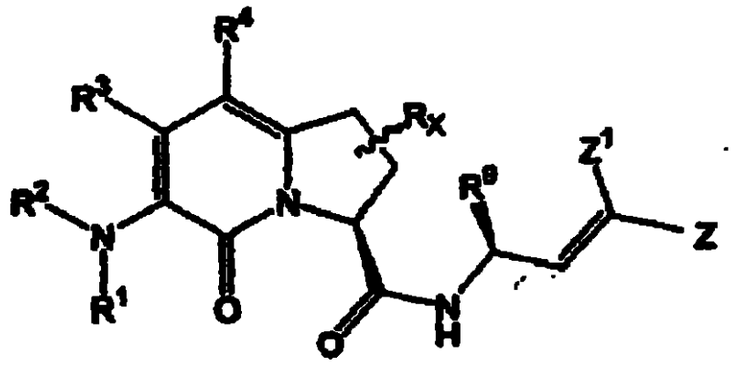
en la cual R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z y Z^1 son tal como se definieron previamente;

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I-b'

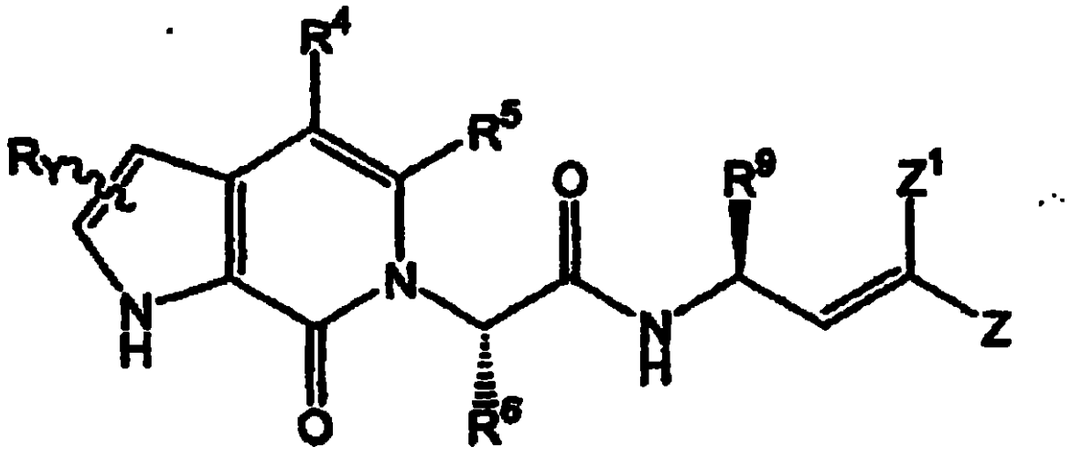
en la cual R^1, R^2, R^3, R^4, R^9, R_x, Z y Z^1 son tal como se definieron previamente;



I-b'

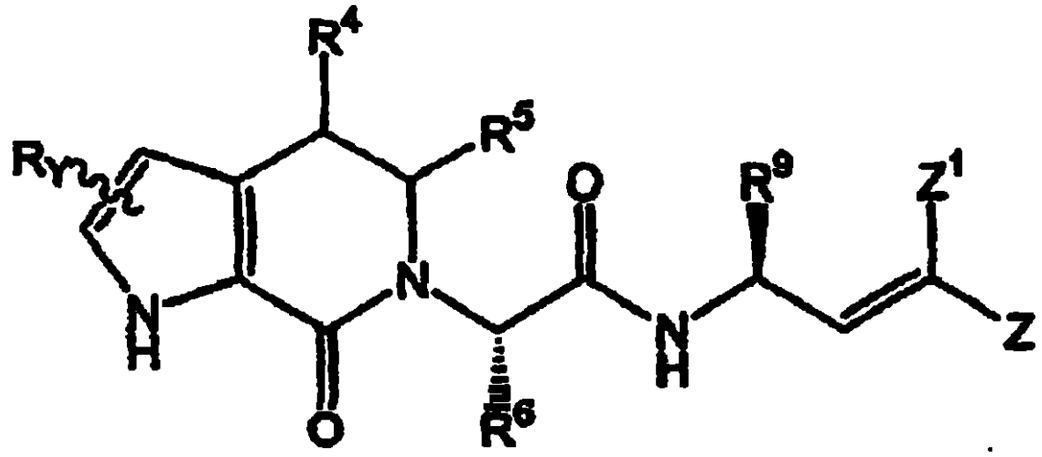
en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son tal como se definieron previamente;

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I-d'

en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son tal como se definieron previamente; y



I-e'

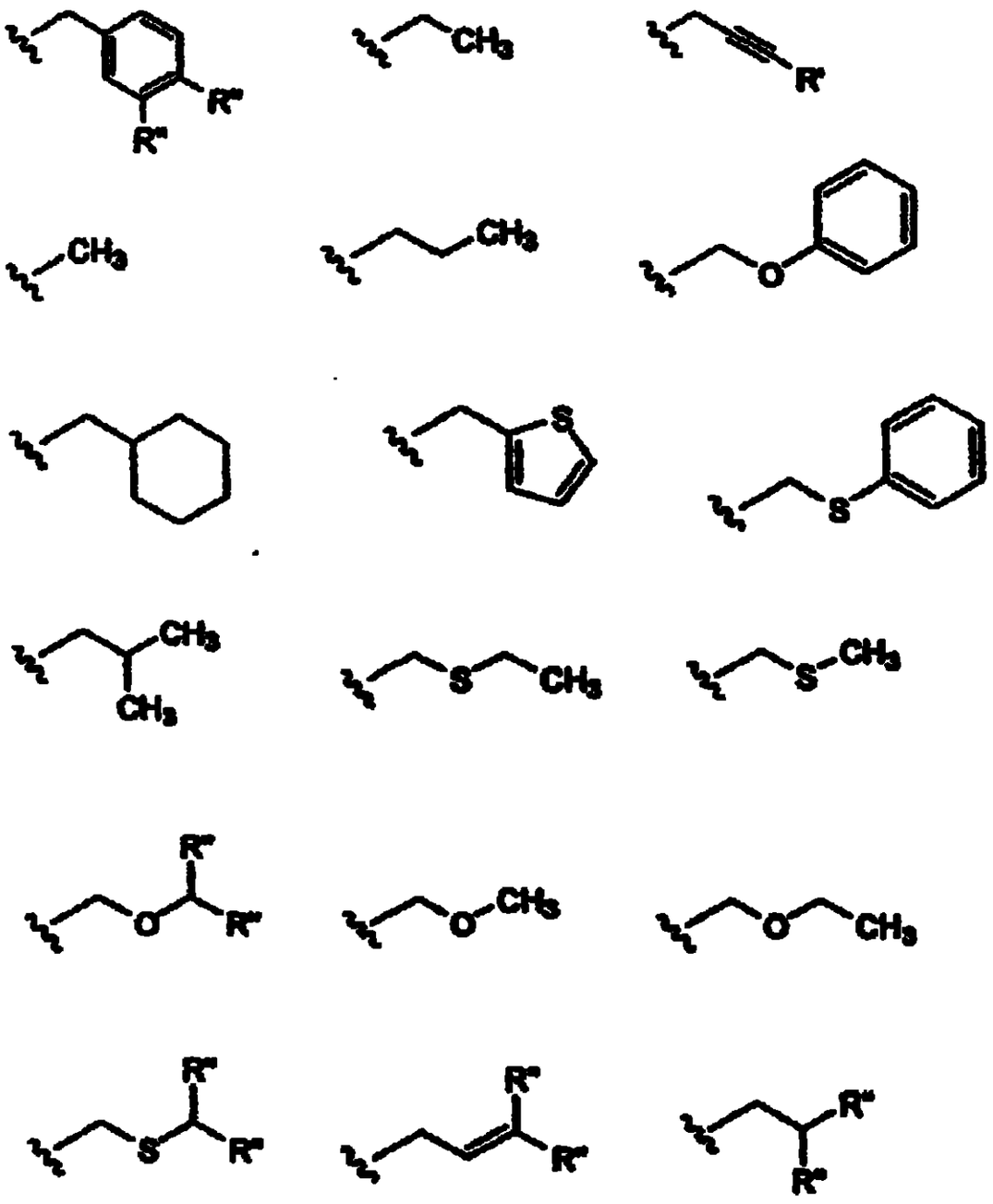
en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son tal como se definieron previamente.

En modalidades especialmente preferidas de las Fórmulas I-a' y I-b', R^2 es bencilioxicarbonilo sustituido o no sustituido, arilioxicarbonilo, o heteroarilicarbonilo, más preferiblemente

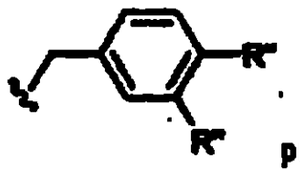
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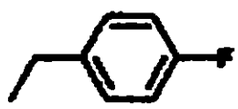
heteroarilcarbonilo, donde la mitad heteroarilo es un heterociclo de cinco-miembros que tienen de uno hasta tres heteroátomos seleccionados de O, N, y S. Más preferiblemente R^2 es heteroarilcarbonilo en el cual la mitad heteroarilo es un heterociclo de cinco-miembros que tiene por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxígeno (por ejemplo, 1,2-oxazolilo sustituido o no sustituido (es decir, isoxazolilo), 1,3-oxazolilo (es decir, oxazolilo), u oxadiazolilo (1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo); los oxadiazolilos preferidos no son suetituidos y monometil-sustituido 1,2,4-oxadiazolilo. En modalidades especialmente preferidas la mitad heteroarilo es 3-isoxazolilo o 5-isoxazolilo, ya sea sustituida o no sustituida con uno o dos sustituyentes seleccionados de metilo y halógeno, con cloro y fluoro siendo sustituyentes de halógeno preferidos.

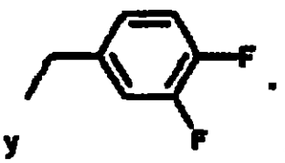
En las modalidades especialmente preferidas de las Fórmulas I-a', I-b', I-c', I-d' y I-e', R^6 es seleccionada de H o:



en la cual R' puede ser H o alquilo y R'' pueden ser H o independientemente de alquilo inferior, alcoxi inferior, hidroxi, amino, alquilamino o dialquilamino, y halógeno.

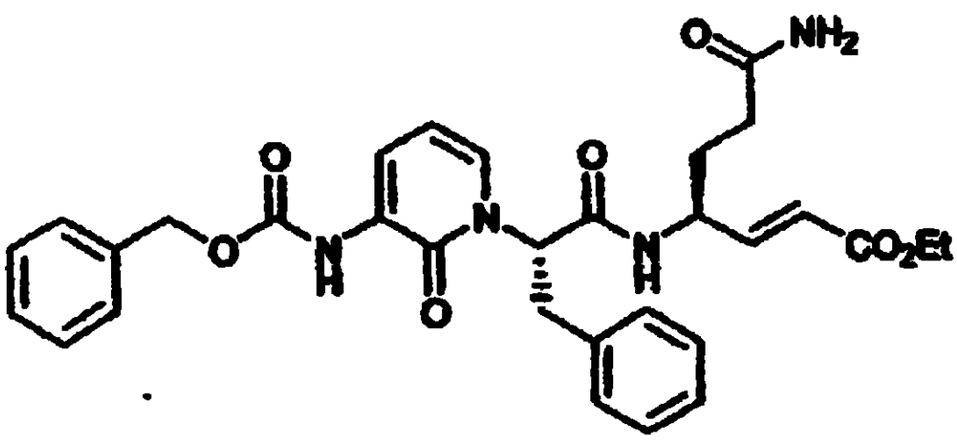


Grupos  preferidos son

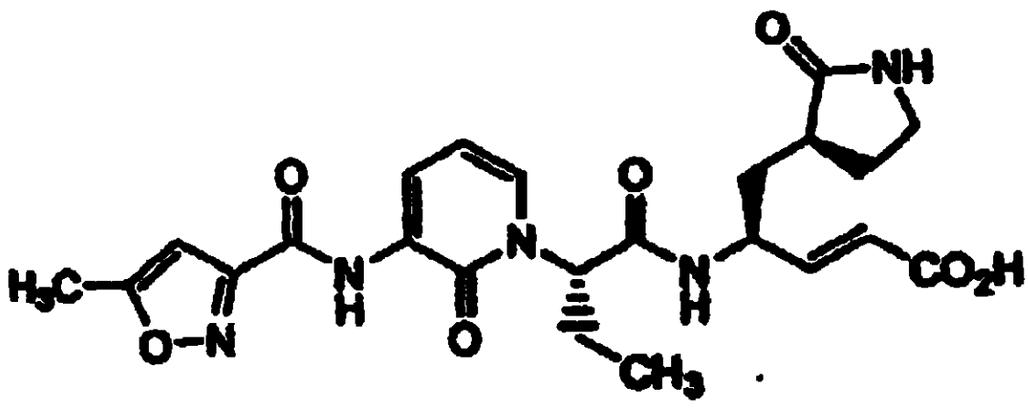


y .

Los compuestos específicos preferidos incluyen aquellos de los Ejemplos abajo, especialmente:



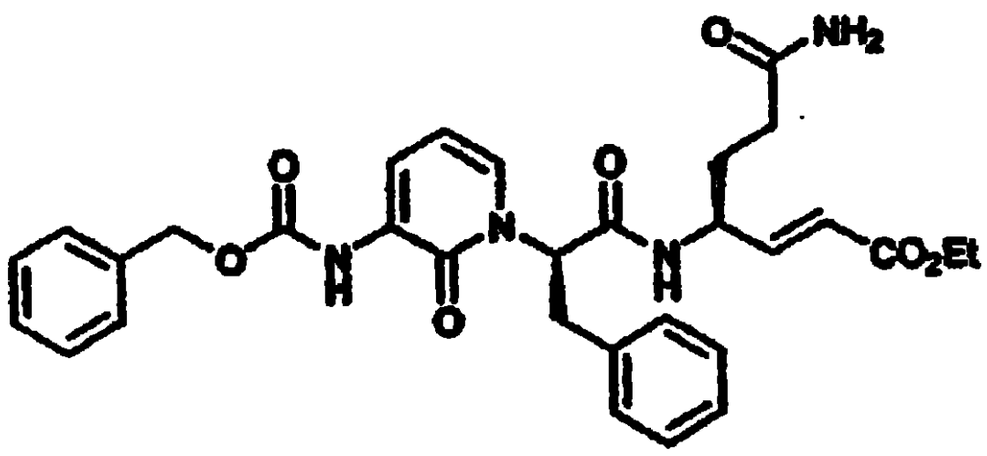
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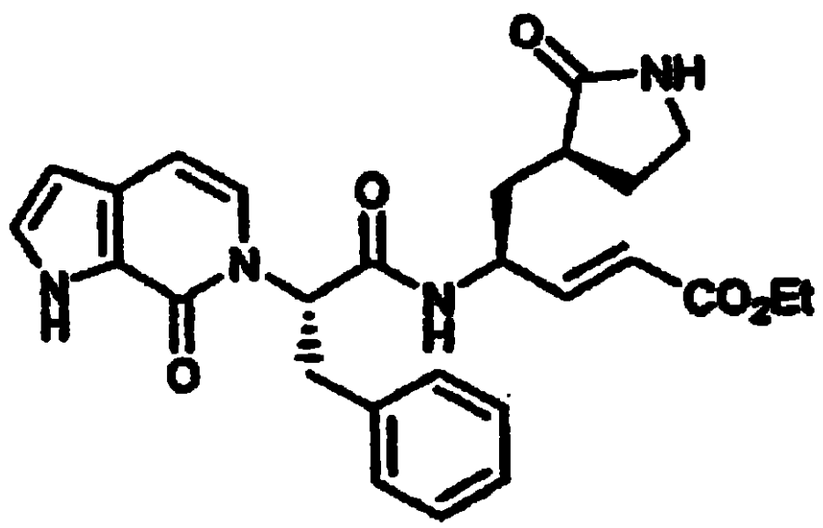
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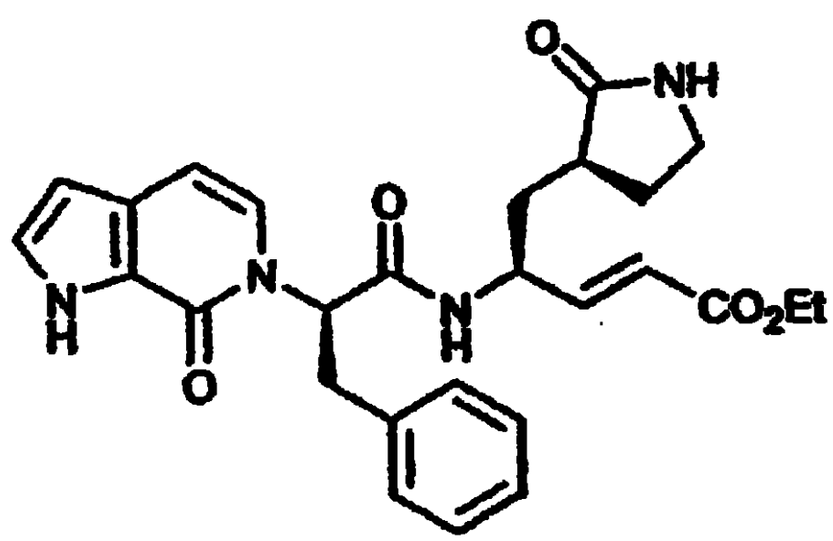
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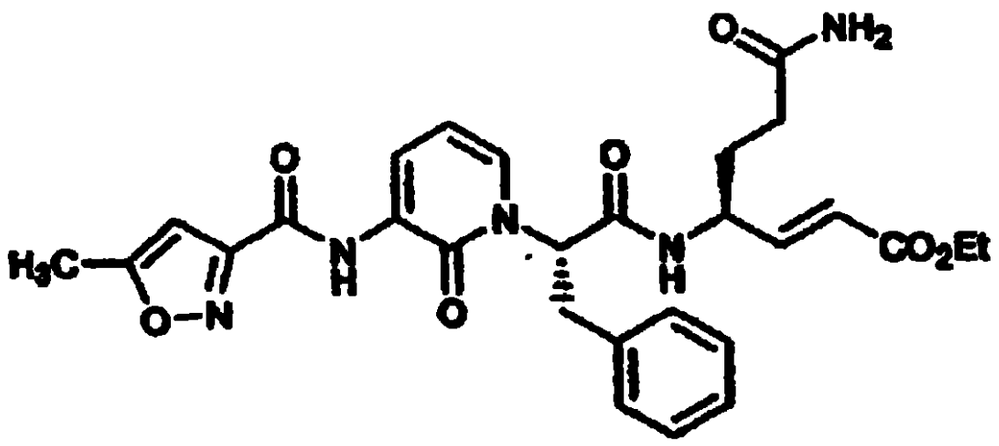


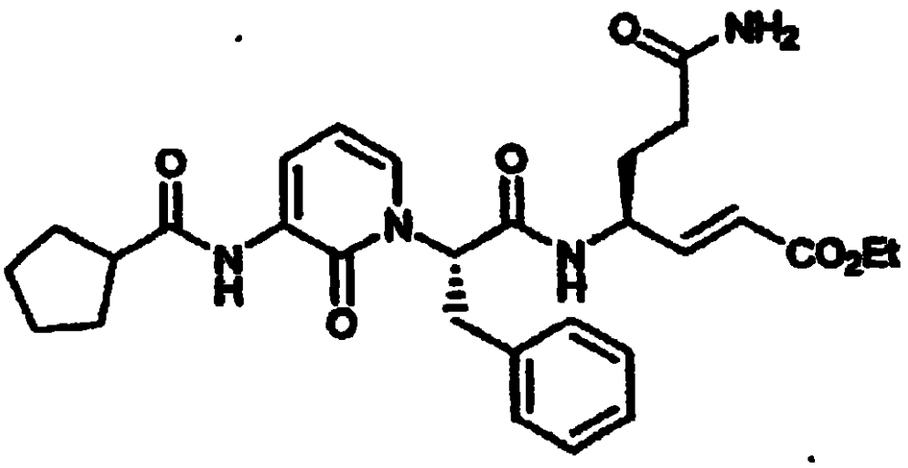
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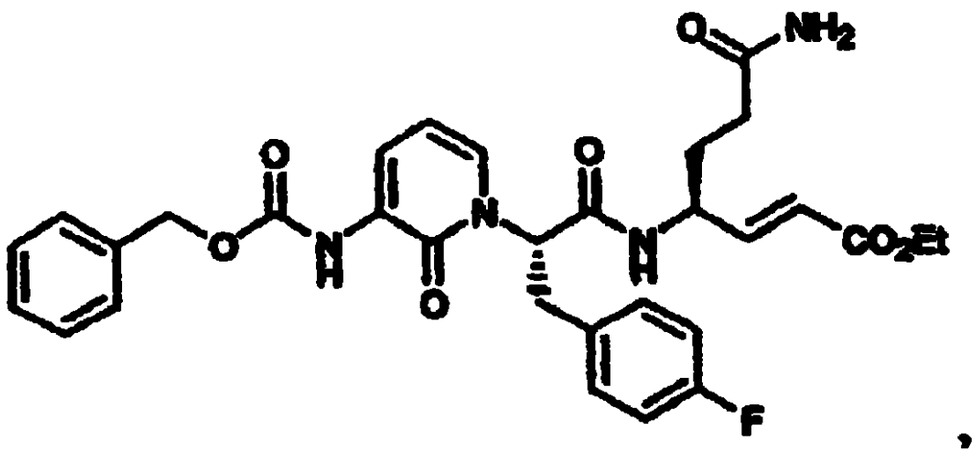


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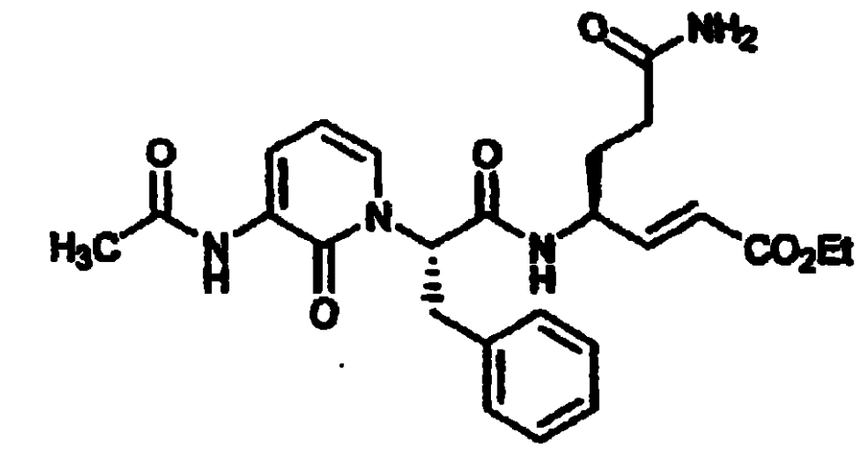
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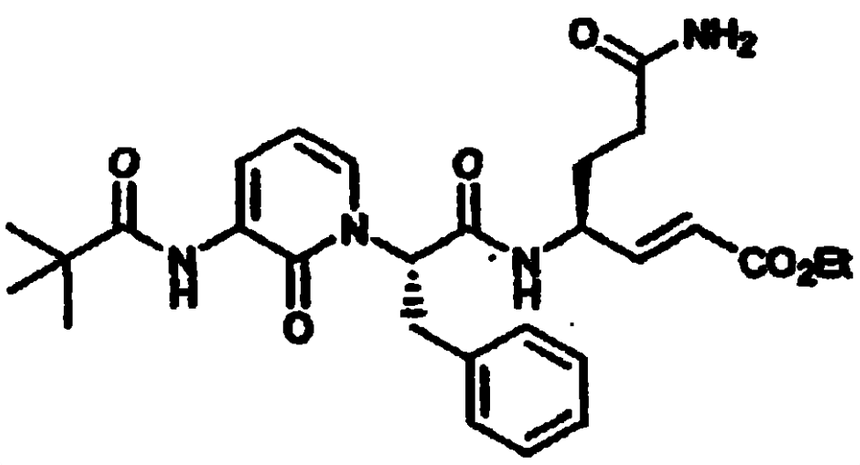


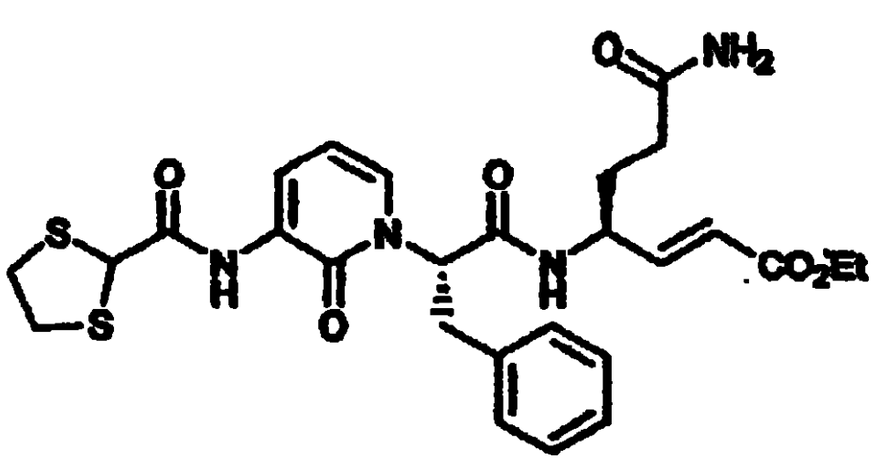




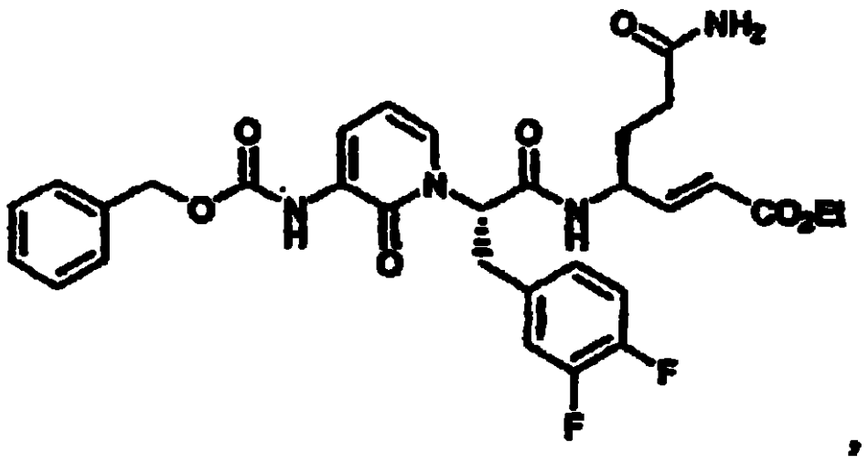
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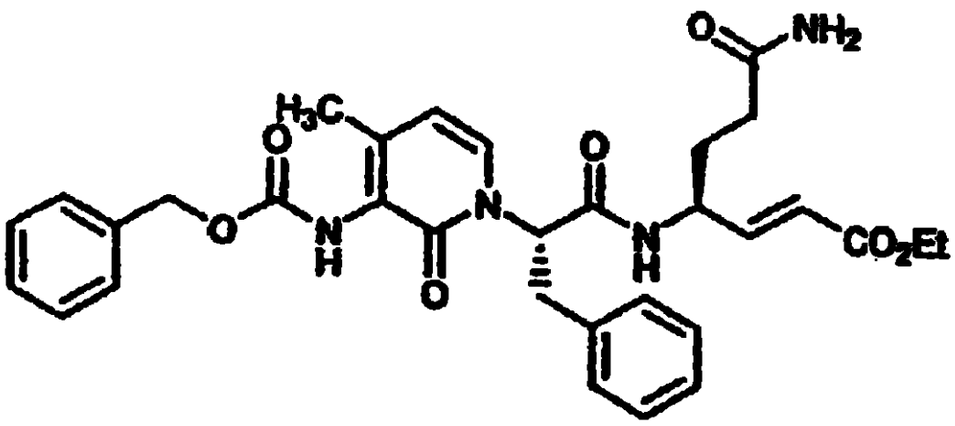


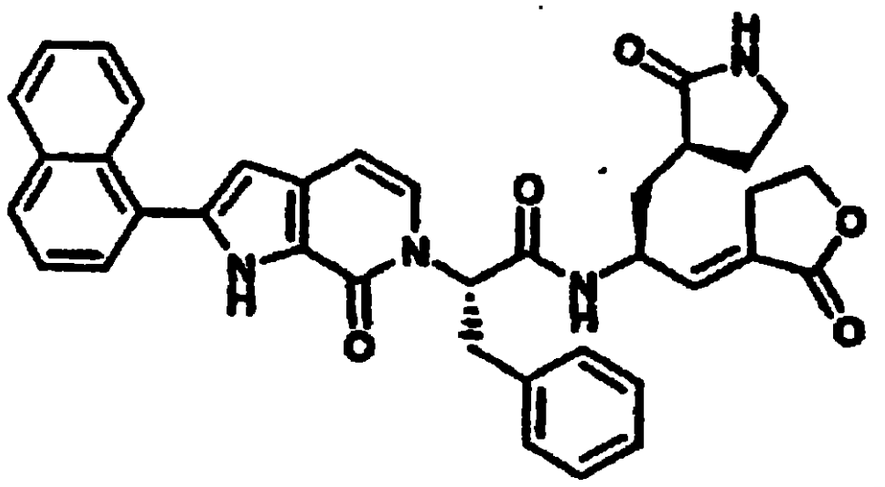




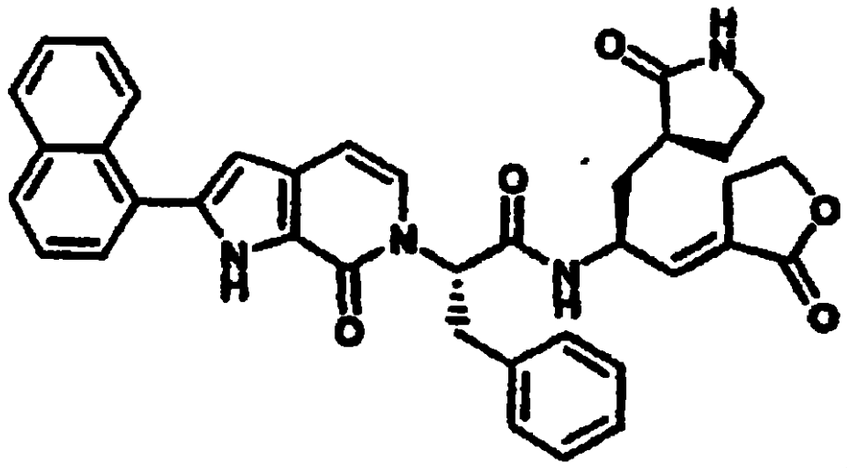
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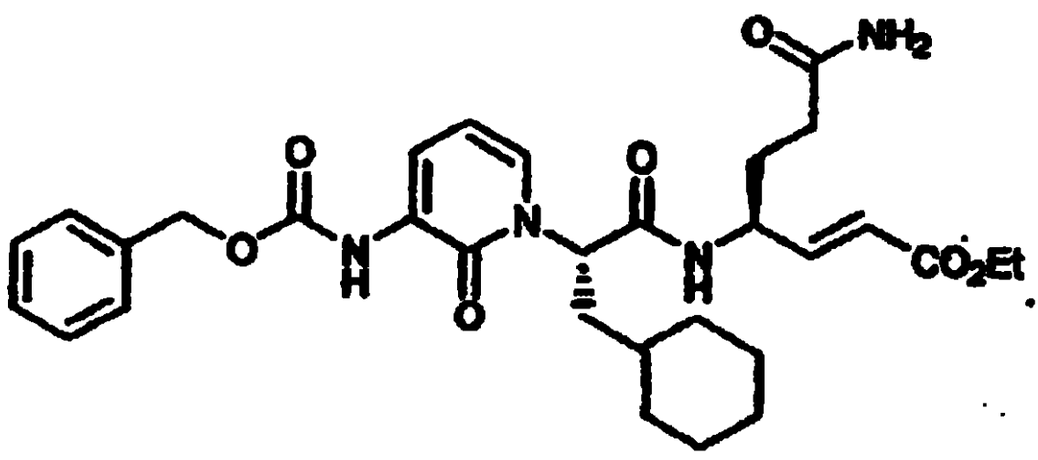


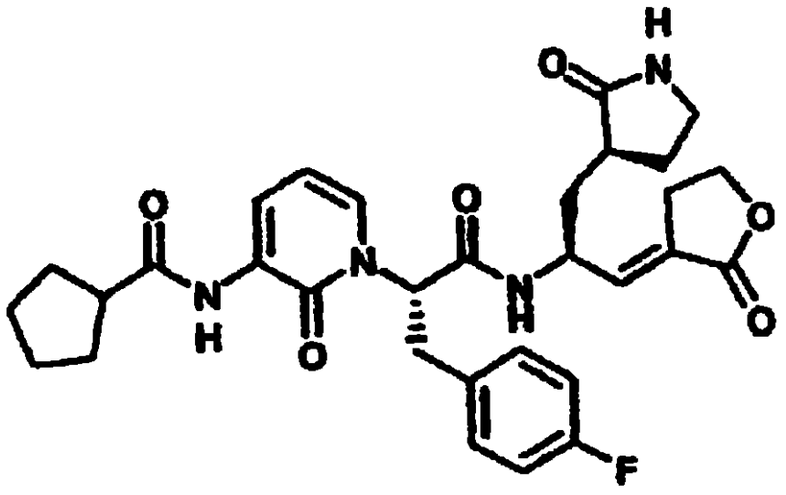




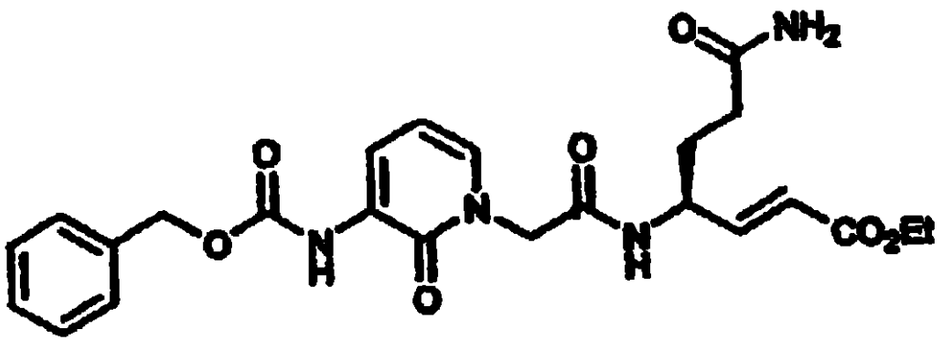
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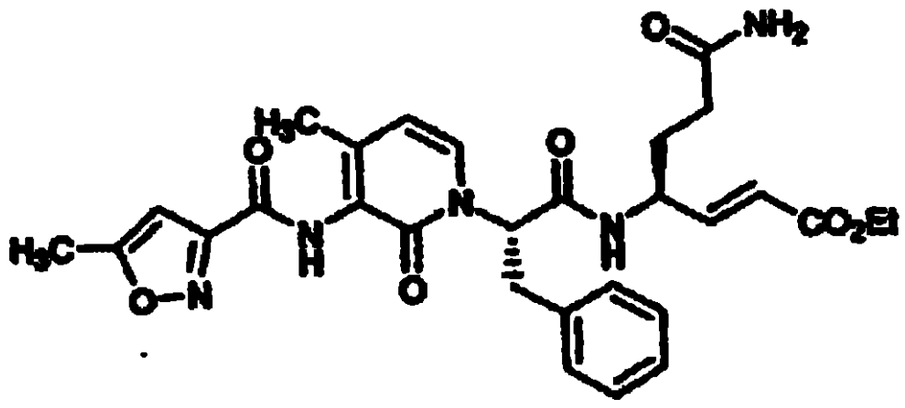


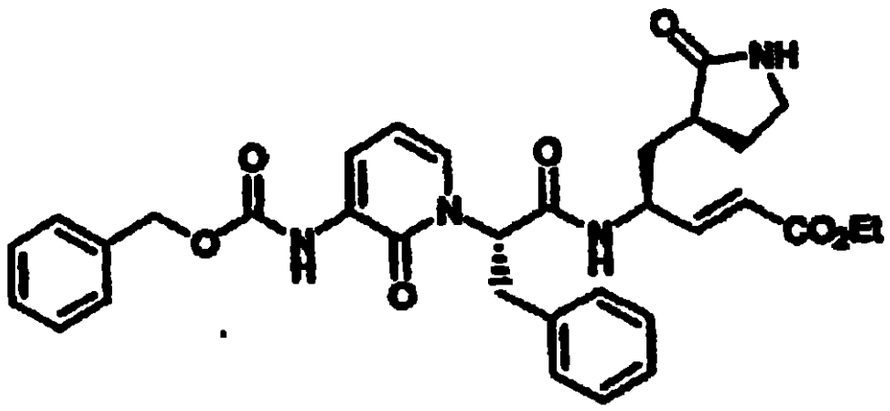


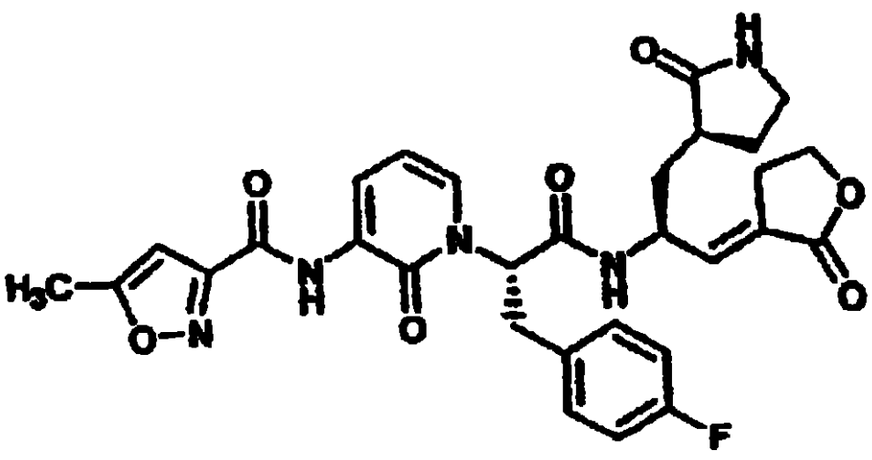


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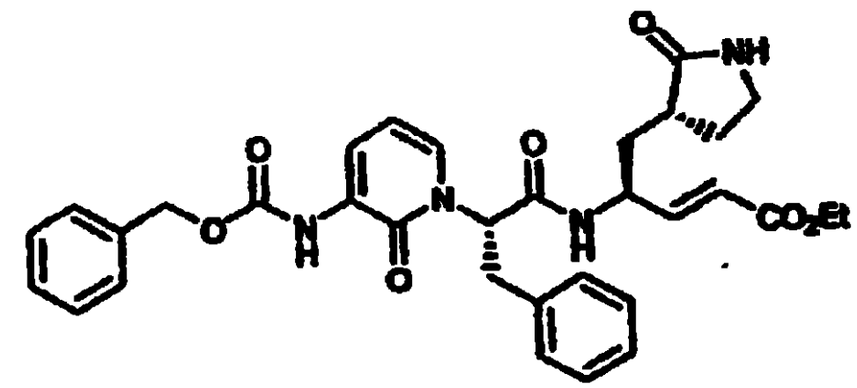




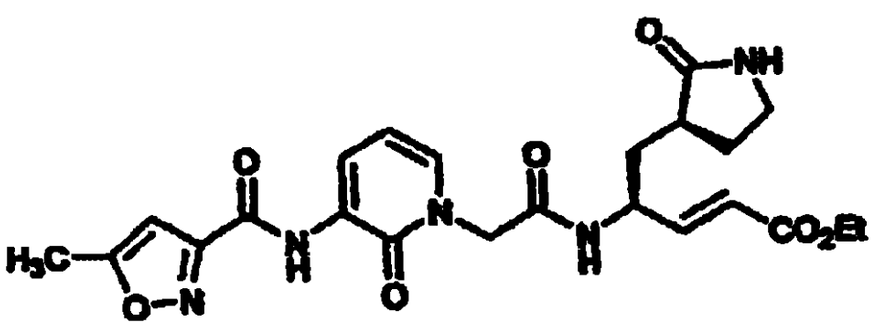




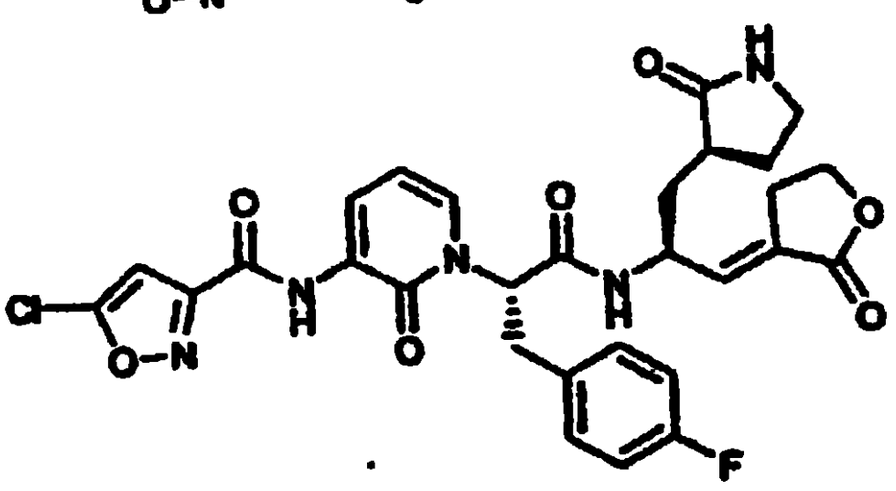
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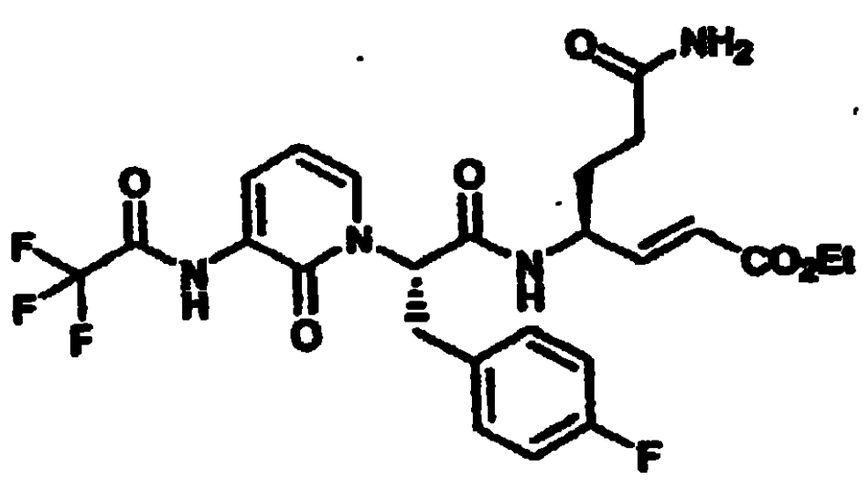
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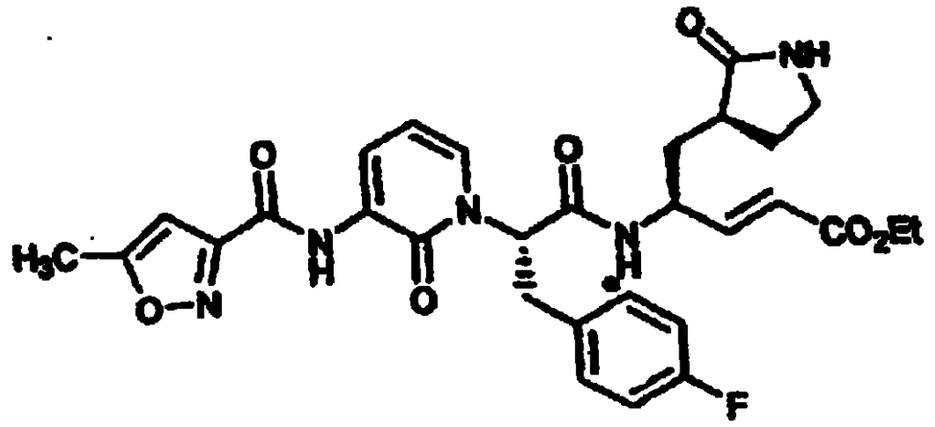
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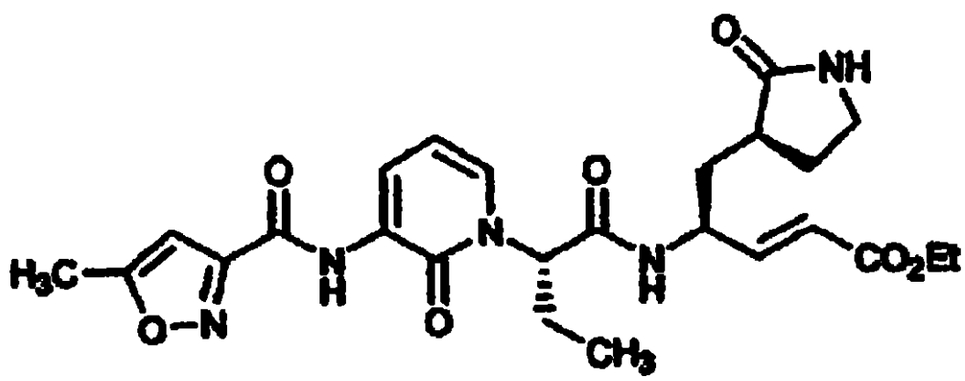


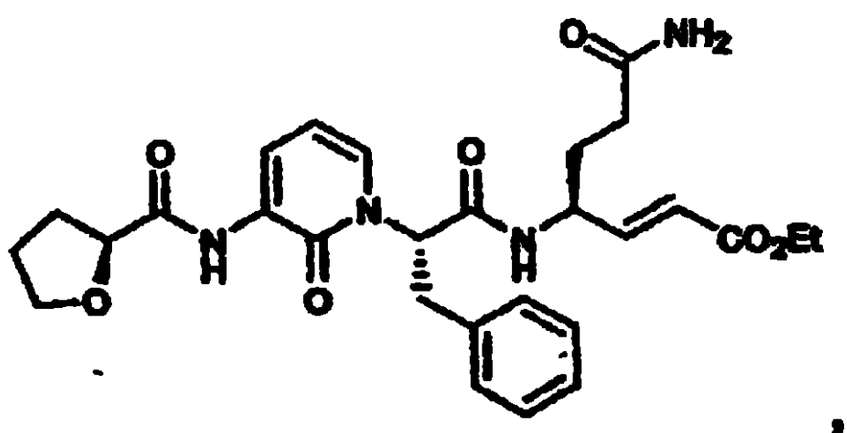
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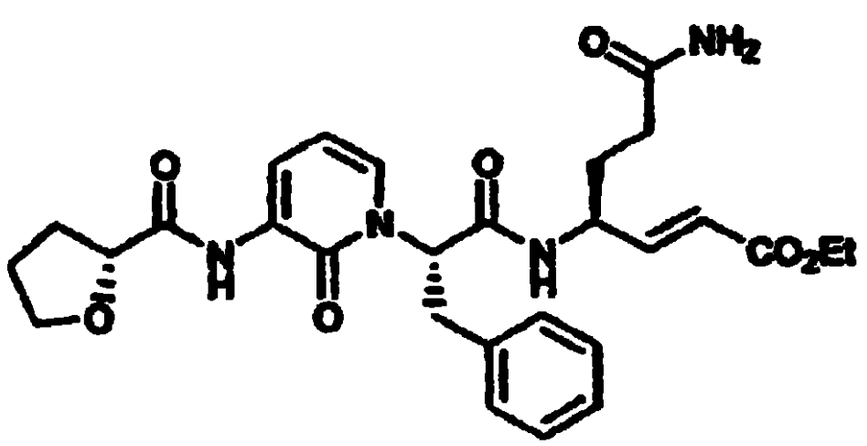
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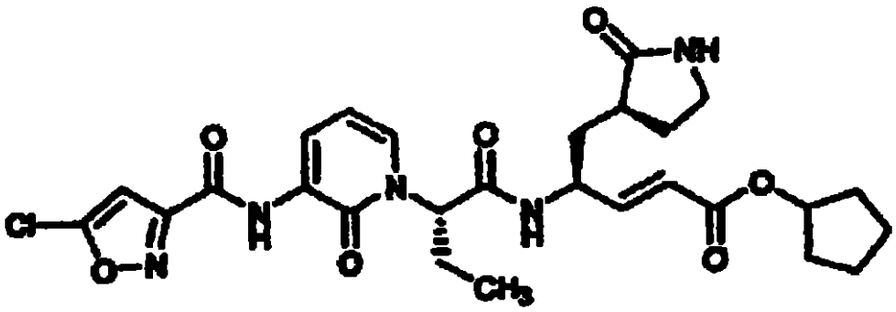


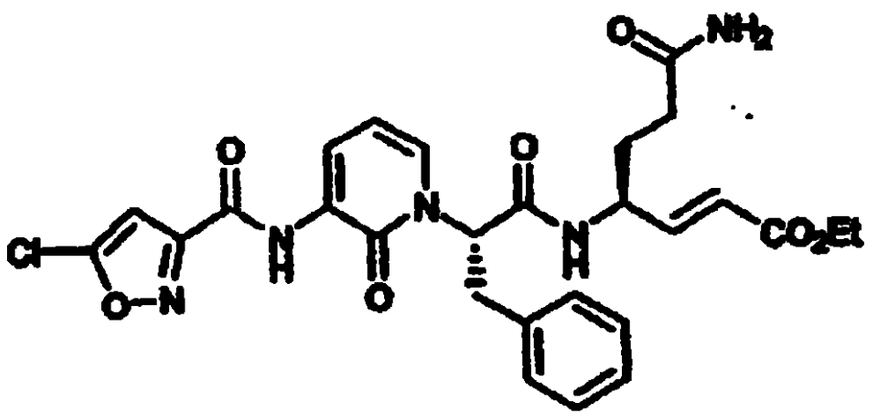


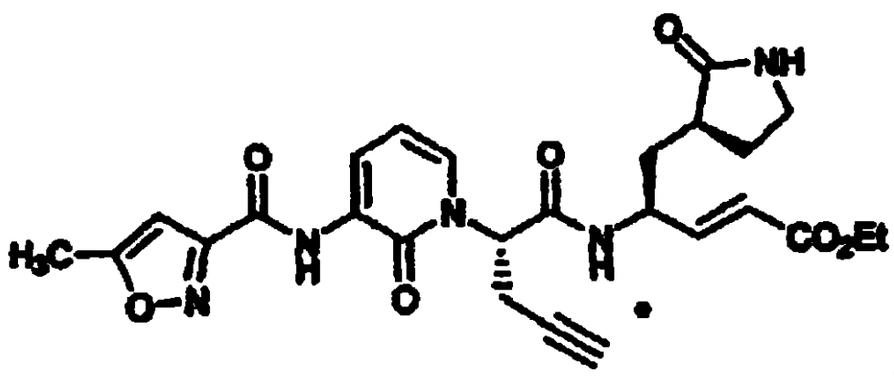


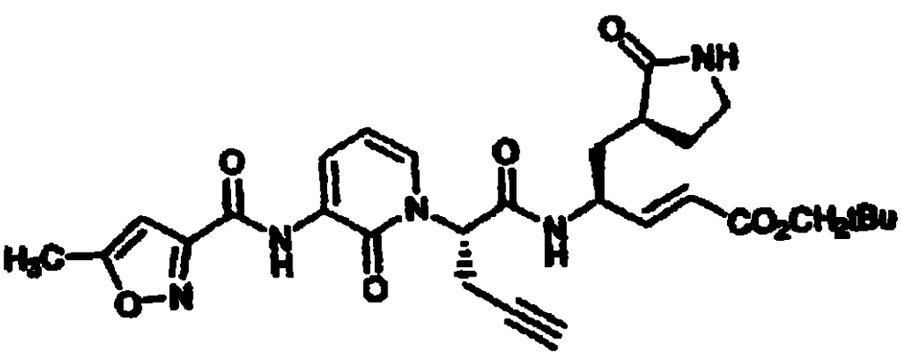


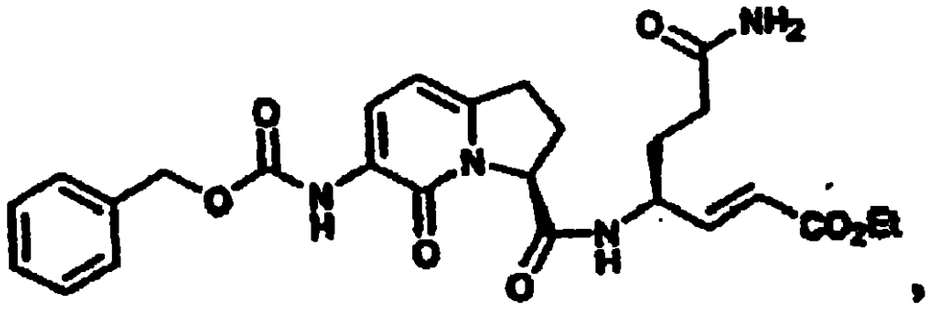
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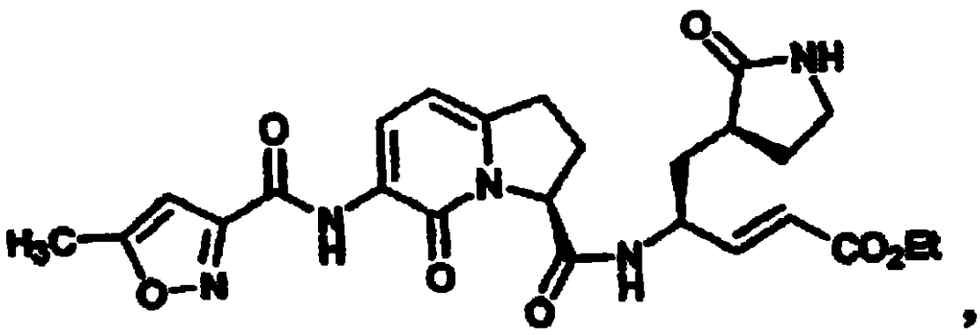


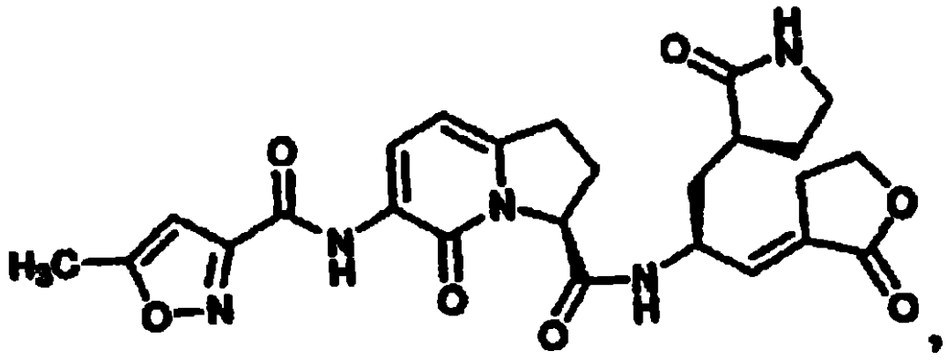


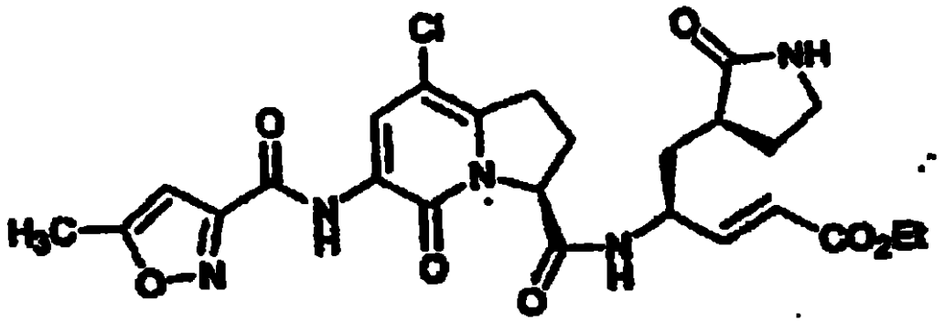






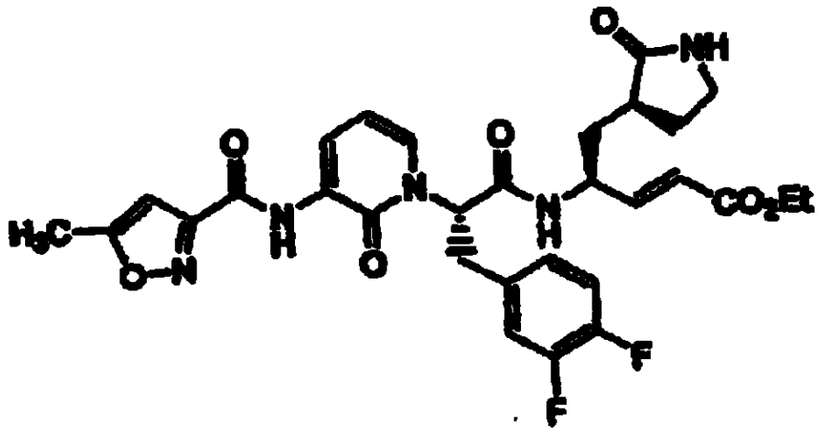


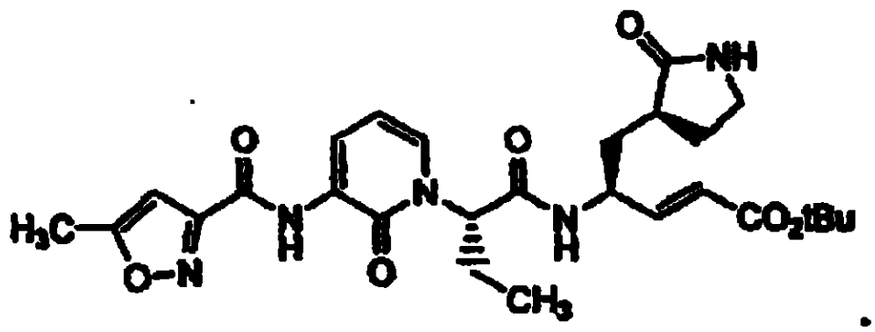




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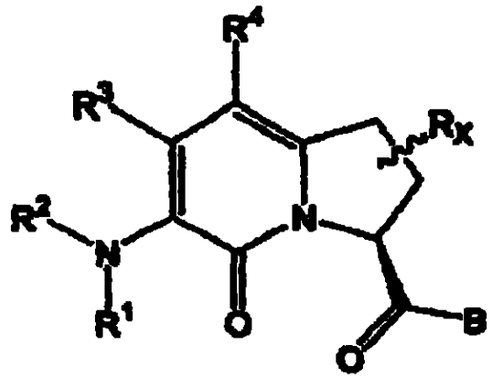
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y

La invención está también dirigida a los intermediarios de la Fórmula II, los cuales son útiles en la síntesis de ciertos compuestos de la Fórmula I:



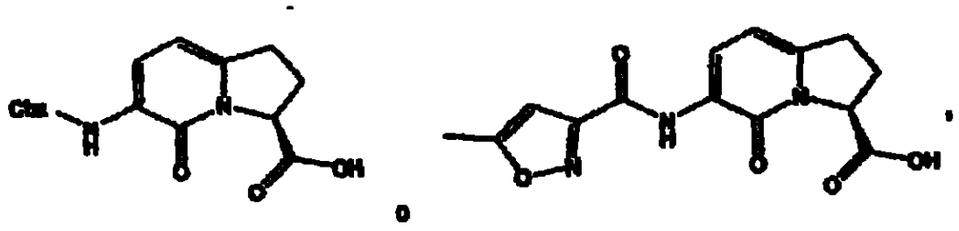
II

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en la cual las variables R^1, R^2, R^3, R^4 y R_x son como se han definido arriba, y B es H, $-OR^{24}$. Cuando R^1 y/o R^2 son independientemente grupos protectores de nitrógeno adecuable, cualquier grupo protector de nitrógeno adecuable conocido en el arte puede ser usado (ver, por ejemplo, Greene & Wuts, supra). Los sustituyentes adecuables R^1 y R^2 incluyen, pero no están limitados a, grupos protectores de carbamato tales como alquiloxicarbonilo (por ejemplo, Boc) y ariloxicarbonilo (por ejemplo, Cbz o FMOC), alquiloxicarbonilos (por ejemplo, metoxicarbonilo), alquilo o arilcarbonilo, alquilo sustituido, especialmente arilalquilo (por ejemplo, tritilo (trifenilmetilo), bencilo y bencilo sustituido) y similares. Preferiblemente, cuando R^1 y R^2 son independientemente grupos protectores de nitrógeno adecuados, el adecuable R^1 y sustituyentes R^2 incluyen, pero no están limitados a, Boc, y Cbz, FMOC, metiloxicarbonilo y tritilo. Cuando R^1 y R^2 tomados juntos son un grupo protector de nitrógeno adecuable, los sustituyentes adecuables R^1/R^2 incluyen ftalimido y una estabase (1,2-bis(dialquil))etileno). R^{24} puede ser H o un grupo protector adecuable para una mitad carbonilo. Los grupos protectores de carbóxilo adecuados son también bien conocidos en el arte, ejemplos de los cuales pueden encontrarse en Greene y Wuts, supra, e incluye, pero no están limitados a, grupos protectores donde R^{24} es alquilo, un arilo sustituido o no sustituido, alquilo y/o sililo sustituido de arilo (por ejemplo t-butildimetilsililo(TBS)), y similares.

La invención está también dirigida a sales farmacéuticamente aceptables de los compuestos de la Fórmula II. Los ejemplos preferidos de la Fórmula II útiles como intermediarios incluyen los siguientes:

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y *sales farmacéuticamente aceptables de éstos.*

Los compuestos antipicornavirales de esta invención incluyen prodrogas, los metabolitos farmacéuticamente activos, y las sales farmacéuticas aceptables y solubles de éstos. En modalidades *preferidas, los compuestos de la Fórmula I, prodrogas, sales* farmacéuticamente aceptables, la actividad antirinoviral más preferiblemente, correspondiente a un EC_{50} menos de o igual a 100 μM en el ensayo de cultivo de célula H1-HeLa. Una "prodroga" está destinada para significar un compuesto que es convertido bajo *condiciones fisiológicas o por solvólisis o metabólicamente a un* compuesto especificado que es un compuesto farmacéuticamente activo producido a través de metabolismo en el cuerpo de un compuesto especificado. Una "sal farmacéuticamente aceptable" está destinada para significar una sal que retiene la efectividad *biológica de los ácidos y bases libres de un compuesto especificado* y que no es biológicamente o de otra manera indeseable. Los ejemplos de sales farmacéuticamente aceptables incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, monohidrogenofosfatos, dihidrogenofosfato, metafosfatos, *pirofosfatos, cloruros, bromuros, yoduros, acetatos, propionatos,* decanoatos, caprilatos, acrilatos, formatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, subacatos, fumaratos, maleatos, butino-1,4-dioatos, hexina-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, *dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos,* sulfonatos silenosulfonatos, feniliacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos, tartratos, metano-sulfonatos, propanosulfonatos, naftaleno-1-

sulfonatos, naftaleno-2-sulfonatos, y mandelatos. Un "soluble" está destinado para significar una forma soluble farmacéuticamente aceptable de un compuestos especificado que retiene la efectividad biológica de tal compuesto. Los ejemplos de solubles incluyen compuestos de la invención en combinación con agua, isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético, o etanolamina. En el caso de compuestos, sales, o solubles que son sólidos, queda entendido por aquellos versados en el arte que los compuestos de la invención, sales, y solubles pueden existir en diferentes formas de cristal, todas las cuales están destinadas a estar dentro del alcance de la presente invención y fórmula especificadas.

La presente invención está también dirigida a un método de inhibir de actividad de proteasa picornaviral 3C, comprendiendo contactar la proteasa con una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable, prodroga, metabolito farmacéuticamente activo, o soluble de éstos. Por ejemplo, la actividad de proteasa picornaviral 3C puede ser inhibida en tejido de mamífero administrando un compuesto de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito farmacéuticamente activo, o soluble de éstos. Más preferiblemente, el presente método está dirigido a inhibir actividad de proteasa rinoviral. "Tratamiento" o "tratamiento" está destinado a significar por lo menos la mitigación de una condición de enfermedad en un mamífero, tal como un humano, que es aliviado por la inhibición de la actividad de poliovirus humano, coxsaquieviruses humanos, viruses de encefalomiocarditis, virus de meningitis, y virus de hepatitis A. Los métodos de tratamiento para la mitigación de una condición de enfermedad incluyen el uso de los compuestos de esta invención en cualquier forma convenientemente aceptable, por ejemplo, tal como un profiláctico. La actividad de los compuestos de la invención como inhibidores de actividad de proteasa picornaviral 3C puede ser medida por cualquiera de los métodos adecuados conocidos por aquellos versados en el arte, incluyendo ensayos in

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vivo e in vitro. Como ejemplo de un ensayo adecuable para actividad de medida en el ensayo de cultivo de célula antiviral H1-HeLa descrito aquí en la presente.

La administración de los compuestos de la Fórmula I, y sus prodrogas, sales, metabolitos activos farmacéuticamente aceptables y solubles pueden ser llevados a cabo de acuerdo con cualquiera de los modos aceptados generalmente de administración disponibles para aquellos versados en el arte. Los ejemplos ilustrativos de modos adecuables de administración incluyen oral, nasal, parenteral, tópico, transdérmico, y rectal.

Un compuesto de la invención de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito activo, o soluble de éste puede ser administrado como una composición farmacéutica en cualquier forma farmacéutica reconocible para los artesanos versados como siendo adecuable. Las formas farmacéuticas adecuables incluyen sólidos, semisólidos, líquido, o formulaciones liofilizadas, tales como tabletas, polvos, cápsulas, supositorios, suspensiones, liposomas, y aerosoles. Las composiciones farmacéuticas de la invención pueden también incluir excipientes adecuados, diluyentes, vehículos, y portadores, así como también otros agentes farmacéuticamente activos, dependiendo sobre el uso intentado o modo de administración. En modalidades preferidas, las composiciones farmacéuticas de la invención son entregadas oralmente, o intranasalmente en la forma de suspensiones. Los métodos aceptables de preparar formas farmacéuticas adecuadas de las composiciones farmacéuticas pueden ser rutinariamente determinados por aquellos versados en el arte. Por ejemplo, las preparaciones farmacéuticas pueden ser preparadas siguiendo técnicas convencionales de la química farmacéutica involucrando etapas tales como mezcla, granulación, y compresión cuando sea necesario para formas de tableta, o mezcla, presentación, y disolución de los ingredientes como sea apropiado, para dar los productos deseados para administración oral, parenteral, tópica,

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intravaginal, intranasal, intrabronquial, intraocular, intraaural, y/o rectal.

Los portadores, diluyentes, vehículos, o excipientes farmacéuticamente aceptables líquidos o sólidos pueden ser empelados en las composiciones farmacéuticas. Los portadores sólidos ilustrativos incluyen almidón, lactosa, dihidrato de sulfato de calcio, terra alba, sacarosa, talco, gelatina, pectina, acacia, estearato de magnesio, y ácido esteárico. Los portadores líquidos ilustrativos incluyen jarabe, aceite de maní, aceite de oliva, solución salina, y agua. El portador y diluyente pueden incluir un material de soltura prolongado, tal como monoestearato de glicerilo o distearato de glicerilo, solo o con una cera. Cuando un portador líquido es usado, la preparación puede ser en la forma de un jarabe, elixir, emulsión, cápsula de gelatina blanda, líquido inyectable estéril (por ejemplo, solución), o una suspensión líquida acuosa o no acuosa. Una dosis de la composición farmacéutica contiene por lo menos una cantidad terapéuticamente efectiva del compuesto activo (es decir, un compuesto de la Fórmula I o una sal farmacéuticamente aceptable, prodroga, metabolito activo, o soluble de ésta), y preferiblemente está hecha de una o más unidades de dosificación farmacéutica. La dosis seleccionada puede ser administrada a un mamífero, por ejemplo, un paciente humano, en necesidad de tratamiento medicado para inhibición de la actividad de proteasa picornaviral 3C, por cualquier método conocido o adecuables de administración de dosis, incluyendo: tópicamente, por ejemplo, como un ungüento o crema; oralmente; rectal, por ejemplo, como un supositorio; parenteralmente por inyección; o continuamente por infusión intraocular, intraaural, intrabronquial, intranasal, intravaginal. Una "cantidad terapéuticamente efectiva" está destinada para significar la cantidad de un agente de la invención que, es administrado a un mamífero en necesidad de éste, es suficiente para efectuar tratamiento para condiciones de enfermedad aliviadas por la inhibición de la actividad de una o más proteasas picornavirales 3C, tales como rinoviruses, poliovirus

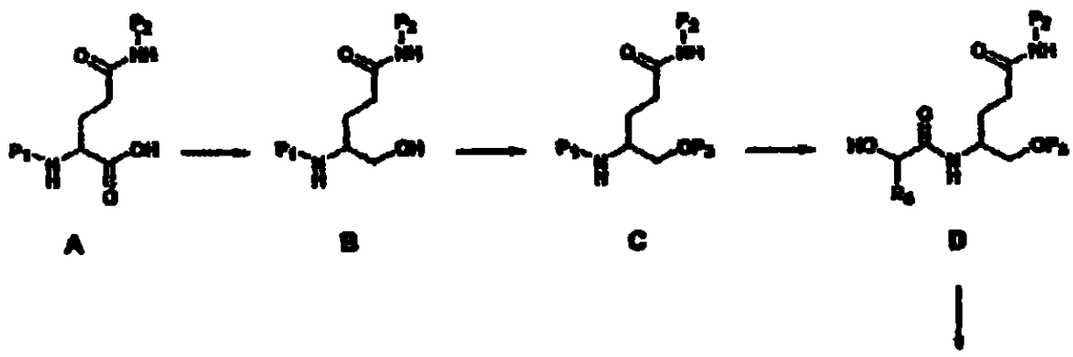
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humano, coxsaquieviruses humanos, viruses de encefalomiocarditis, menigovirus, y virus de hepatitis A. La cantidad de un compuesto dado de la invención que será terapéuticamente efectivo variará dependiendo sobre los factores tales como compuesto particular, la condición de enfermedad y la severidad de la misma, la identidad de un mamífero en necesidad de éste, dicha cantidad puede ser rutinariamente determinada por artesanos.

METODOS SINTÉTICOS GENERALES

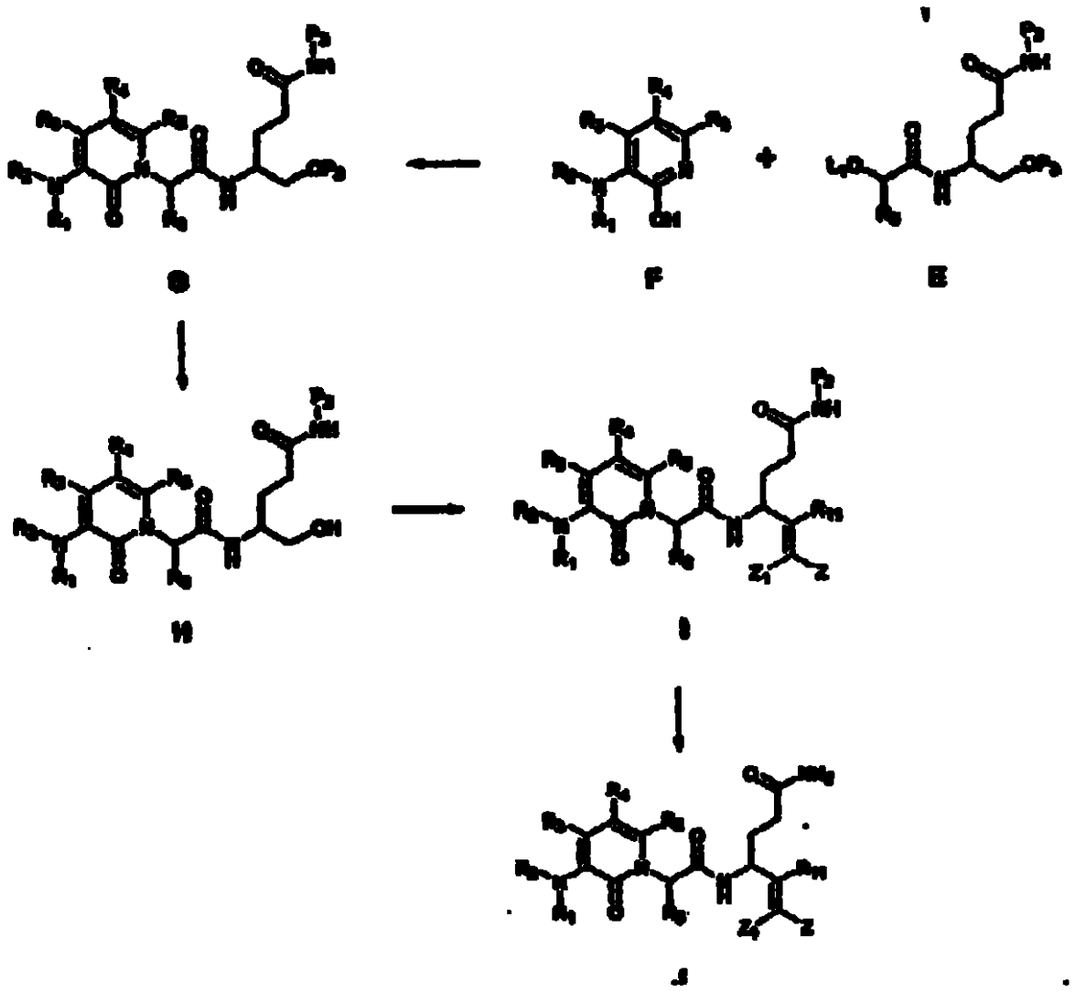
Preferiblemente, los compuestos de la invención de la Fórmula I y II son preparados por los métodos de la presente invención, que incluyen los *Métodos Generales* mostrados abajo. Cuando la estereoquímica en no está especificada las estructuras químicas, ya sea en estereocentro puede ser utilizada. Aunque varios intermediarios están descritos y determinados como 2-hidroxipiridinas, queda entendido que tales entidades pueden también existir como los correspondientes tautómeros 2-piridina. Las siguientes abreciaciones también se aplican: Boc (terl-butoxicarbonilo), Ac (acetilo), Cbz (benciloxicarbonilo), DMB (2,4-dimetoxibencilo), TBS (terl-butildimetilzililo), TBDPS (terl-butildifenilzililo), Ms (metanosulfonato), Ts (toluenosulfonato), Bn (*bencilo*), y Tr (*trifenilmetilo*).

Método General 1



A B C D

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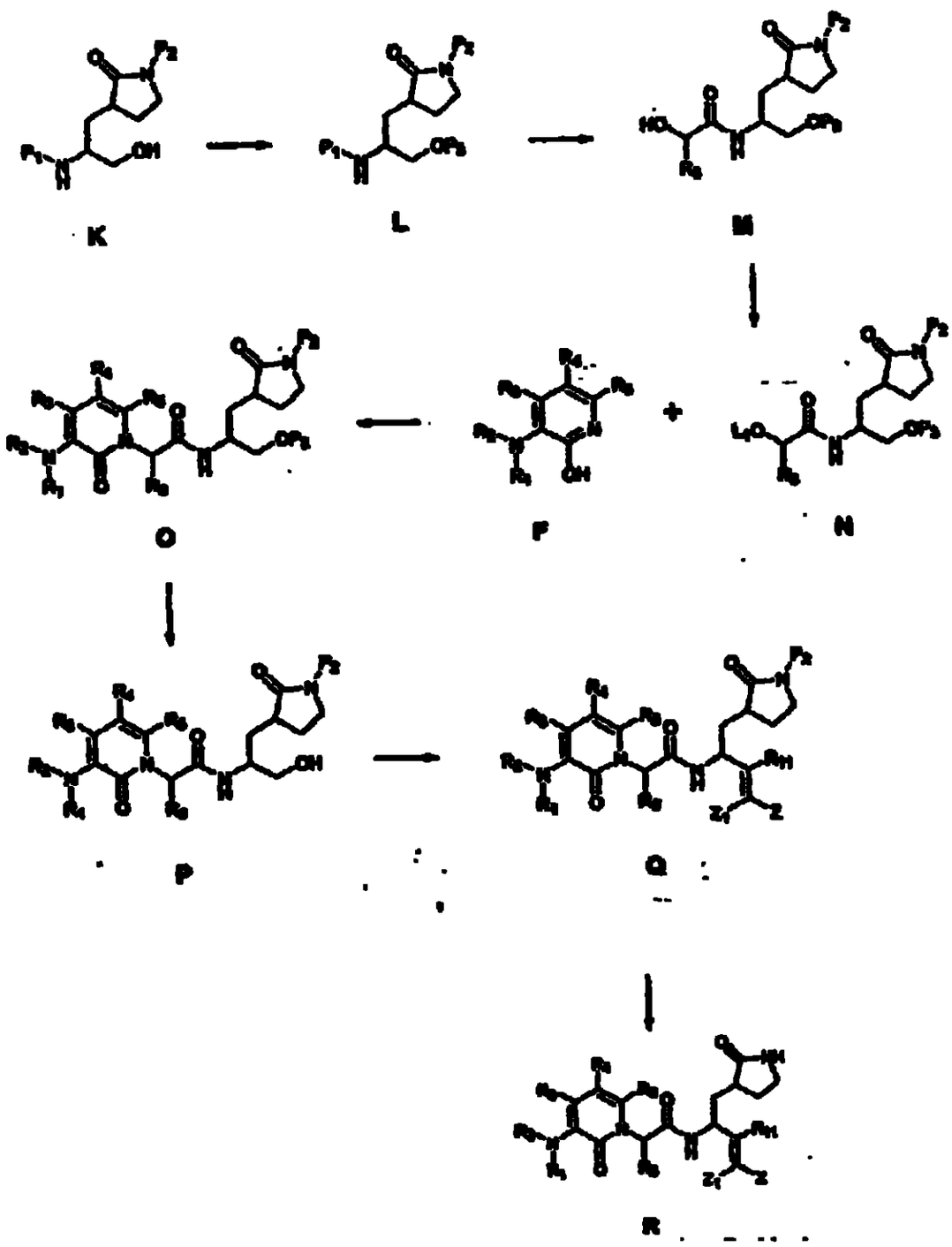
En el Método General 1, un amino ácido A (comercialmente disponible o preparado por métodos descritos en la literatura química) donde P_1 es un grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac), y P_2 es un grupo protector apropiado para el nitrógeno de amida (por ejemplo, Tr), es reductivamente transformada en alcohol B. El compuesto B es secuencialmente convertido a compuestos C donde P_3 es un grupo protector apropiado para la funcionalidad de alcohol (por ejemplo, TBS). En este punto, el grupo protecto P_1 presente en C es removido y la amina resultante o sal de éste (no mostrada) está sometida a una unión amida formando reacción con un ácido α-hidroxicarboxílico (el cual incorpora R_8 y en la cual R_7 es H; tampoco mostrados) para proporcionar intermediario D. La presente funcionalidad de alcohol en D es entonces convertida a un grupo de partida (por ejemplo, mesilato, tosilato) E y es acoplado con 2-

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hidroxipiridina F (el cual incorpora R_1, R_2, R_3, R_4 y R_5) para dar el intermediario G. Note que las mitades R_1 y R_2 presentes en F pueden ser grupos protectores apropiados para la funcionalidad de amina. El grupo protector P_3 es subsiguientemente removido de G y el alcohol resultante (H) es oxidado al correspondiente aldehido (no mostrado) y sometido a una reacción formadora de aolefino para proporcionar el intermediario I (el cual incorpora R_{11}, Z, y Z_1). El grupo protector P_2 presente en I es entonces removido para dar el producto J. Si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, el/ellos puede ser removido de intermediarios G, H, I o producto J y reemplazado con un sustituyente diferente R_1 y/o R_2 para proporcionar intermediarios alternos G, H, I o productos J.

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Método General 2

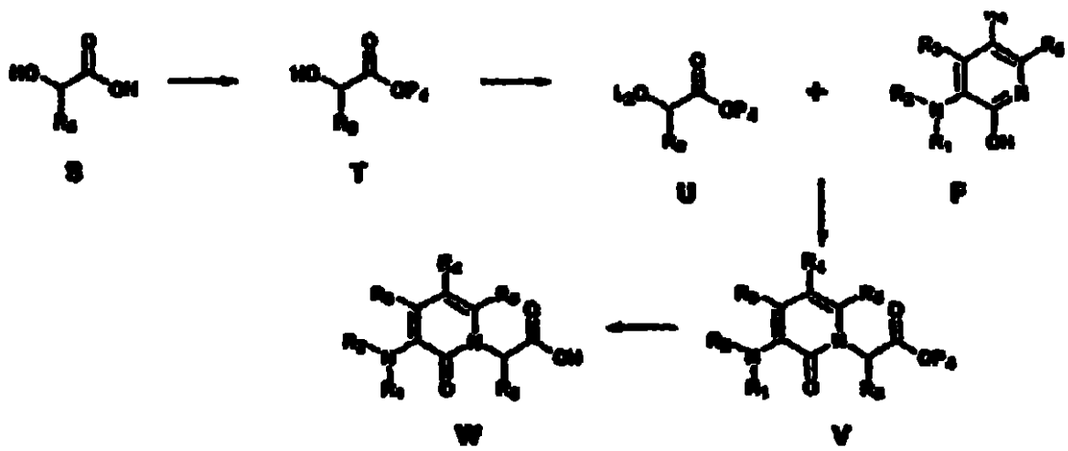


En el Método General 2, el alcohol de amino K (preparado por los métodos descritos en la literatura química), el cual incorpora R_9 y en el cual R_{10} es H, P_1 es un grupo protector apropiado para funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac), y P_2 es un

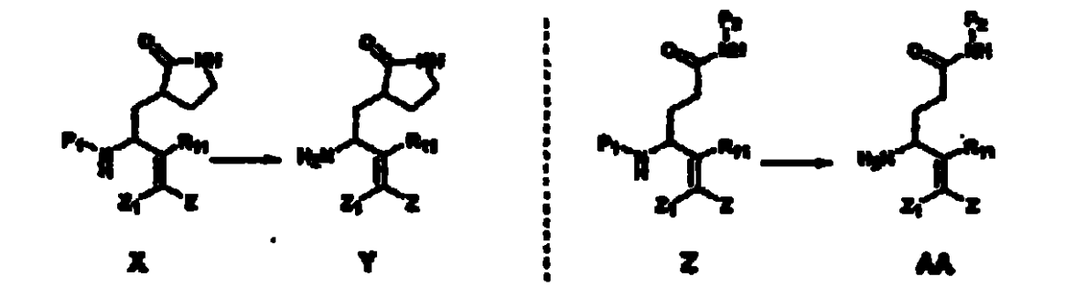
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grupo protector apropiado para el nitrógeno de amida (por ejemplo, DMB), es convertido a compuesto L donde P_3 es un grupo protector apropiado para la funcionalidad de alcohol (por ejemplo, TBDPS). El grupo protector P_1 presente en L es entonces removido y la amina resultante o sal de ésta (no mostrado) está sometida a una unión de amida formando reacción con ácido α-hidroxicarboxílico apropiado (el cual incorpora R_8 y en el cual R_2 es H; también no mostrado) para proporcionar intermediario M. La funcionalidad de alcohol presente en M es entonces convertida a un grupo de partida apropiado (por ejemplo, mesilato, tosilato) N y es acoplado con 2-hidroxipiridina F (la cual incorpora R_1, R_2, R_3, R_4 y R_5) para dar intermediario O. Note que las mitades R_1 y R_2 presentes en F pueden ser un grupo protector apropiado para la funcionalidad de amina. El grupo protector P_3 es subsiguientemente removido de O y el alcohol resultante (P) es oxidado para el correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para proporcionar intermediario Q (el cual incorpora R_{11}, Z, y Z_1). El grupo protector P_2 presente en Q es entonces removido para dar producto R. Si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, ellos pueden ser removidos de intermediarios O, P, o Q o producto R y reemplazado con un sustituyente diferente R_1 y/o R_2 para producir intermediarios alternos O, P, o Q o productos R.

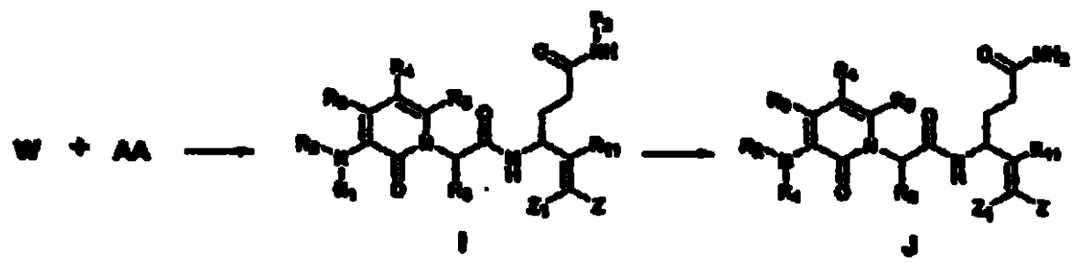
Método General 3



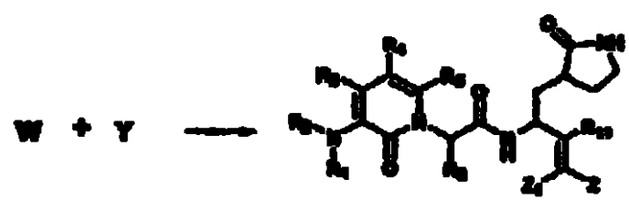
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X Y Z AA



I J



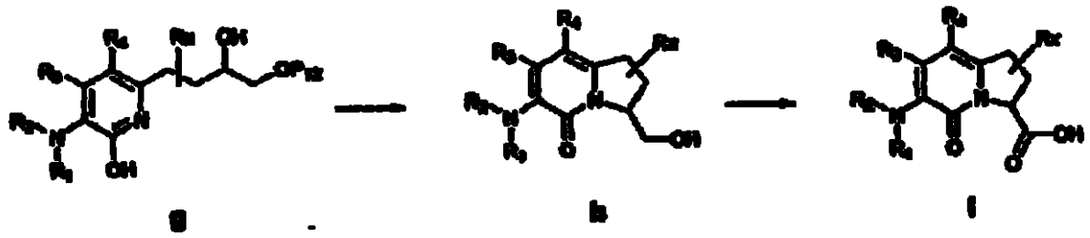
R

Un método alterno para preparar ya sea producto J o producto R está ilustrado en el Método General 3. Un ácido α-carboxílico S (ya sea comercialmente disponible o preparados por métodos descritos en la literatura química) el cual incorpora R_8 y el cual R_7 es H es convertido a α-hidroxiéster T donde P_4 es un grupo protector apropiado para el grupo funcional de ácido carboxílico (por ejemplo metilo, bencilo, o tert-butilo). La presente funcionalidad de alcohol en T es entonces convertida a un grupo de partida apropiado (por ejemplo, mesilato, tosilato, trifiato) U y es acoplado con 2-hidroxipiridina F (el cual incorpora R_1, R_2, R_3, R_4, y R_5) para dar intermediario V. Note que las mitades R_1 y R_2 presentes en F pueden ser un grupo protector apropiado para la funcionalidad de amina. El grupo protector P_4 es subsiguientemente removido de V para proporcionar ácido carboxílico W. Independientemente, los intermediarios X y Z_1 y en el cual P_1 es un

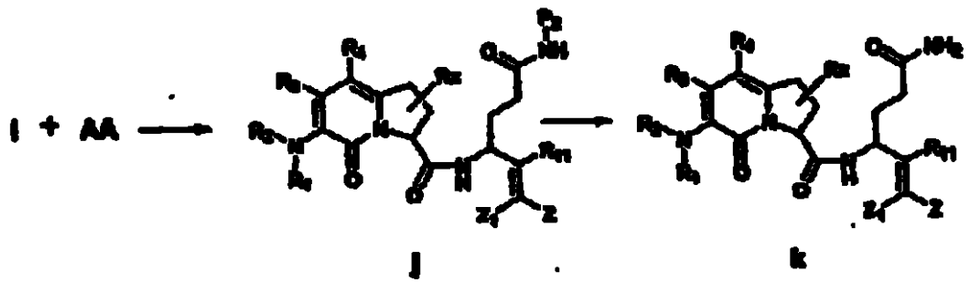
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grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz, Boc, o Ac) y P_2 es un grupo protector apropiado para el nitrógeno de amida (por ejemplo, Tr), son convertidos a sus correspondientes aminas Y y AA (o sales de éstas), respectivamente. Las aminas AA y Y son entonces independientemente acopladas con ácido carboxílico W para proporcionar intermediario I y producto R, respectivamente. El grupo protector P_2 presente en el intermediario I es subsiguientemente removido para proporcionar J. Note que, aunque no está descrito en el Método General 3, el nitrógeno de lactam presente en el intermediario X puede ser protegido por un grupo protector adecuable (por ejemplo, DMB). Si tal mitad está presente en X, ésta puede ser removida después del acoplamiento de W con Y para proporcionar R.

Método General 4

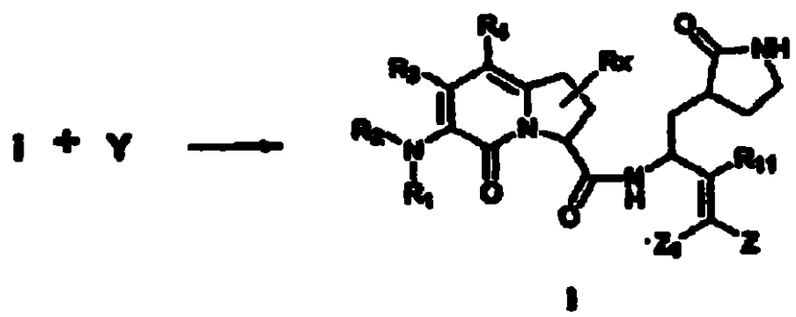


g h i



I + AA

j k



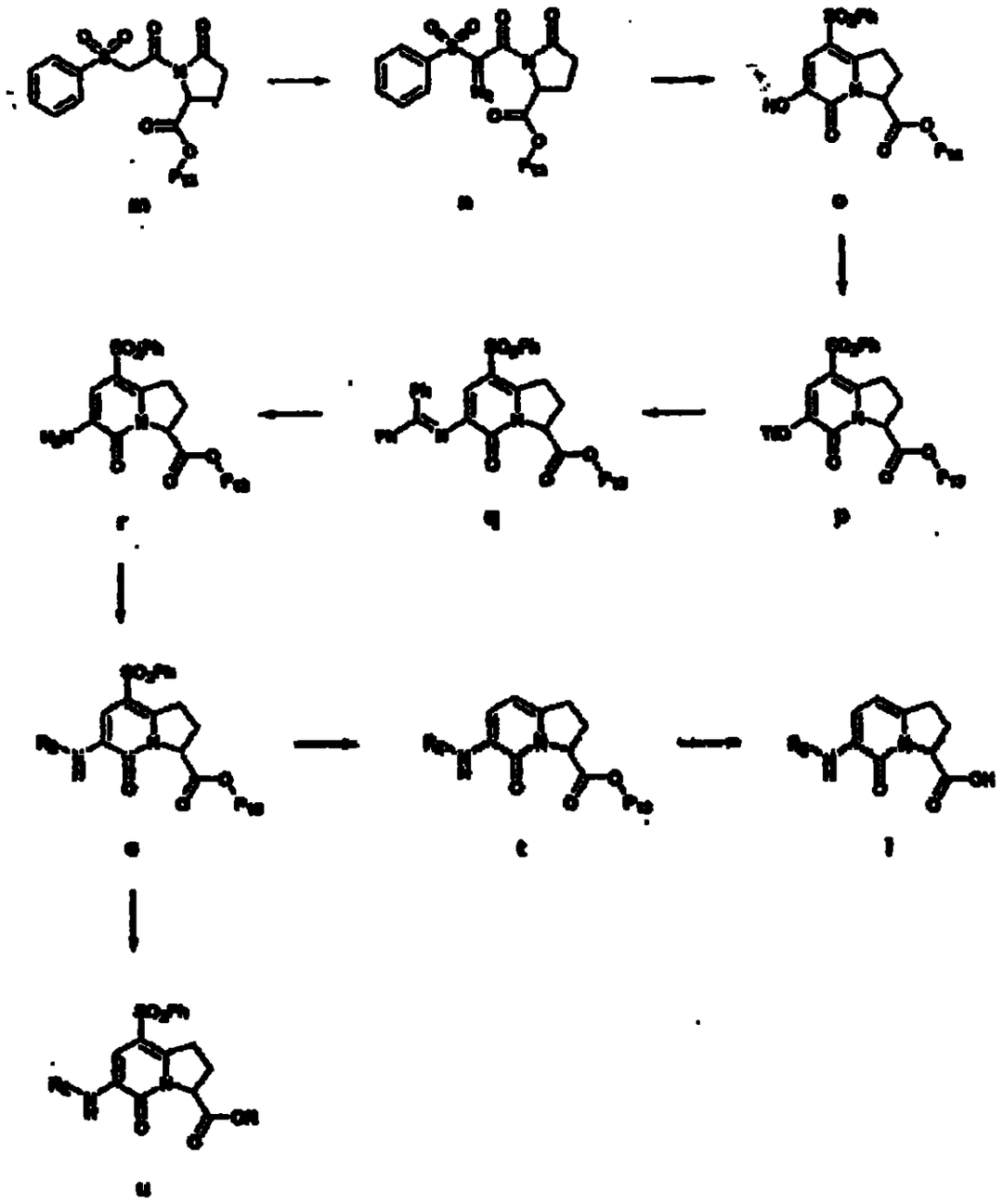
I + Y

l

Un método para preparar de productos bicíclicos K y I está ilustrado en el Método General 4. Además, una piridina apropiada g (la cual incorpora R_1 R_2, R_3, y R_4, y el cual puede ser opcionalmente sustituido con R_x como se muestra (un ejemplo del cual puede ser preparado tal como se describió en el Método Específico 7 abajo) en el cual P_{11} y P_{12} son grupos protectores para la funcionalidad de alcohol (por ejemplo, éter de sililo, metilo) está sometido a un protocolo de desprotección/ciclisación intramolecular en el cual ambos P_{11} y P_{12} son removidos para dar piridona H. Note que las mitades R_1 y R_2 presentes en g pueden ser un grupo protector apropiado para la funcionalidad de amina (por ejemplo, Cbz). La mitad de alcohol presente en h es entonces oxidada al correspondiente ácido carboxílico. Esta oxidación puede estar acompañada por vía de un intermediario de aldehído (no mostrada). Ácido carboxílico I es entonces independientemente acoplado con las aminas AA, y Y (o sales de ésta) (preparadas como se describió en el Método General 3 arriba) para proporcionar intermediario j y producto I, respectivamente. El grupo protector P_2 presente en el intermediario j es subsiguientemente removido para proporcionar producto k. Note que, aunque no descrito en el Método General 4, el nitrógeno de lactam presente en el intermediario Y puede ser protegido con un grupo protector adecuable (por ejemplo, DMB). Si tal mitad está presente en Y, ésta puede ser removida después del acoplamiento de I con Y para proporcionar producto I. En adición, si R_1 y/o R_2 es/son inicialmente un grupo protector para la funcionalidad de amina, éstos/ellos pueden ser removidos de intermediarios g, h, I, o j o productos k o I y reemplazados con un sustituyente diferente de R_1 y/o R_2 para proporcionar intermediarios alternos g, h, I, o j o productos k o I.

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~~799~~

Método General 5

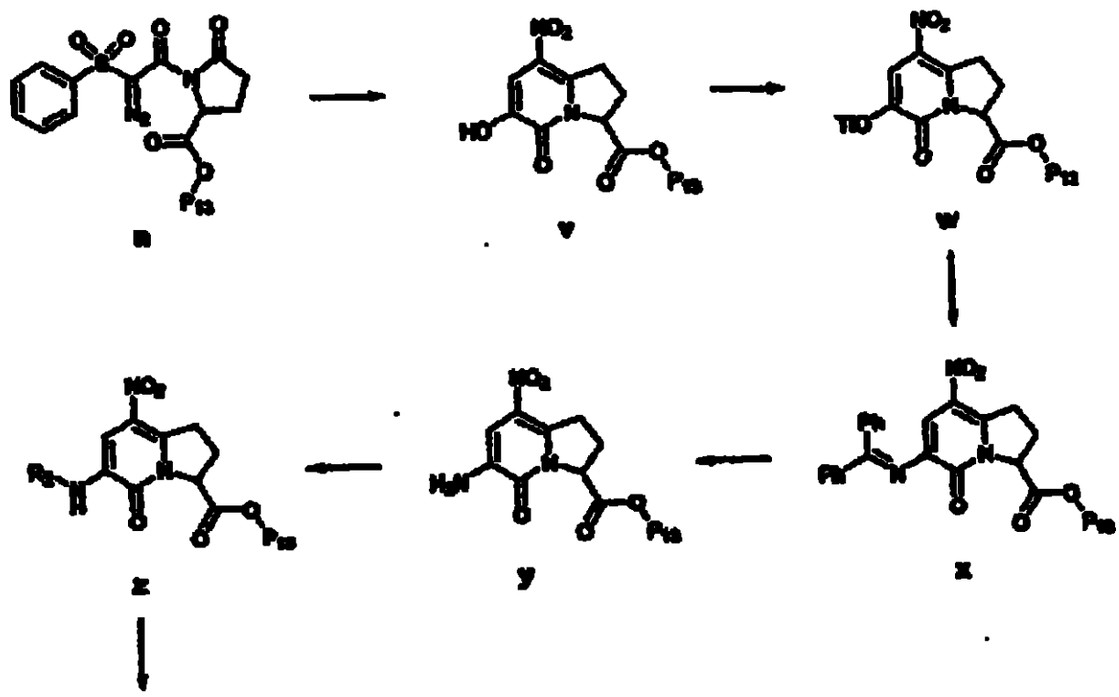


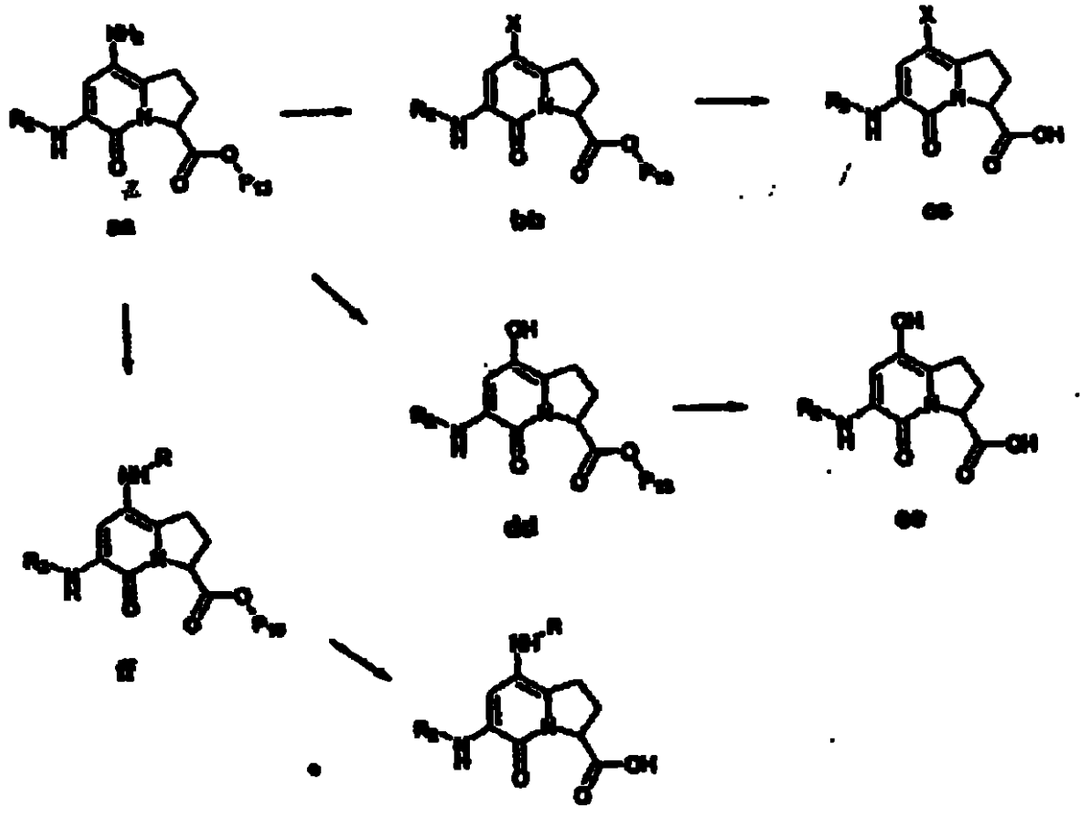
Un método alterno para preparar un tipo particular de intermediario I está ilustrado en el Método General 5. Además, el sulfono m (el cual puede ser preparado por el método descrito en Org. Lett., 1999, 1, 83) en el cual R_x es/son H y P_{13} es un grupo protector apropiado para la funcionalidad de ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de tert-butilo) es

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~~800~~

transformado en compuesto diaso n. Este intermediario está sometido a una reacción de ciclización catalizada de rodio que involucra sulfono de fenilvinilo para dar intermediario o (en el cual R_3 es H). El grupo hidróxilo presente en o es convertido al correspondiente sulfonato de trifluorometano (Otf) p, y este intermediario es además transformado a la amina r vía de la inmina q. La amina presente en r es derivada con una mitad apropiada para proporcionar intermediario s (el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario s está sometido a una reacción de desulfurización para dar el intermediario t y esta entidad es desprotegida para dar ácido carboxílico I (en el cual R_1, R_3, R_4 y R_x son H). Alternativamente, el intermediario s puede ser desprotegido para dar ácido carboxílico u (en el cual R_1, R_3, y R_x son H) el cual puede ser utilizado en lugar de I en el Método General 4.

Método General 6

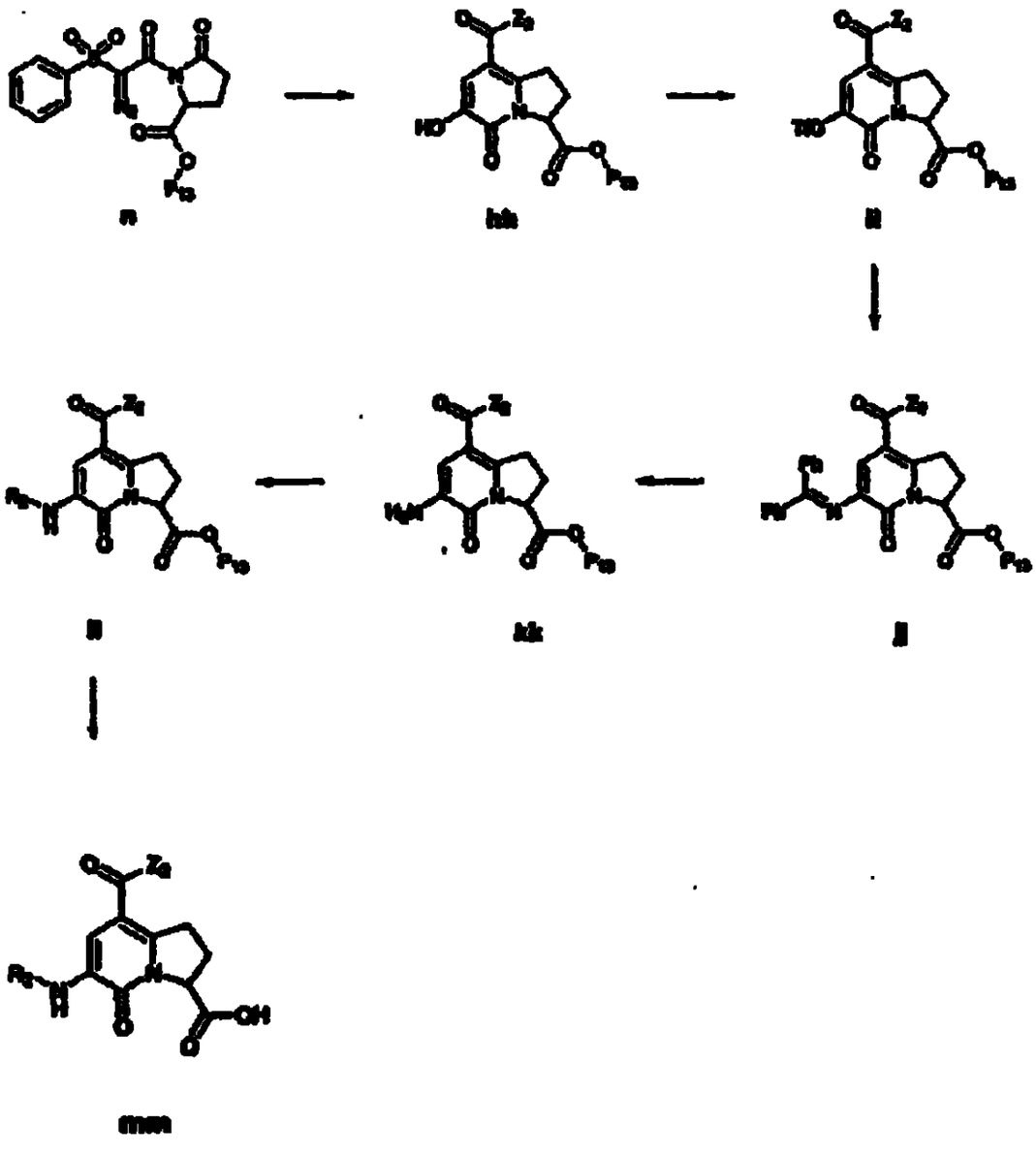




Un método adicional para preparar intermediarios relacionados con I está ilustrado en el Método General 6. Además, el compuesto diaso n (preparado en el Método General 5 arriba) en el cual R_x es/son H y en el cual P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de terl-butilo) está sometido a una reacción de ciclización catalizada de rodio involucrando nitroetileno para dar intermediario v (en el cual R_3 es H). El grupo hidróxilo presente en v es convertido al correspondiente sulfonato de trifluorometano (OTf) w, y este intermediario es además transformado a la amina y vía de la inmina x. La amina presente en y es derivada con una mitad apropiada para proporcionar intermediarios z (en el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario z es reducido para dar intermediario aa y esta entidad es transformada a intermediario bb en el cual X es un halógeno. El intermediario w es subsiguientemente desprotegido para dar ácido carboxílico cc. Si se desea, el intermediario aa puede también ser transformado en intermediario t (Método General 5 arriba).

Alternativamente, el intermediario aa es transformado a intermediario a dd el cual es subsiguientemente desprotegido para dar ácido carboxílico ee. Alternativamente, el intermediario aa es transformado a intermediario ff en el cual R es alquilo, acilo, sulfonilo, o aciloxi. El intermediario ff es subsiguientemente desprotegido para dar ácido carboxílico gg. Los ácidos carboxílicos cc, ee, y gg pueden cada uno ser utilizado en lugar de I en el Método General 4 arriba.

Método General 7

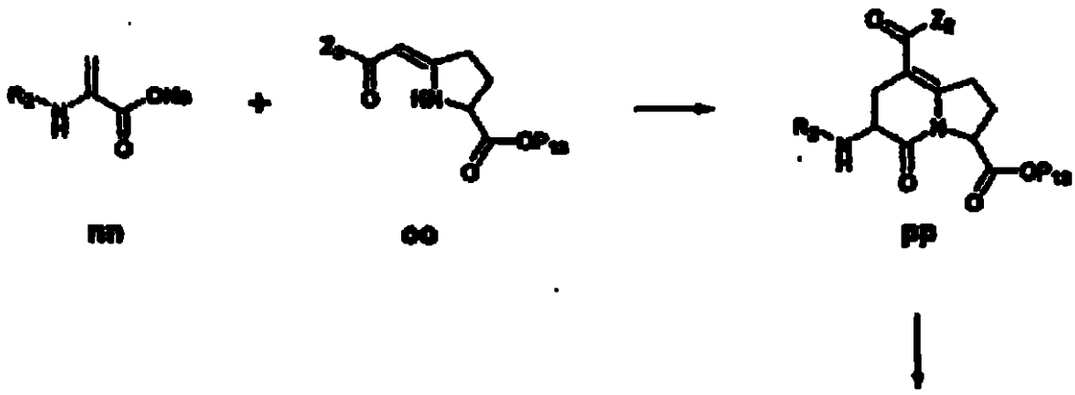


mm

~~803~~ 800

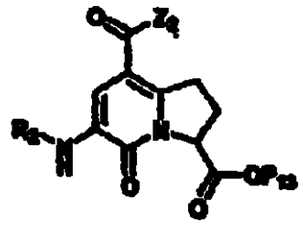
Un método adicional para preparar intermediarios relacionados con I está ilustrado en el Método General 7. Además, el compuesto diazo n (preparado en el Método General 5 arriba) en el cual R_x es/son H y en el cual P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo o éster de terl-butilo) es sometido a una reacción de ciclización catalizada de rodio involucrando ésteres de acrilato o quetonas de vinilo para dar intermediario hh (en el cual R_3 es H y Z_2 es alquilo, arilo, alcoxi, y benciloxi). El grupo hidróxilo presente en hh es convertido el correspondiente sulfonato de trifluorometano (OTf) ii, y este intermediario es además transformado a la amina kk vía de la inmina jj. La amina presente en kk es derivada con una mitad apropiada para proporcionar intermediario ll (el cual contiene el grupo funcional R_2 y en el cual R_1 es H). El intermediario ll es subsiguientemente desprotegido para dar ácido carboxílico mm el cual puede ser utilizada en lugar de I en el Método General 4 arriba. En cualquier punto en la secuencia de arriba, si Z_2 es alcoxi o benciloxi ésta puede ser reorganizada para la correspondiente amina usando métodos establecidos y el contenido de intermediarios de amina puede ser utilizado como está descrito en el Método General 6. Por ejemplo, el intermediario ll (cuando Z_2 es OH) puede ser reorganizado a intermediario aa (Método General 8).

Método General 8



mm oo pp

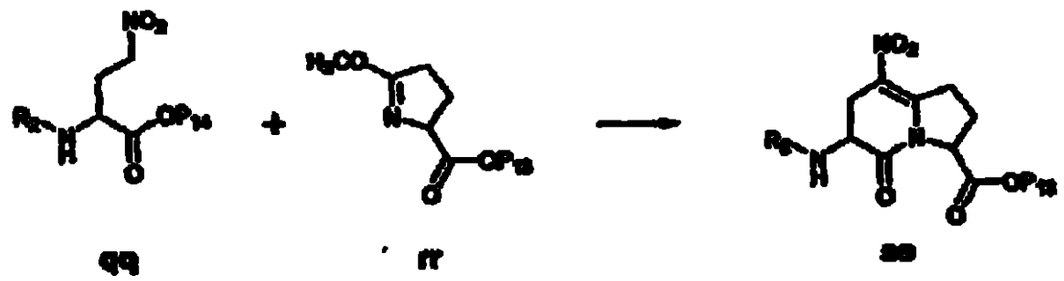
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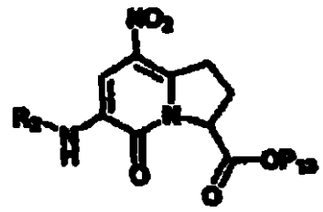
II

Todavía otro método para preparar intermediario II está descrito en el Método General 8. Además la sal de sodio, del derivado α-dehidroalanina nn (el cual incorpora R_2 y en el cual R_1 es H) (el cual ya sea comercialmente disponible o puede ser preparado de serina por una variedad de técnicas de literatura) es condensado con intermediario oo (el cual puede ser preparado como está descrito en Tetrahedron Lett., 1988, 30, 3621) en el cual R_x es/son H y P_{13} es un grupo protector apropiado para la funcionalidad del ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o éster de tert-butilo) en el cual Z_2 es alquilo, arilo, alcoxi, o benciloxi para dar el intermediario pp. El intermediario pp es subsiguientemente oxidado (por una variedad de métodos de la literatura) para proporcionar el intermediario II el cual puede ser utilizado tal como se describió arriba en el Método General 7.

Método General 9



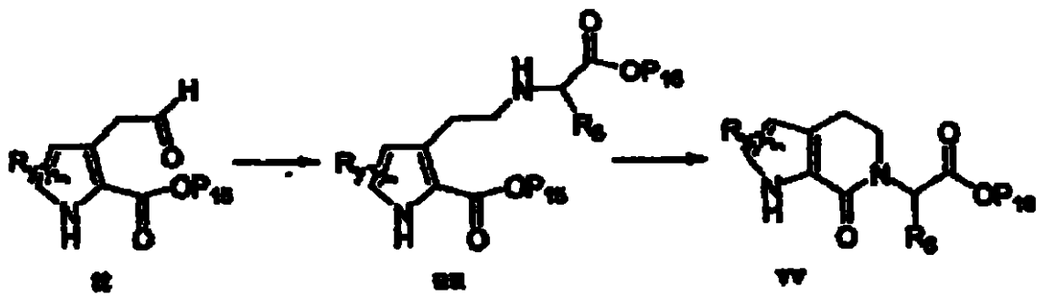
qq rr ss



z

Un método alterno para preparar intermediarios z (del Método General 6 arriba) está descrito en el Método General 9. Además el compuesto nitro qq (preparado por analogía con el método descrito en: J. Chem. Soc., Perkin Trans. 1 1998, 1113) el cual incorpora R_2 y en el cual R_1 es H y P_{14} es un grupo protector adecuable para la funcionalidad del ácido carboxílico (por ejemplo, metilo o etilo) es condensado con intermediario rr (preparado de acuerdo con: J. Heterocicliyc. Chem. 1992, 29, 1285) en el cual R_z es/son H y P_{13} es un grupo protector adecuable para la funcionalidad de ácido carboxílico (por ejemplo, metilo, etilo, bencilo, o terl-butilo) para dar el intermediario ss. El intermediario ss es subsiguientemente oxidado (por una variedad de métodos de la literatura) para proporcionar intermediario z el cual puede ser utilizado tal como se describió en el Método General 6.

Método General 10



tt ss vv

El Método General 10 describe la preparación del biciclicio pirrol vv, iniciado con aldehído tt, preparado de acuerdo a el procedimiento descrito en Smith, K. M., *J. Chem. Soc. Perkin Trans. I*,1973, p. 516. Este compuesto está sometido a condiciones aminación reducida con una amina para dar compuesto uu. El grupo protector de ácido carboxílico P_{18} es removido, y el ácido resultante

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es condensado intramolecularmente con la amina secundaria para dar biciclo vv. Este compuesto biciclo puede estar unido a la aminas Y o AA de acuerdo a el método descrito en el Método General 3.

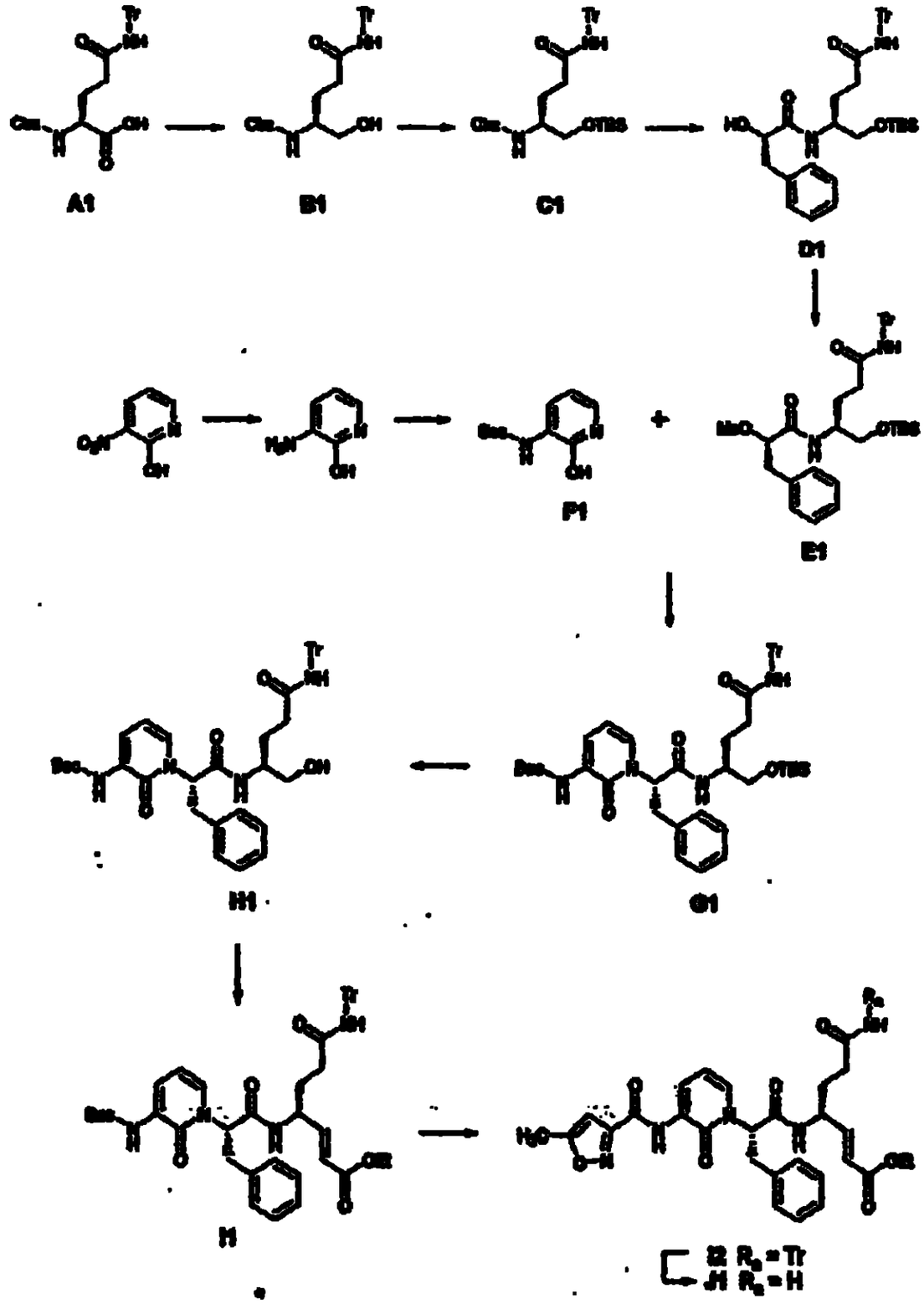
METODOS ESPECIFICOS

Los siguientes Métodos Especificos pueden también ser utilizados para preparar algunos de los compuestos descritos en esta invención.

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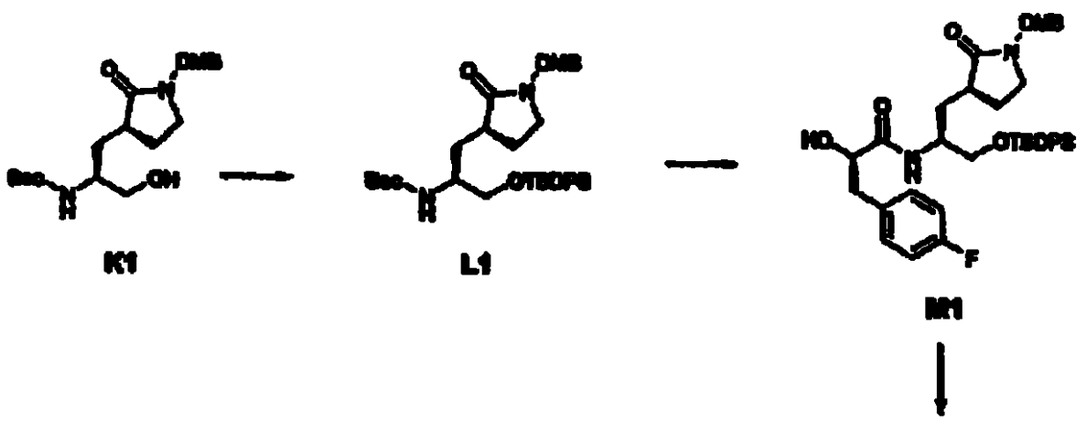
Método Específico 1



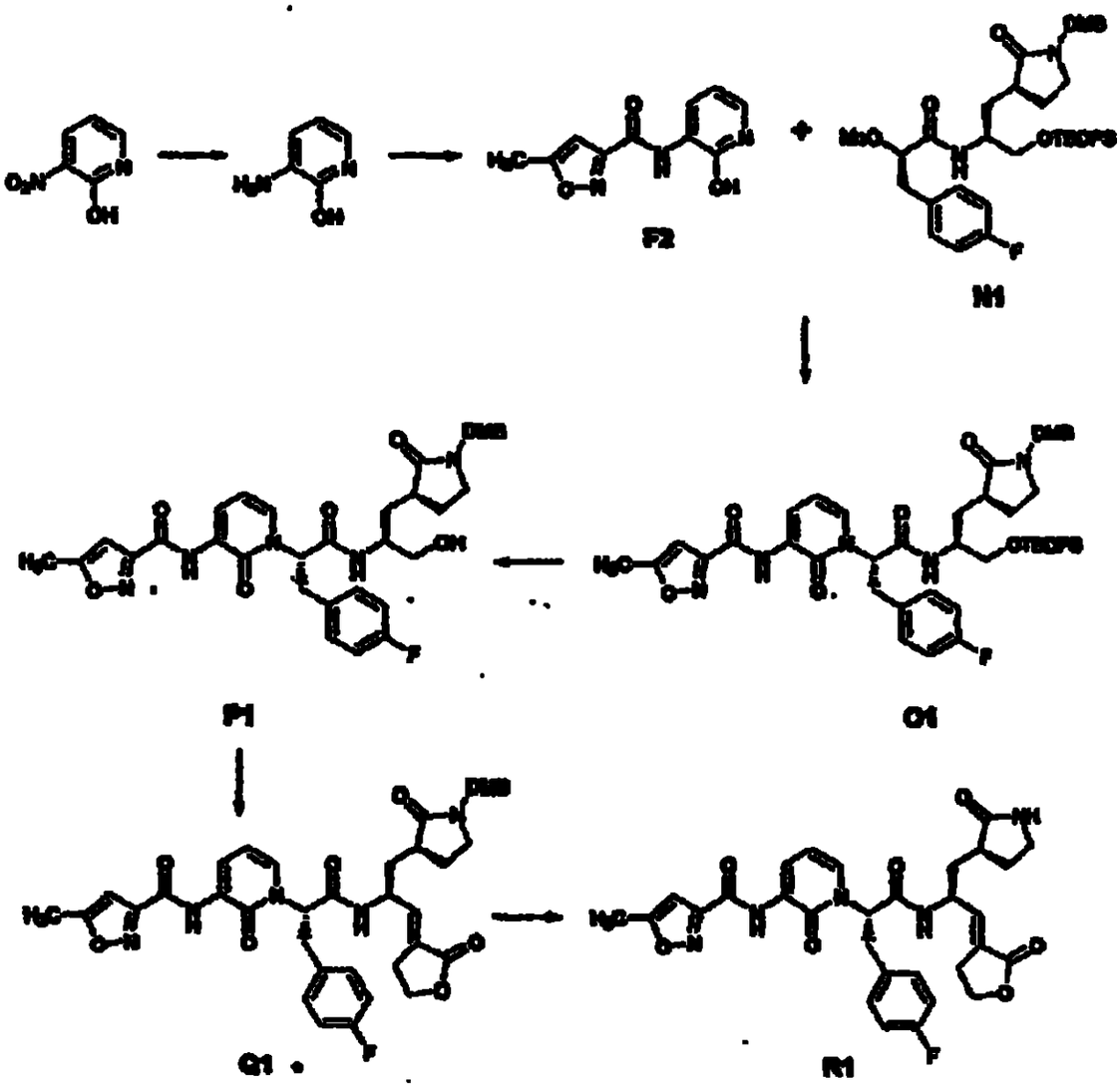
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El Método Específico 1 describe la preparación del compuesto específico J1 (compuesto 5). Además, comercialmente disponible el amino ácido A1 fue reducido a alcohol B1 el cual, a su turno, fue transformado en el compuesto C1. La mitad Cbz presente en C1 fue removida por hidrogenación y la amina resultante (no mostrada) fue acoplada con ácido D-3-fenilacético (comercialmente disponible) para proporcionar el intermediario D1. Esta última entidad fue subsiguientemente transformada al correspondiente metanosulfonato (mesilato) (E1) y fue acoplada con la sal de sodio de 2-hidroxipiridina F1 para proporcionar el intermediario G1. El 2-hidroxipiridina F1 fue preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reacción y subsiguiente protección Boc de la amina resultante. El grupo de protección sililo presente en G1 fue removido y el alcohol además obtenido (H1) fue oxidado para el correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario I1. La mitad Boc contenida en I1 fue entonces térmicamente desprotegida y la amina resultante (no mostrada) fue derivada de comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo para dar el intermediario I2. El grupo protector tritilo presente en I2 fue subsiguientemente removido bajo condiciones acídicas para completar la preparación del compuestos específico J1 (compuesto 5).

Método Específico 2



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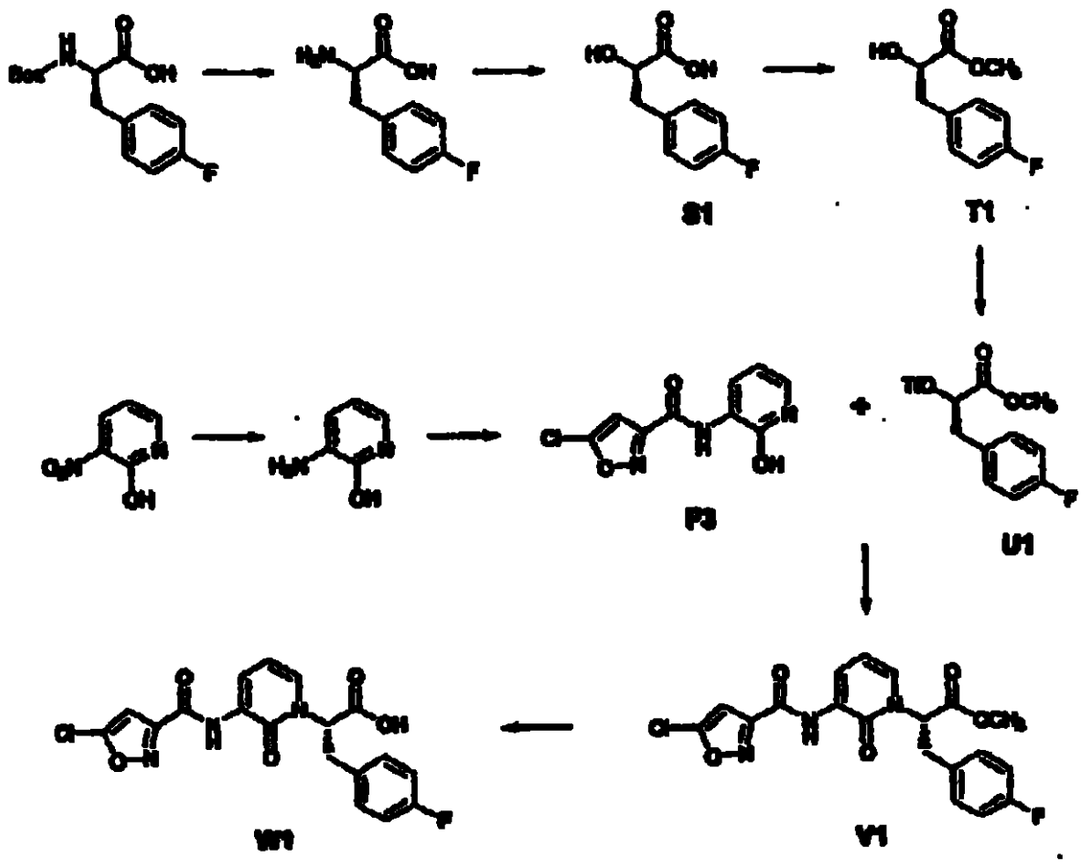


El Método Específico 2 describe la preparación del compuesto específico R_1 (compuesto 20). Además, el alcohol K1 (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1999, 42, 1213) protegido para dar el intermediario L1. El grupo protector Boc presente en L1 fue removido bajo condiciones acídicas y la sal de amina resultante (no mostrada) fue acoplada con (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (S1 preparado tal como se describió en el Método Específico 3 abajo) para proporcionar el intermediario M1. Esta entidad última fue subsiguientemente transformada al correspondiente metanosulfonato (mesilato) (N1) y fue acoplada con la sal de sodio de 2-hidroxipiridina F2 para proporcionar el intermediario O1. El 2-hidroxipiridina F2 fue

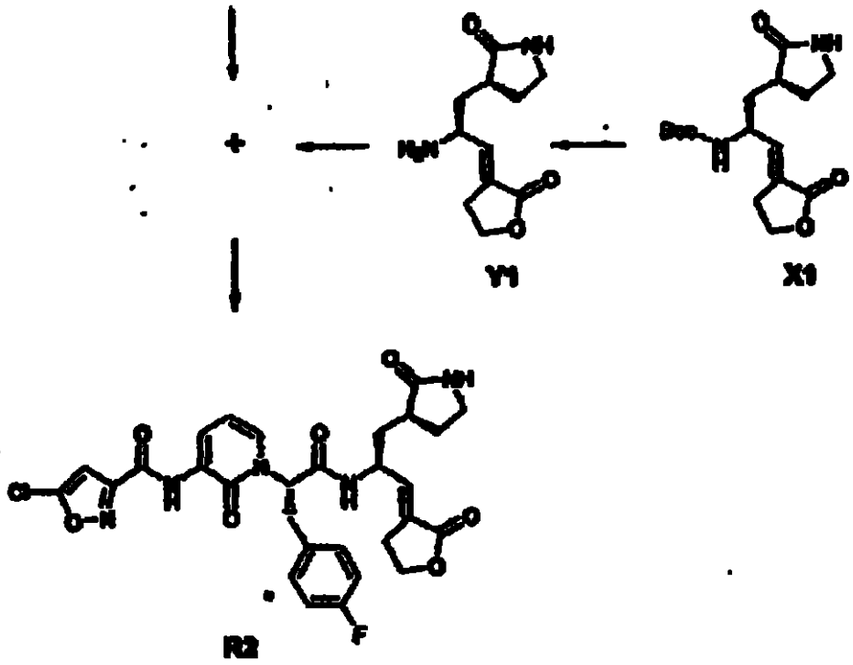
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preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con el comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo. El grupo protector sililo presente en O1 fue removido y el alcohol además obtenido (P1) fue oxidado al correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario Q1. La mitad del compuesto DMB contenida en Q1 fue entonces desprotegida para completar la preparación del compuesto específico R1 (compuesto 20).

Método Específico 3



BAA 808

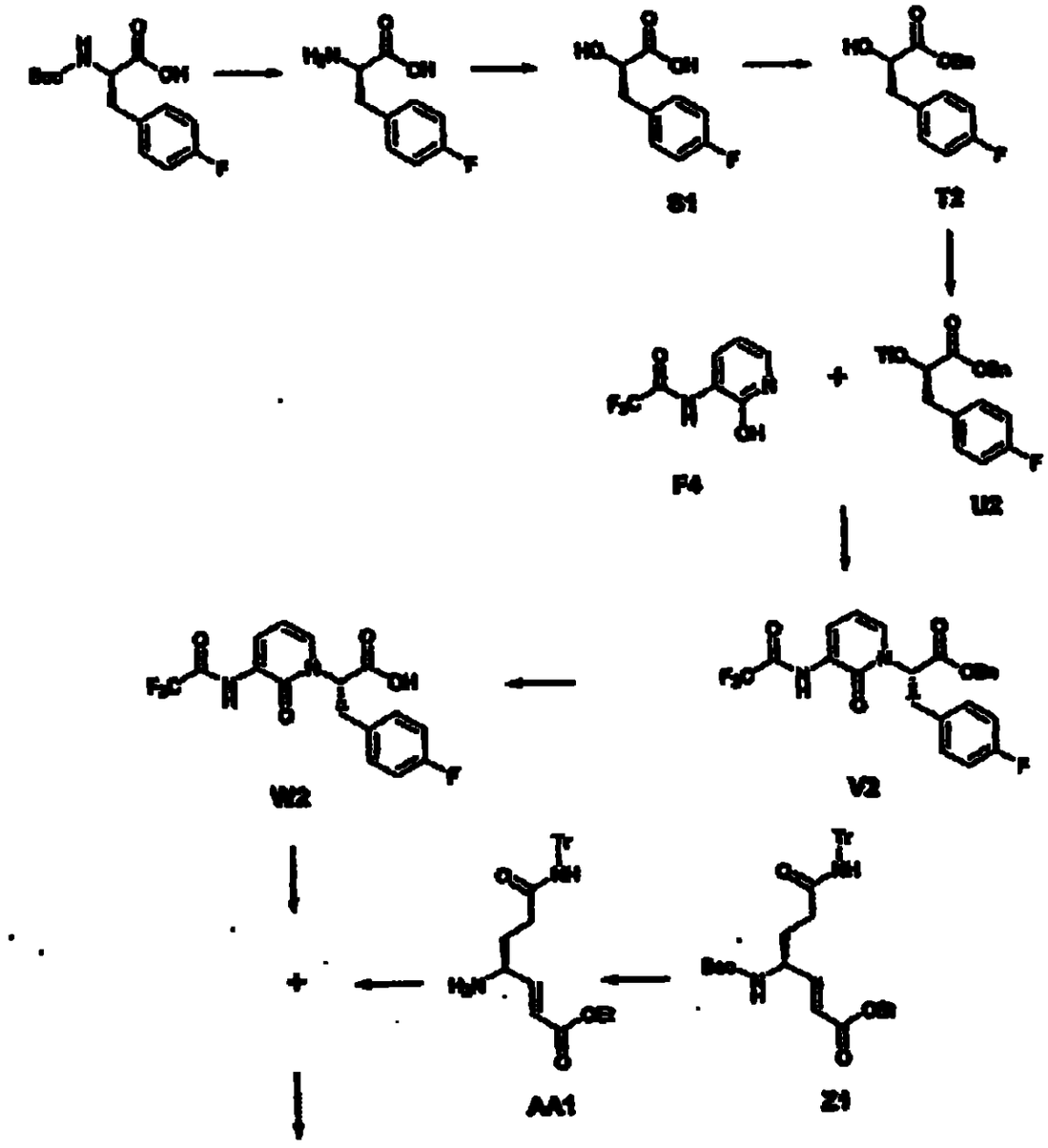


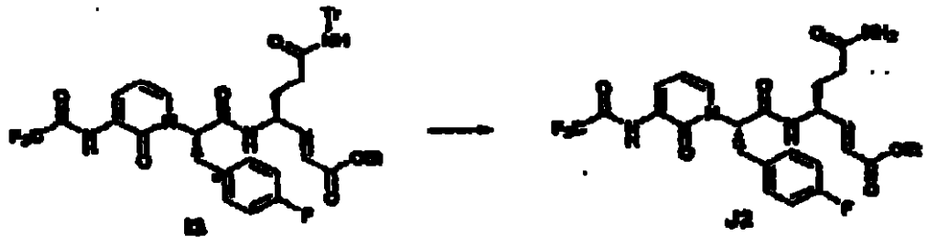
El método específico 3 describe la preparación del compuesto específico R_2 (compuesto 23). Además, el comercialmente disponible Boc-D-(4-F)PHe-OH fue desprotegido bajo condiciones acídicas y la sal de amina resultante fue sometida a un protocolo de desplazamiento/diazotización para proporcionar (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (S1). Este material fue subsiguientemente transformado en el correspondiente sulfonato de trifluorometano (triflato) U1 vía del éster de metilo T1 y fue acoplado con la sal de sodio de 2-hidroxipiridina F3 para proporcionar el intermediario V1. El 2-hidroxipiridina F3 fue preparado del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con cloruro de 5-cloroisoxazol-3-carbonilo (preparado tal como se describió en la Sección Experimental de este trabajo. El ester de metilo presente en V1 fue subsiguientemente hidrolizado bajo condiciones básicas y el ácido carboxílico resultante (W1) fue acoplado con amina Y1 (o sal de ésta) para completar la preparación del compuesto específico R2 (compuesto 23). La amina Y1 (o sal de ésta) fue preparada por desprotección del

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Intermediario X1 (preparado de una manera análoga a aquella descrita en Baldwin y otros, J. Org. Chem. 1971, 36, 1441)

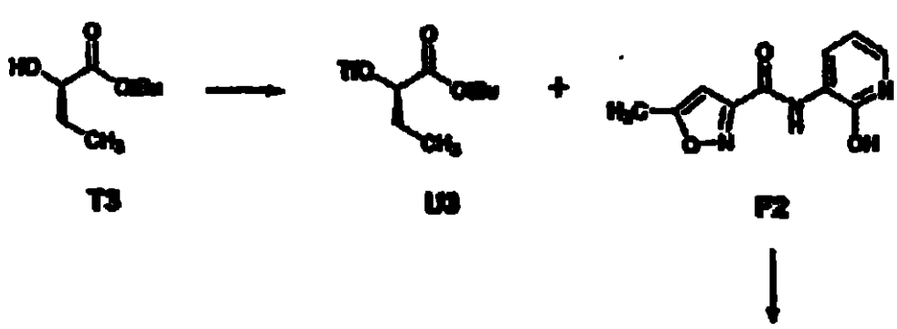
Método Específico 4

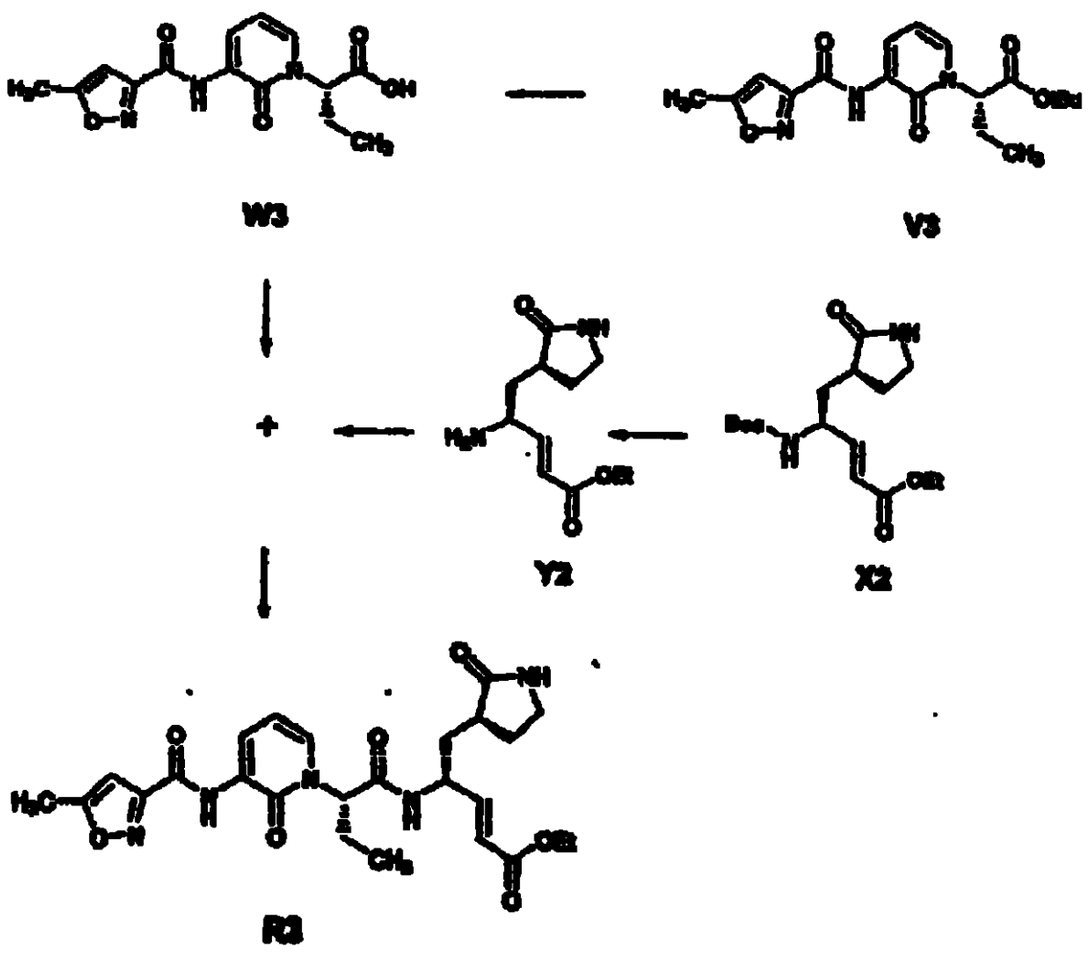




El Método Específico 4 describe la preparación del compuesto específico J2 (compuesto 24). Además, (2R)-3-(4'-fluorofenil)-2-ácido hidroxipropiónico (S1, preparado tal como se describió arriba en el Método Específico 3) fue transformado en el correspondiente sulfonato de trifluorometano (triflato) U2 vía del éster de bencilo T2 y fue acoplado con la sal de sodio de 2-hidroxipiridina F4 para proporcionar el intermediario V2. La 2-hidroxipiridina F4 fue preparada del comercialmente disponible 2-hidroxi-3-nitropiridina por reducción y subsiguiente derivación de la amina resultante con anhídrido trifluoroacético. El éster de bencilo presente en V2 fue subsiguientemente removido por hidrogenación y el ácido carboxílico resultante (W2) fue acoplado con amina AA1 (o sal de ésta) para dar el intermediario I3. El grupo protector tritol presente en I3 fue entonces removido bajo condiciones acídicas, para completar la preparación del compuesto específico J2 (compuesto 24). La amina AA1 (o sal de ésta) fue preparada por desprotección del intermediario Z1 (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1998, 41, 2806).

Método Específico 6

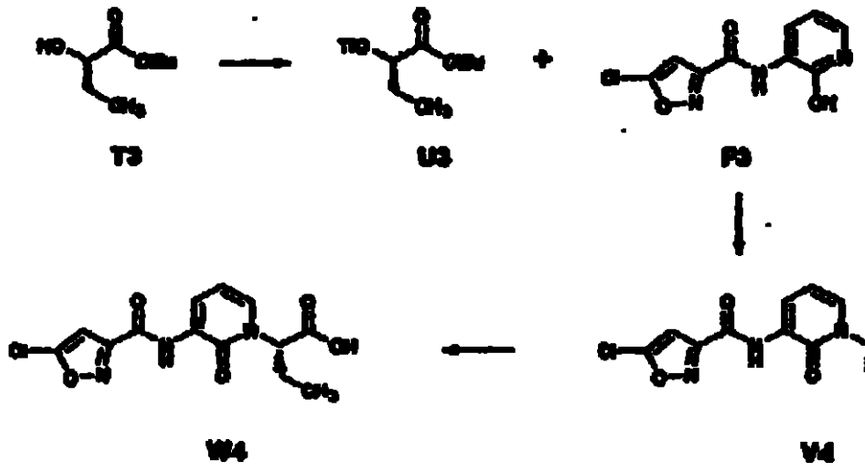


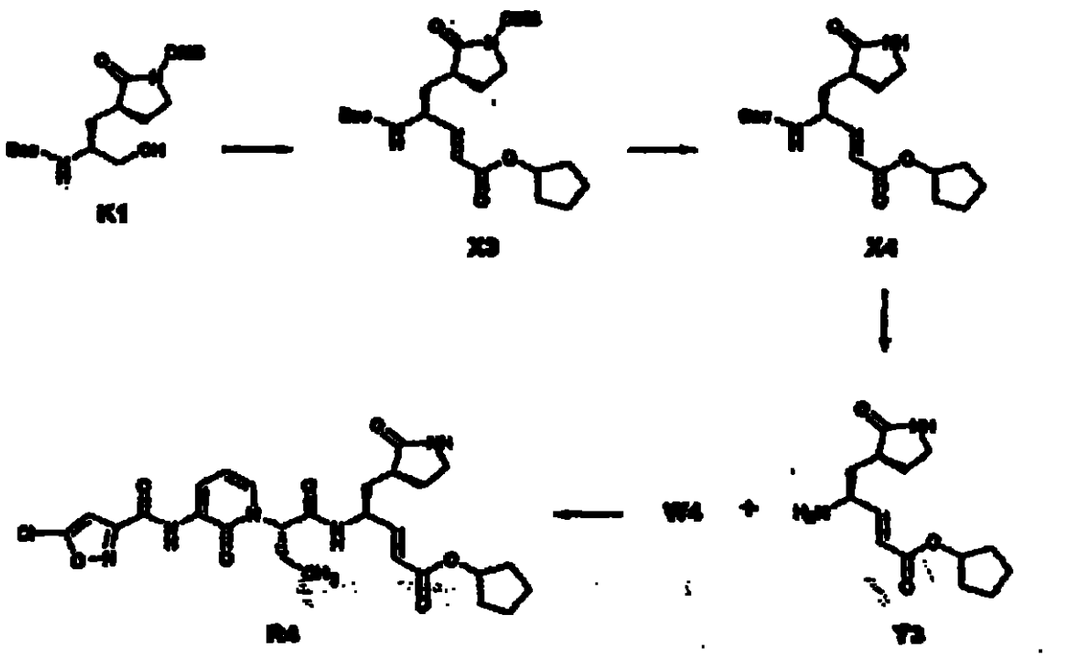


El Método Específico 5 describe la preparación del compuesto específico R3 (compuesto 26). Además, el disponible comercialmente tert-butilo (R)-2-hidroxibutirato (T3) fue transformado en el 2-hidroxipiridina F2 (preparada tal como se describió en el Método Específico 2) para proporcionar el intermediario V3. El éster de tert-butilo presente en V3 fue subsiguientemente hidrolizado bajo condiciones acídicas y el ácido carboxílico resultante (W3) fue acoplado con amina Y2 (o sal de ésta) para completar la preparación del compuesto específico R3 (compuesto 26). La amina Y2 (o sal de ésta) fue preparada por desprotección del intermediario X2, preparado de acuerdo con el método revelado en la solicitud co-pendiente, Solicitud de Patente Provisional de los E.U. No. 60/150,358, presentada en Agosto 24 de 1999, la revelación de la cual está incorporada aquí por referencia.

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Método Específico 6

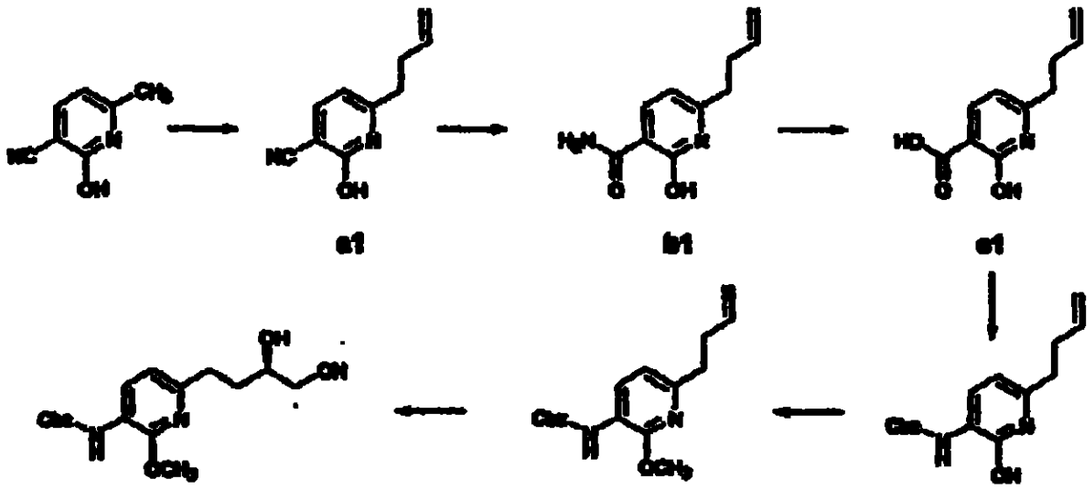




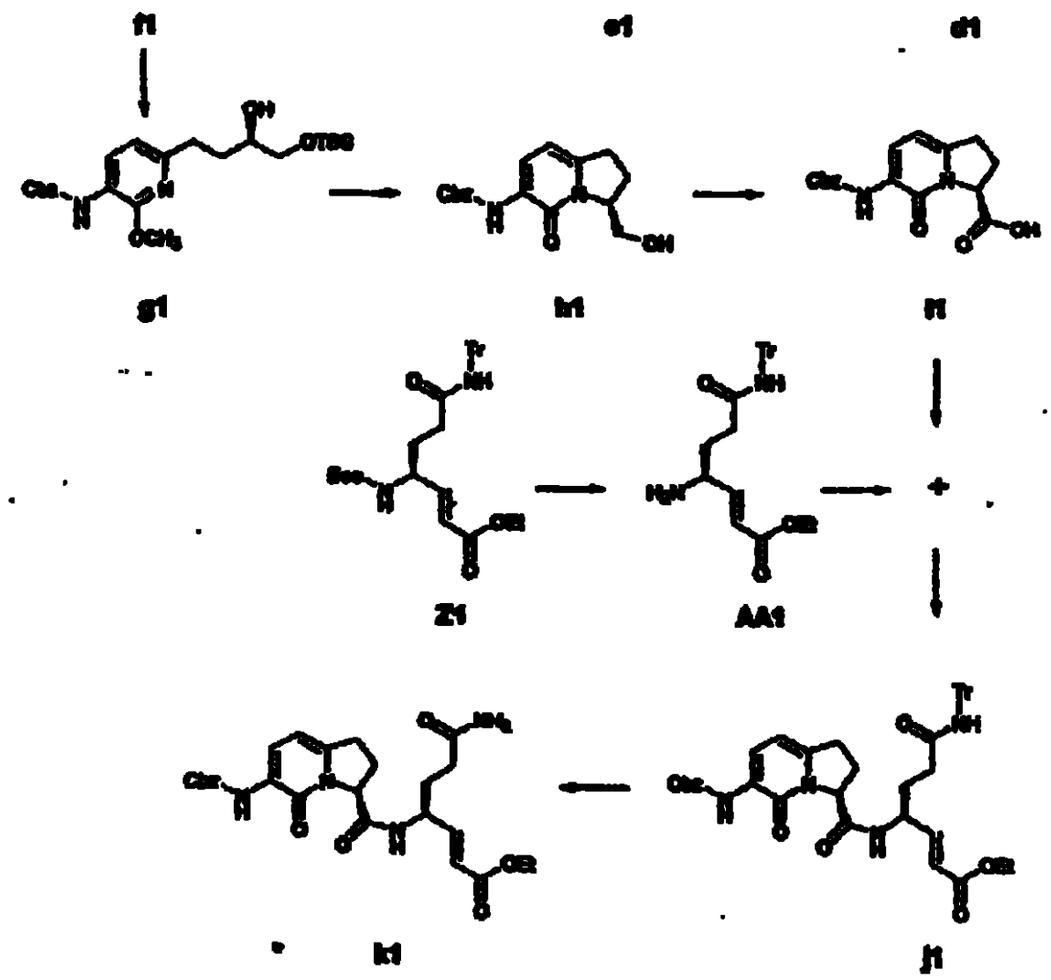
El Método Específico 6 describe la preparación del compuesto específico R4 (compuesto 29). Además, sulfonato de trifluorometano (triflato) U3 (preparado tal como se describió en el método Específico 5 arriba) fue acopiado con la sal de sodio de 2-hidroxipiridina F3 (preparada tal como se describió en el Método específico 3 arriba) para proporcionar el intermediario V4. El éster de tert-butilo presente en V4 fue subsiguientemente hidrolizado

bajo condiciones acídicas y el ácido carboxílico resultante (W4) fue acoplado con amina Y3 (o sal de ésta) para completar la preparación del compuesto específico R4 (compuesto 29). La amina Y3 (o sal de ésta) fue sintetizada de alcohol K1 (preparado como se describió en Dragovich, y otros, J. Med. Chem. 1999, 42, 1213) por el siguiente método. Alcohol K1 fue oxidado al correspondiente aldehído (no mostrado) y sometido a una reacción formadora de olefino para dar el intermediario X3. La mitad DMB contenida en X3 fue entonces desprotegida para proporcionar el intermediario X4, y esta entidad fue desprotegida bajo condiciones acídicas para proporcionar amina Y3 (o sal de ésta).

Método Específico 7



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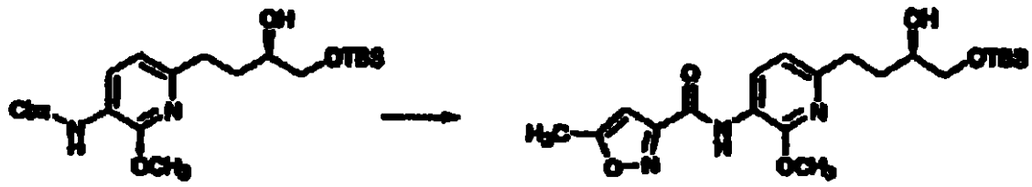


El Método Específico 7 describe la preparación del compuesto específico K1 (compuesto 36). Además, el dianión del comercialmente disponible 2-hidroxi-6-metilnicotinonitrilo fue convertido a intermediario a1 por métodos relacionados a aquellos descritos en la literatura (Dejohn, D; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. J. Hterocilcic Chem., 1983, 20, 1285). La funcionalidad de nitrilo presente en este intermediario fue entonces convertida al correspondiente ácido carboxílico c1 vía de la amida primaria V1. El intermediario c1 fue sometido a un arreglo Curtius y el isocianato resultante fue enlazado con alcohol de bencilo para proporcionar carbamato d1. La mitad de hidróxilo contenida en d1 fue selectivamente metilada y el éter de metilo resultante (e1) fue sometido a una reacción de dihidroxilación asimétrica para dar diol

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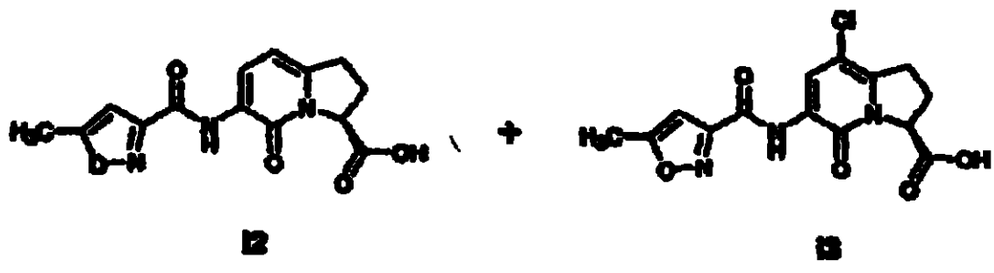
f1. Esta reacción de dihidroxilación asimétrica puede ser efectuada utilizando una variedad de aditivos quirales comerciales y no comerciales. La mitad de hidróxilo primario contenida en F1 fue selectivamente protegida como el correspondiente éter de terf-butildimetilsililo (g1). Este intermediario fue tratado con anhídrido trifluorometanosulfónico en la presencia de 2,6-lutidina a baja temperatura seguida por exposición a fluoruro de tetrabutilamonio para efectuar (i) ciclización intramolecular y (ii) desprotección de éter de sililo y proporcionar alcohol h1. El alcohol h1 fue oxidado al correspondiente aldehído (no mostrado), y este intermediario fue además oxidado al correspondiente ácido carboxílico i1. El ácido i1 fue acoplado con amina AA1 (o sal de ésta) para dar el intermediario j1. El grupo protector de tritilo presente en j1 fue entonces removido bajo condiciones acídicas para completar la preparación del compuesto específico k1 (compuesto 36). La amina AA1 (o sal de ésta) fue preparada por desprotección del intermediario Z1 (preparado tal como se describió en Dragovich, y otros, J. Med. Chem. 1998, 41, 2806).

Método Específico 8

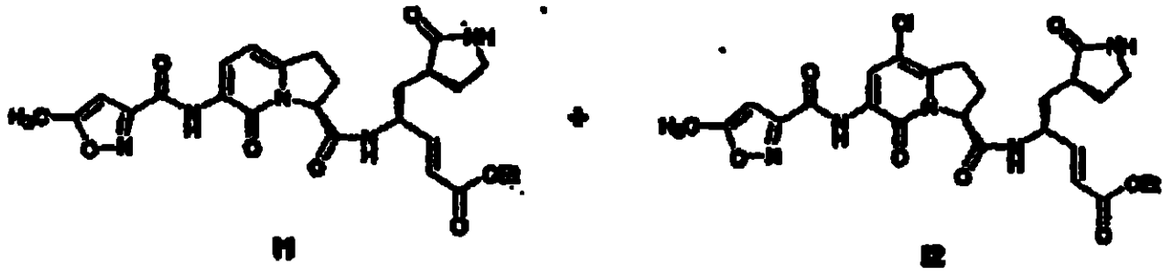


g1 g2

819 816



I2 I3

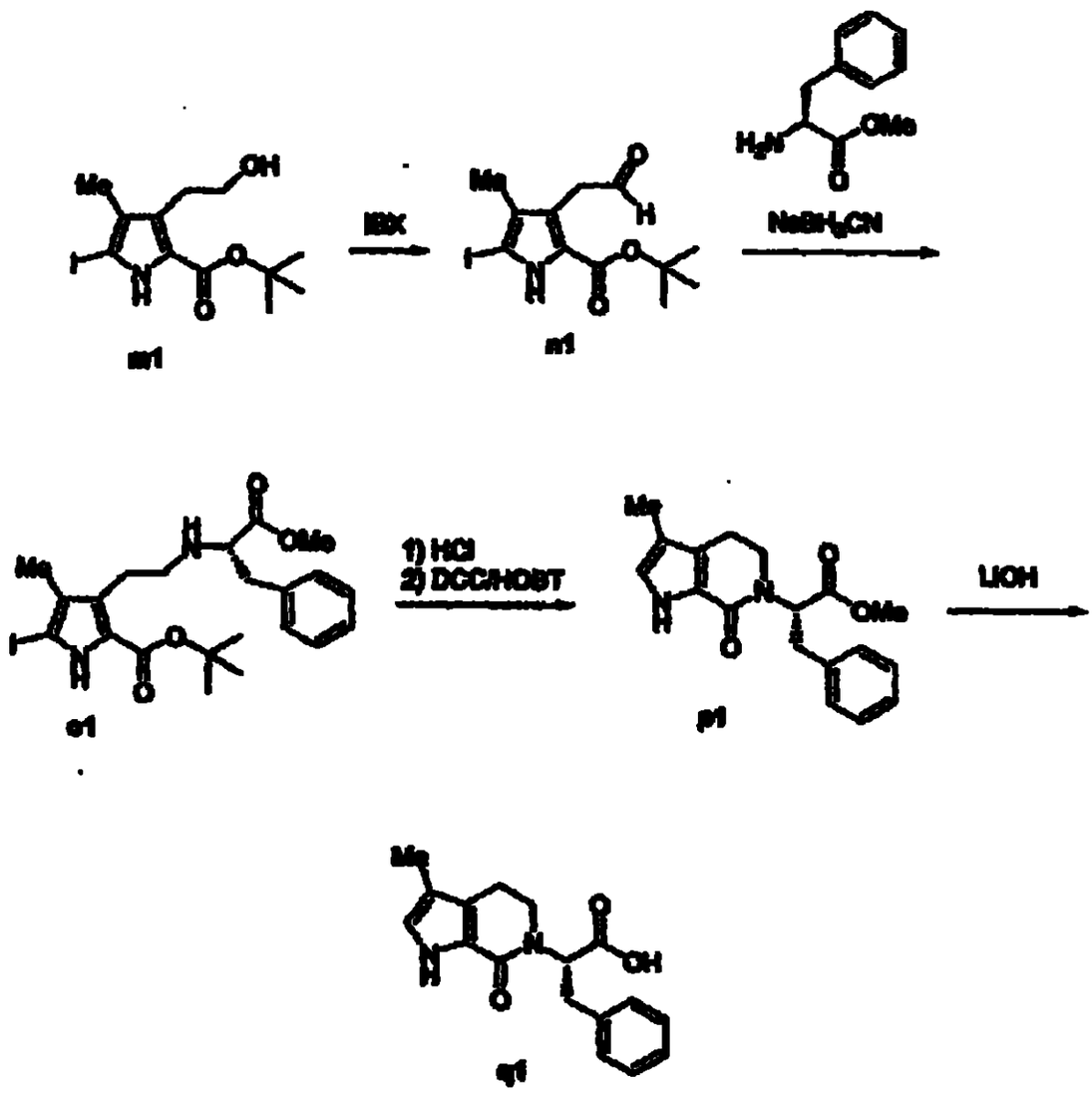


I1 I2

El Método Específico 8 describe la preparación de los compuestos específicos 11 y 12 (compuestos 37 y 39, respectivamente). Además, la mitad Cbz presente en el intermediario g1 (preparada tal como se describió en el Método Específico 7 arriba) fue removida y la amina resultante (no mostrada) fue derivada con comercialmente disponible cloruro de 5-metilisoxazol-3-carbonilo para proporcionar el intermediario g2. Este intermediario fue convertido al compuesto específico 11 (compuesto 37) por un proceso análogo a aquél descrito en el Método Específico 7 para la conversión de intermediario g1 a intermediario j1 utilizando amina Y2 (Método Específico 5) donde fuere apropiado. Durante este proceso, una pequeña cantidad de intermediario I3 fue también generada "serendipituosly". Este intermediario fue transformado al compuesto específico I2 (compuesto 39) por un proceso análogo a aquél descrito en el Método Específico 7 para la conversión del intermediario g1 a intermediario j1 utilizando amina Y2 (Método Específico 5) donde fuere apropiado.

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Método Específico 9



El Método Específico 9 describe la síntesis de un pirrol bicíclico. Alcohol m1 fue oxidado con 2-ácido iodoxibenzoico para dar aldehído n1, entonces aminatado reductivamente con éster de metilo de fenilalanina y cianoborohidruro de sodio para dar amina o1. El grupo t-butil-protector fue selectivamente removido, y el ácido de amino resultante fue ciclizado con DCC-HOBT para dar p1. El éster de metilo fue partido con hidróxido de litio para dar ácido q1. Boc-protegido de 4S-amino-5-(2-oxo-pirrolidin-3S-il)-pent-2(trans)-éster de etilo de ácido enóico X2 fue desprotegido con HCl,

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entonces unido con q1, usando HATU, para completar la preparación del compuesto 43.

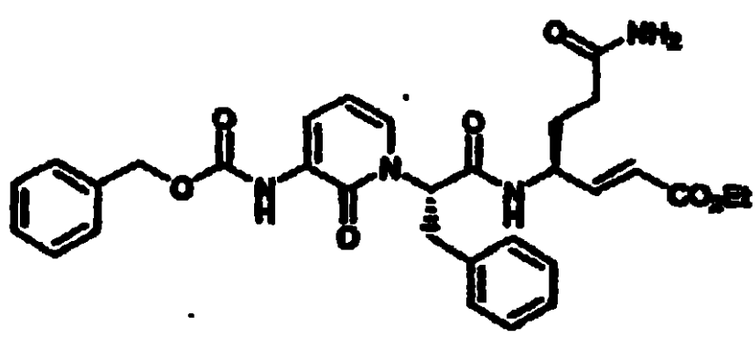
EJEMPLOS

Los ejemplos de los procesos usados para hacer varios de los compuestos de las Fórmula I y II están estipulados abajo. Las estructuras de los compuestos de los siguientes compuestos fueron confirmadas por uno o más de lo siguiente: espectroscopia de resonancia magnética protón, espectroscopia infrarroja, microanálisis elemental y punto de derretimiento. El espectro de resonancia magnética protón (^{1}H NMR) fue determinado usando ya sea una UNITYplus Varian 300 o una operación de espectrómetro QE-300 General Electric a una fuerza de campo de 300 megahertz (MHz). Los traslados químicos son reportados en partes por millón (ppm, δ) campo debajo de un tetrametilciliano interno normal. Alternativamente, el espectro ^{1}H NMR fue referenciado para señales de solvente prótico residual como sigue: $CHCl_3$ = 7.26 ppm; DMSO = 2.49 ppm, C_6HD_5 = 7.15 ppm. Las multiplicidades periódicas son designadas como sigue: s, simple; d, doble; dd, doble de doble; t, triple; q, cuarto; br, resonancia amplia; m, múltiple. Las constantes acopladoras son dadas en Hertz. El espectro de absorción infrarroja (IR) fue obtenido usando un espectrómetro FTIR series 1600 de Perkin-Elmer. Los microanálisis elementales fueron llevados a cabo por Atlantic Microlab Inc., Norcross, GA y dieron resultados para los elementos declarados dentro ± 0.4% de los valores teóricos. La cromatografía de columna de destello fue llevada a cabo usando gel de Sílice 60 (Merc Art 9385). La cromatografía analítica de capa delgada (TLC) fue llevada a cabo usando láminas prerrevestidas de Sílice 60 F_{254} (Merc Art 5719). Los puntos de derretimiento fueron determinados sobre un aparato Mel-Temp y son incorrectos. Todas las reacciones fueron llevadas a cabo en frascos septum-sellados bajo una presión positiva ligera de argón a menos que de otra manera sea notado. Todos los reactivos comerciales fueron usados como recibidos de sus respectivos suministradores con las siguientes excepciones. Tetrahidrofurán (THF) fue destilado de

quetilo de benzolferona de sodio anterior al uso. Diclorometano (CH_2Cl_2) fue destilado de hidruro de calcio anterior al uso. Et_2O se refiere a éter de dietilo. DMF se refiere a N, N-dimetilformamida. DMSO se refiere a dimetilsulfóxido. MTBE se refiere a éter de metilo de tert-butilo. Otras abreviaciones incluyen: CH_3OH (metanol), EtOH (etanol), EtOAc (acetato de etilo), DME (éter de dimetilo de glicol etileno) Ac (acetilo), Me (metilo), Ph (fenilo), Tr (trifenilmetilo), Cbz (Bencilloxicarbonilo), Boc (tert-butoxicarbonilo), TFA (ácido trifluoroacético), DIEA (N,N-diisopropiletilamina), TMEDA (N,N,N',N'-tetrametiletilenodiamina), AcOH (ácido acético), Ac_2O (anhidrido acético), NMM (4-metilmorfolina), HOBt (hidrato de 1-hidroxibenzotriazol), HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-hexafluorofosfato de tetrametil uronio], EDC [1-(3-dimetilaminopropil)-3-hidroxicloruro de etilcarbodiimida], DCC (diclorohexil-carbodiimida), DDQ (2,3-dicloro-5,6-diciano-1,4-benzoquinona), DMAP (4-dimetilaminopiridina), Gln (glutamina), Leu (leucina), Phe (fenilalanina), Phe (4-F) (4-flurorofenilalanina), Val (valina), amino-Ala (2,3-ácido diaminopropiónico), y (S)-Pirrol-Ala [(2S, 3'S)-2-amino-3-(2'oxopirrolidin-3'-il)ácido propiónico]. Adicionalmente, "L" representa la configuración de amino ácidos que ocurren naturalmente.

EJEMPLO 1

Preparación del Compuesto 1: trans-(2'S,4S)4-[2'-(3-Benzilloxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3'-fenilpropionil amino]-6-carbamoilhex-2-Ester de Etilo de Acido enóico



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Preparación del intermediario (2-hidroxipiridin-3-il)Ester de Bencilo de Acido carbámico

Una suspensión de 10% de paladio sobre carbono (0.20g) y 2-hidroxi-3-nitropiridina (3.00g, 21.4mmol, un equiv) en EtOH (100mL) fue sometida a una atmósfera de hidrógeno durante 4 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada y el filtrado evaporado para dar 2-hidroxi-3-aminopiridina la cual fue usada sin más purificación. Este material crudo fue agitado en THF (70mL) a 23°C. Cloroformato de bencilo (3.37mL, 23.6mmol, 1.1 equiv) y Na_2CO_3 (5.00g, 47.2mmol, 2.2 equiv) fueron agregados y la mezcla de reacción fue agitada durante 60 h entonces diluida con EtOAc (250mL) y lavada subsiguientemente con $NaHCO_3$ saturado y salmuera (50mL cada uno). La fase orgánica fue secada sobre $MgSO_4$, filtrada y concentrada. El residuo fue purificado por cromatografía de columna de destello (elución gradiente, 3→5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (3.69g, 71%) como un sólido blanco: ^1H NMR ($CDCl_3$) δ 5.21 (s, 2H), 6.33 (t, 1H, *J*=6.8), 7.00 (dd, 1H, *J*=6.8, 1.6), 7.31-7.43 (m, 5H), 7.80 (s, 1H), 8.12-8.17 (m, 1H), 12.97 (s, 1H).

Preparación del intermediario 5-(3-Benziloxicarbonilamino-2-oxo-2H-piridin-1-il)-6-fenil-4-[2-(tritilcarbamoil)etil]hex-2-Ester de Etilo de Acido enóico

(2-Hidroxipiridin-3-il)éster de bencilo de ácido carbámico fue convertido a el intermediario del título por vía de condensación con E1 (ver Ejemplo 5) por un proceso análogo aquel descrito en el Ejemplo 5 para la conversión de F1 a el intermediario I1: ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.2), 1.55-1.69 (m, 1H), 1.86-2.00 (m, 1H), 2.06-2.23 (m, 2H), 3.12 (dd, 1H, *J*=13.6, 7.8), 3.46 (dd, 1H, *J*=13.6, 8.2), 4.17 (q, 2H, *J*=7.2), 4.43-4.54 (m, 1H), 5.14 (d, 1H, *J*=12.1), 5.18 (d, 1H, *J*=12.1), 5.49-5.57 (m, 1H), 5.62 (dd, 1H, *J*=15.7, 1.7), 6.14 (t, 1H, *J*=7.3), 6.59-6.75 (m, 3H), 7.08-7.41 (m, 26H), 7.73 (s, 1H), 7.93-7.98 (m, 1H).

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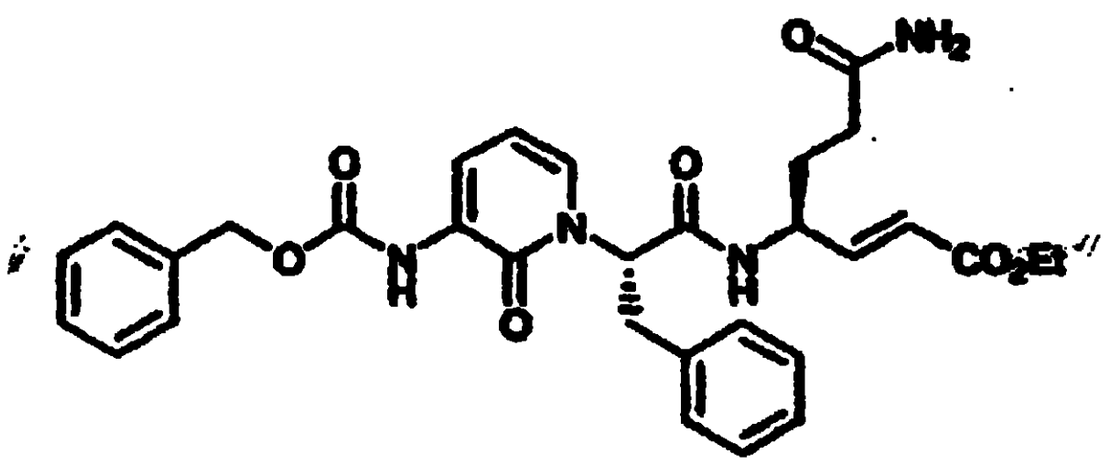
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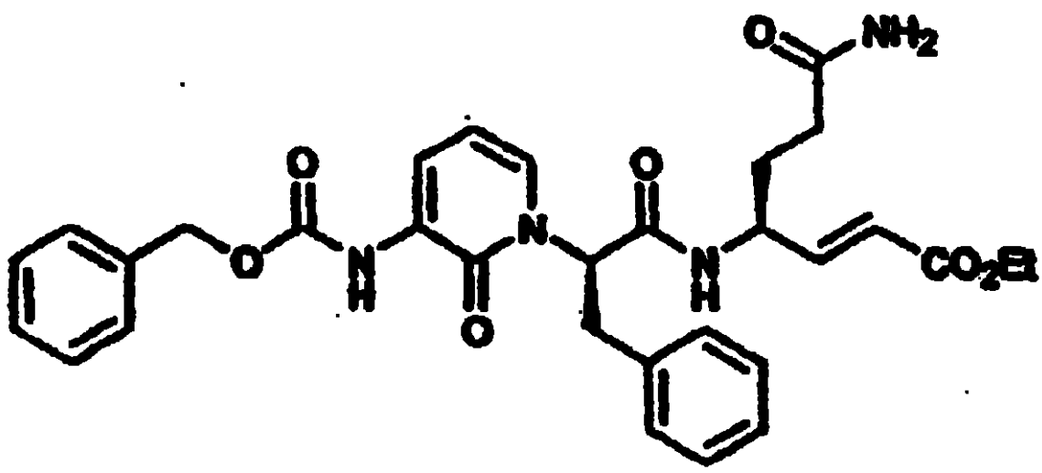
Preparación del Compuesto 1

El intermediario presedente fue convertido a compuesto 1 por un proceso análogo aquel descrito en el Ejemplo 5 para la conversión de I2 a producto J1: IR (cm^{-1}) 3298, 1713, 1655, 1590, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.1), 1.65-1.96 (m, 2H), 2.02-2.19 (m, 2H), 3.15 (dd, 1H, *J*=13.8, 7.6), 3.49 (dd, 1H, *J*=13.8, 8.3), 4.18 (q, 2H, *J*=7.1), 4.42-4.53 (m, 1H), 5.17 (s, 2H), 5.62-5.81 (m, 4H), 6.28 (t, 1H, *J*=7.2), 6.66 (dd, 1H, *J*=15.6, 5.4), 7.12-7.40 (m, 12H), 7.81 (s, 1H), 7.97-8.04 (m, 1H). Anal. $C_{31}H_{34}N_4O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 2

Preparación 1:1 mezcla del Compuesto 1 (arriba) y el Compuesto 2: trans-(2'R,4S)-4-[2'-(3"-Benziloxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3'-fenilpropionilamino]-6-carbamoilhex-2-Ester de Etilo de Acido enóico



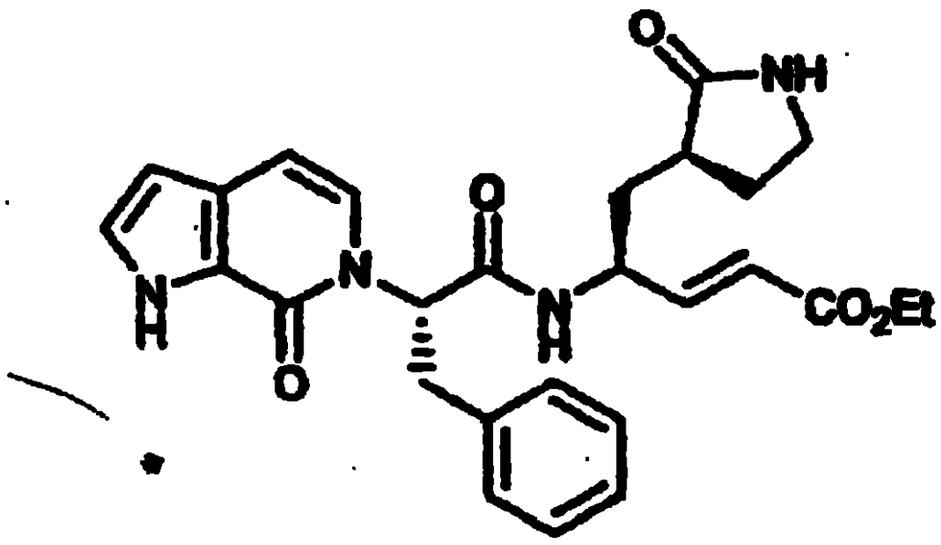


Los productos del título fueron preparados del comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico por un proceso análogo aquel descrito en el Ejemplo 22 para la conversión S1 a producto R2 utilizando intermediarios (2-hidroxipiridin-3-il)Ester de Bencilo de Acido carbámico (Ejemplo 1) y AA1 (Ejemplo 23) donde el apropiado: ^{1}H NMR ($CDCl_3$) (mezcla de isómeros) δ 1.20 (t, *J*=7.0), 1.29 (t, *J*=7.2), 1.64-2.25 (m), 3.08 (dd, *J*=13.6, 6.4), 3.14 (dd, *J*=13.6, 7.8), 3.41-3.52 (m), 4.09 (q, *J*=7.2), 4.18 (q, *J*=7.0), 4.39-4.50 (m), 5.16 (s), 5.69-5.82 (m), 6.12-6.22 (m), 6.25-6.34 (m), 6.65 (dd, *J*=15.6, 5.6), 6.70 (dd, *J*=15.6, 5.3), 7.10-7.41 (m), 7.47-7.58 (m), 7.79-7.86 (m), 7.97-8.07 (m).

EJEMPLO 3

Preparación del Compuesto 3: trans-(2'S,3'''S,4S)-4-[2'-(7''-Oxo-1'',7''-dihidropirrol[2'',3''-c-piridin-6''-il)-3-fenilpropionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Acido enóico

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Preparación del Intermediario (2S)-2-(2',2'-Dietiloxietilamino)-3-Ester de Etilo de Acido fenilpropiónico.

Una solución de ester de etilo de L-fenilalanina (8.37g, 46.8mmol, 1 equiv), acetal de dietilo de bromoacetaldehido (10.6mL, 70.1mmol, 1.5 equiv), y DIEA (16.2mL, 93.4mmol, 2.0 equiv) en DMF (100mL) fue calentada a 80°C durante 2 d. La solución resultante fue enfriada a 23°C, tomada en cloroformo (200mL), lavada con 10% de carbonato de potasio acuoso (3 x 50mL), secada sobre carbonato de potasio, y concentrada. La purificación del residuo por cromatografía de gel de sílice rindió 7.4g (54%) de producto. ^{1}H NMR ($CDCl_3$) δ 1.13-1.23 (m, 9H), 2.61 (dd, 1H, *J*=11.8, 5.9), 2.78 (dd, 1H, *J*=11.8, 5.9), 2.96-3.03 (m, 2H), 3.46-3.53 (m 1H), 3.55-3.70 (m, 4H), 4.18 (q, 2H, *J*=7.1), 4.57 (t, 1H, *J*=5.5), 7.19-7.33 (m, 5H).

Preparación del Intermediario (2S)-2-[(2,2-Dietoxietil)-(1H-pirrol-2-carbonil)-amino]-3-Ester de Etilo de Acido fenilpropiónico

Pirrol-2-ácido carboxílico (0.82g, 7.41mmol, 1.42 equiv) en CH_2Cl_2 (30mL) fue tratado con cloruro de oxalilo (1.0mL, 11.1mmol, 2.13 equiv), seguido por DMF (1 gota). La mezcla de reacción fue mantenida a 23°C toda la noche, entonces fue concentrada bajo

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presión reducida. El sólido resultante fue tomado en CH_2Cl_2 (30Ml), y fue tratado con intermediario precedente (1.60g, 5.2mmol, 1 equiv), y colidina (1.96mL, 14.8mmol, 2.85 equiv). La solución resultante fue mantenida 23°C toda la noche, entonces fue tomada en EtOAc (100mL), y lavada secuencialmente con ácido cítrico acuoso saturado (20mL), bicarbonato de sodio acuoso saturado (20mL), y salmuera (2 x 20mL). La capa orgánica fue secada sobre $MgSO_4$, entonces fue concentrada para rendir 2.18g del producto crudo. El producto fue purificado por cromatografía de gel de sílice para dar 1.42g (68%) de producto. ^1H NMR ($CDCl_3$) δ 1.15-1.30 (m, 9H), 3.24 (d, 2H, *J*=5.8), 3.75-4.43 (m, 2H),4.15-4.28 (m 6H), 4.50-4.57 (m, 1H), 5.05 (dd, 1H, *J*=13.6, 5.8), 6.22-6.24 (m, 1H), 6.56-6.59 (m, 1H), 6.94-6.96 (m, 1H), 7.19-7.33 (m, 5H), 9.76 (s, 1H).

Preparación del Intermediario (2S)-(7-Oxo-1,7-dihidropirrolo [2,3-c]piridin-6-il)-3-Ester de-Etilo de Acido fenilpropiónico

Una solución del intermediario precedente (1.04g, 2.59mmol) en tolueno (30mL), fue tratada con PTSA (5mg), entonces calentada a reflujo durante 1 h. La solución fue tomada en EtOAc (100mL), lavada con bicarbonato de sodio acuoso saturado (30mL), luego salmuera (30mL), entonces concentrada. La purificación del residuo por cromatografía de gel de sílice dio 0.14g (18%) de producto. ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, *J*=7.1), 3.25 (dd, 1H, *J*=14.2, 9.8), 3.49 (dd, 1H, *J*=14.2, 5.7), 4.11 (q, 2H, *J*=7.1), 5.57 (dd, 1H, *J*=9.6, 5.7), 6.26 (t, 1H, *J*=2.3), 6.42 (d, 1H, *J*=7.2), 6.70 (d, 1H, *J*=7.2), 7.00-7.20 (m, 6H), 10.33 (s, 1H).

Preparación del Compuesto 3

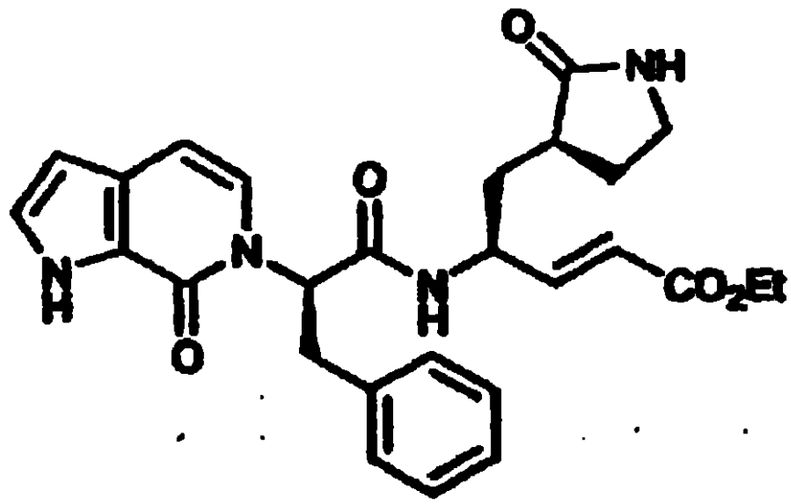
Una solución del intermediario precedente (0.14g, 0.45mmol, 1 equiv) en 1:1 1.4-dioxano-agua (5mL) fue tratada con hidrato de LIOH (28mg, 0.68mmol, 1.42 equiv), y calentada a reflujo durante 30 min. La solución resultante fue tomada en acetato de etilo (50mL), lavada con ácido cítrico acuoso saturado (10mL), seguido por salmuera (2 x 15mL), secada sobre $MgSO_4$, entonces evaporada

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para rendir 61mg del ácido correspondiente. Esta fue tomada en DMF (5mL), tratada con intermediario Y2 (Ejemplo 25, 49mg, 0.22mmol, 0.48 equiv), DIEA (0.07mL, 0.43mmol, 0.95 equiv), y HATU (82mg, 0.22mmol, 0.49 equiv), entonces mantenida a 23°C toda la noche. La solución fue tomada en acetato de etilo (30mL), lavada con salmuera (10mL), entonces evaporada. La purificación de residuo por cromatografía de gel de sílice rindió 0.12g (56%) de producto como una mezcla de 2:1 de 2S:2R diastereómeros (compuestos 3 y 4, respectivamente). Los diastereómeros fueron separados por fase reversa preparativa HPLC (acetonitrilo-H_2O gradiente). Compuesto 3: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.1), 1.42-1.65 (m, 2H), 1.90-2.10 (m, 2H), 2.20-2.35 (m, 1H), 2.82-2.95 (m, 1H), 3.05-3.25 (m, 2H), 3.53 (dd, 1H, *J*=13.9, 7.9), 4.17 (q, 2H, *J*=7.1) 4.45-4.58 (m, 1H), 5.76-5.90 (m, 2H), 6.32 (t, 1H, *J*=2.1), 6.63 (d, 1H, *J*=7.3), 6.69-6.78 (m, 2H), 7.08-7.35 (m, 7H), 8.11 (d, 1H, *J*=7.1), 11.22 (s, 1H).

EJEMPLO 4

Preparación del Compuesto 4: trans-(2'R,3'''S,4S)-4-[2'-(7''-Oxo-1'',7''-dihidropirrolo[2'',3''-c-piridin-6''-il)-3-fenilpropionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Acido enóico



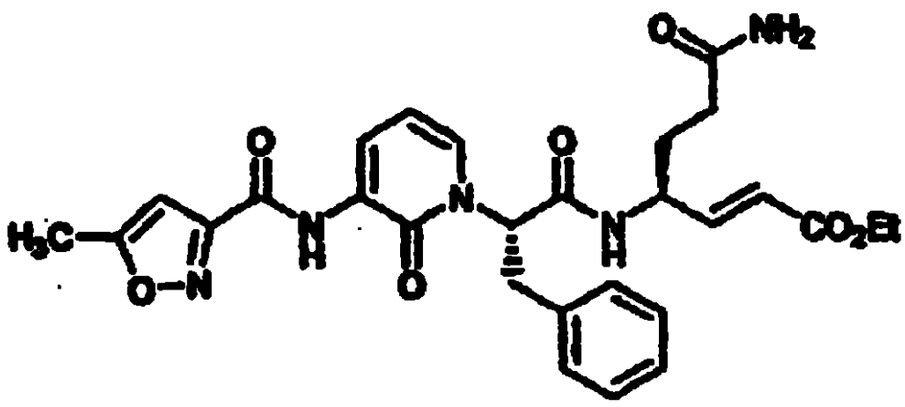
Ver preparación para el Ejemplo precedente: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, *J*=7.1), 1.42-1.52 (m, 1H), 1.58-1.70 (m, 1H), 1.90-

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2.28 (m, 3H), 3.12 (dd, 1H, *J*=13.3, 7.1), 3.20-3.28 (m, 2H), 3.57 (dd, 1H, *J*=13.3, 9.0), 4.07 (q, 2H, *J*=7.0), 4.45-4.58 (m, 1H), 5.80 (d, 1H, *J*=15.7), 6.04 (t, 1H *J*=7.7), 6.37 (t, 1H, *J*=2.3), 6.48 (s, br, 1H), 6.60-6.80 (m, 2H), 7.00-7.40 (m, 6H), 8.11 (d, 1H, *J*=7.8), 10.61 (s, 1H).

EJEMPLO 6

Preparación del Compuesto 5: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3"-[(5'"-metilisoxazol-3'"-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3-fenilpropionilamino)hex-2-Ester de Etilo de Acido enóico (J1)



Preparación del Intermediario (1S)-[1-Hidroximetil-3-(tritilcarbamoil)propil]Ester de Bencilo de Acido carbámico (B1)

4-Metilmorfolin (1.89mL, 17.2 mmol, 1 equiv) y cloroformato de etilo (165 mL, 17.3 mmol, 1equiv) fueron agregados para una mezcla de comercialmente disponible Cbz-Gln(Trt)-Oh (9.00 g, 17.2 mmol, 1equiv) en THF (23 mL) a –10°C. Después de la agitación 20 min, la reacción de mezcla fue filtrada y el filtrado fue agregado gota a gota para una suspensión de $NaBH_4$ (1.47 g, 38.9 mmol, 2.25 equiv) en H_2O (10 mL) a 0°C. La mezcla resultante fue dejada calentar a 23°C y agitada durante 5 h. Esta fue entonces enfriada de nuevo a 0°C, calmada por la cuidadosa agregación de 1 N HCl (30 mL) y entonces las partes por medio de MTBE (500 mL) y

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salmuera (2 x 100 mL). La fase orgánica fue secada bajo Na_2SO_4 y evaporada hasta proporcionar el intermediario titulado el cual fue usado sin además de la purificación.

Preparación del Intermediario (1S)-[1-(tert-Butildimetil silanilloximetil)-3-(tritilcarbamoil)propil]Ester de Bencilo de Ácido carbámico (C1)

Intermediario B1, preparado arriba, fue disuelto en DMF (10 mL). Imidazol (2.69 g, 39.5 mmol, 2.3 equiv) y tert-cloruro de butildimetilsilil (2.86 g, 19.0 mmol, 1.1 equiv) fueron agregados. La reacción de mezcla fue agitada toda la noche, entonces diluida con MTBE (500 mL) y lavado secuencialmente con 2.5% de $KHSO_4$, H_2O, y salmuera (100 mL cada una). La fase orgánica fue secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elusión de gradiente, 25→40% de EtOAc en hexanos) para proporcionar el intermediario titulado (7.6 g, 71%) como un sólido amorfo blanco: IR (cm^{-1}) 3307, 1708, 1660, 1496, 1249; ^1H NMR ($CDCl_3$) δ -0.01-0.05 (m, 6H), 0.89 (s, 9H), 1.76-1.93 (m, 2H), 2.29-2.40 (m, 2H), 3.66-3.77 (m, 3H), 5.03-5.16 (m, 3H), 7.00 (s, 1H), 7.18-7.39 (m, 20H); Anal. $C_{38}H_{46}N_2O_4Si$; C, H, N.

Preparación del Intermediario (2'R, 4S)-5-(tert-Butildimetilsilaniloxi)-4-(2'-hidroxi-3'fenilpropioniIamino)Tritilamida de Acido pentanóico (D1)

El intermediario C1 de arriba (7.6 g, 12 mmol, 1 equiv) y 10% de paladio sobre carbono (0.45 g) fueron suspendidos en EtOH (140 mL) e hidrogenado a 50 psi toda la noche. La mezcla de reacción fue filtrada a través de Whatmn papel #3, el papel fue lavado con EtOH (120 mL) y los filtrados combinados fueron evaporados. El residuo fue combinado con D-3-ácido fenilactico (1.42 g, 12.2 mmol, 1 equiv), iPr_2Net (4.25 mL, 24.4 mmol, 2 equiv) y HATU (4.64 g, 12.2 mmol, 1 equiv) en DMF (35 mL) a 0°C. Después de la agitación 1 h,

la mezcla de reacción fue dejada calentar a 23°C y agitada 20 min más. Entonces 5% de $KHSO_4$ (80 mL) y MTBE (600 mL) fueron agregados y las fases fueron separadas. La fase orgánica fue lavada con H_2O (80 mL) y salmuera (70 mL9, secada bajo Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (50% EtOAc en hexanos) para proporcionar el intermediario titulado como una sopa blanca (4.85 g, 62%): IR (cm^{-1}) 3394, 3295, 1666, 1649, 1519, 1255, 1114, 1085; ^1H NMR ($CDCl_3$) δ -0.03-0.02 (m, 6H), 0.85 (s, 9H), 1.70-1.89 (m, 2H), 2.18-2.42 (m, 3H), 2.83 (dd, 1H, *J*=10.0, 3.1), 3.83-3.94 (m, 1H), 4.17-4.23 (m, 1H), 6.79 (d, 1H, *J*=8.7), 7.09 (s, 1H), 7.17-7.32 (m, 20H); Anal. $C_{39}H_{48}N_2O_4Si \cdot 0.30H_2O$: C, H, N.

Preparación del intermediario (1'S,2R)-Ácido metanosulfónico 1-[1'-(tert-butildimetilsilaniloximetil)-3'-(tritilcarbamoil) propilcarbamoil]-2-Ester feniletilo (E1)

Intermediario D1 de arriba (1.96 g, 3.08 mmol, 1 equiv) y iPr_2Net (0.752 mL, 4.32 mmol, 1.4 equiv) fueron disueltos en CH_2Cl_2 (30 mL) y enfriado a -10°C. Cloruro Metanosulfonilo (0.286 mL, 3.70 mmol, 1.2 equiv) fue agregado gota a gota, lentamente, con agitación vigorosa. Después de 30 min, la mezcla de reacción fue diluido con CH_2Cl_2 (200 mL), lavado con salmuera (50 mL), secada bajo Na_2SO_4 y evaporada para proporcionar el intermediario titulado el cual fue usado sin más purificación.

Preparación del intermediario (2-Hidropiridin-3-il)Ester de tert-Butilo de ácido carbámico (F1)

Una suspensión de 10% de paladio sobre carbono (0.35 g) y 2-hidroxi-3-nitropiridina (5.00 g, 35.7 mmol, 1 equiv) en EtOH (170 mL) fue sujetado a una atmósfera de hidrógeno durante 16 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-3-aminopiridina el cual fue usado sin más

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purificación. Este material crudo fue agitado en THF (100 mL) a 23°C. Dicarbonato de di-tert-butilo (7.79 g, 35.7 mmol, 1 equiv) fue agregado y la mezcla de reacción fue calentada a reflujo durante 4 h. Más dicarbonato de di-tert-butilo (6.0 g, 27 mmol, 0.8 equiv) fue agregado y la mezcla de reacción fue calentada a reflujo durante toda la noche. El solvente fue evaporado y el residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 50→60% EtOAc en hexanos) para proporcionar el intermediario del título como un sólido blanco (6.48 g, 83%): IR (cm^{-1}) 3226,1725, 1649, 1614; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.33 (dd, 1H, J= 7.4,6.6), 7.01 (dd, 1H, J= 6.6,1.8), 7.56 (s, 1H), 8.11 (d, 1H, J= 7.1), 12.61 (s, 1H); Anal. $C_{10}H_{14}N_2O_3$: C, H, N.

Preparación del Intermediario (1''S,2'S)-(1-{1'-[1''-(tert-Butildimetil silaniloximetilo)-3''-(tritilcarba moil)propilcarbamoil]-2'-feniletil}-2-oxo-1,2-dihidropiridin-3-il)- Ester de tert-Butilo de ácido carbámico (G1)

El intermediario F1 de arriba (0.838 g, 3.99 mmol, 1.3 equiv) fue agitado en THF (20 mL). Hidruro de sodio (60% de dispersión en aceite mineral, 0.148 g, 3.70 mmol, 1.2 equiv) fue agregado. Después de la agitación de 20 min, una solución del intermediario E1 de arriba (1 equiv basado sobre D1) en THF (15 mL) fue agregado. La mezcla resultante fue calentada a reflujo durante 40 h, pero la cromatografía de capa delgada mostró la reacción para ser solamente 50% completa. En un frasco separado, más hidruro de sodio (60% de dispersión en aceite mineral, 0.111 g, 2.78 mmol, 0.9 equiv) fue agregado a una suspensión de F1 (0.847 g, 3.08 mmol, 1 equiv) en THF (10 mL). Después de la agitación de 20 min, esta mezcla fue agregada a vasija de reacción original y la mezcla resultante fue calentada a reflujo durante 21 h. Después de la agitación a 23°C durante la semana, la mezcla de reacción cruda fue diluida con MTBE (600 mL) y lavada con una mezcla de salmuera y 10% de $KHSO_4$ (3:1, 80 mL) y salmuera (80 mL), entonces secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de

gradiente, 30→35% EtOAc en hexanos) para proporcionar el intermediario deseado G1 como una espuma blanca (1.98 g, 77%): IR (cm^{-1}) 3389, 3307, 1725, 1678, 1649, 1590, 1502; ^1H NMR ($CDCl_3$) δ -0.02-0.04 (m, 6H), 0.86 (s. 9H), 1.52 (s, 9H), 1.55-1.88 (m, 2H), 2.08-2.14 (m, 2H), 3.19 (dd, 1H, *J*= 13.7,8.1), 3.39-3.51 (m, 2H), 3.53 (dd, 1H, *J*=14.2,7.8), 3.82-3.93 (m, 1H), 5.60-5.67 (m, 1H). 6.17 (t, 1H. *J*=7.3), 6.44 (d, 1H, *J*=8.3), 7.04 (s, 1H), 7.12-7.36 (m, 21H), 7.59 (s, 1H), 7.94 (d, 1H, *J*=7.1); Anal. $C_{49}H_{50}N_4O_5Si$: C, H, N.

Preparación del Intermediario (1"S,2'S)-(1-{1'-[1"-Hidroximetil- 3"-(tritilcarbamoil)propilcarbamoil]- 2'-feniletil}-2-oxo-1,2-dihidropiridin 3-il)-Ester de tert-Butilo de ácido carbámico (H1)

El intermediario G1 de arriba (1.92g, 2.32 mmol, 1 equiv) fue disuelto en una mezcla de CH_3CN (30 mL) y H_2O (3 mL) en un tubo plástico. Trihidrofluoruro de trietilamina (21 gotas) fue agregada y la solución de reacción fue agitada durante toda la noche. Esta fue entonces diluida con EtOAc (750 mL), lavada con salmuera (3 x 80 mL), secada sobre $MgSO_4$ y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(2'S,4'S)-4-[2'-(3"-tert-Butoxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3"-fenilpropionilamino]-6-tritilcarbamoil)hex-2- Ester de Etilo de Acido enóico (I1)

El intermediario H1 de arriba (1 equiv basado sobre G1) fue disuelto en CH_2Cl_2 (20 mL). Comercialmente disponible Dess-Martin Periodinane (1.09 g, 2.55 mmol, 1.1 equiv) fue agregado. Después de la agitación de 2 h, el solvente fue evaporado y el residuo fue suspendido en tolueno y de nuevo evaporado (70 mL, entonces 2% mL) para dar una espuma amarilla. Una mitad de este material (1.16 mmol basada sobre G1) fue disuelta en THF (17 mL). (Carbetoximetileno) trifenilfosforano (0.563 g, 1.62 mmol, 1.4 equiv) fue agregado y la mezcla de reacción fue calentada a reflujo durante 1 h y entonces agitada a 23°C toda la noche. Después de la evaporación del solvente, el residuo fue purificado por

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cromatografía de columna de destello (elución de gradiente, 40→50% EtOAc en hexanos) para proporcionar el intermediario del título (0.710 g, 77%): IR (cm-^{1}) 3378, 3284, 1719, 1649, 1596, 1508, 1267; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.47 (s, 9H). 1.54-1.69 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.22 (m, 2H), 3.12 (dd, 1H, *J*= 13.7,7.7), 3.47 (dd, 1H, *J*= 13.7,8.1), 4.17 (q, 2H, *J*= 7.1), 4.43-4.54 (m, 1H), 5.51-5.58 (m, 1H), 5.64 (dd, 1H, *J*= 15.7,1.6), 6.12 (t, 1H, J= 7.2), 6.60-6.68 (m, 3H), 7.08-7.31 (m, 21H), 7.51 (s, 1H), 7.90 (d, 1H, *J*= 7.1); Anal. $C_{47}H_{50}N_4O_7$•0.50H_2O: C, H, N.

Preparación del intermediario trans-(2'S,4S)-4-(2'-{3"-[(5"'-metilisoxazol-3"'-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3"-fenilpropionilamino)-6-(tritilcarbamoil)hex-2-Ester de Etilo de Acido enóico (I2)

El intermediario I1 de arriba (0.088 g, 0.11 mmol, 1 equiv) fue calentado (neto) a entre 190 y 200°C durante 65 minutos, entonces dejado enfriar proporcionando la amina cruda como un residuo oscuro la cual fue disuelta en CH_3CN (2 mL) y enfriada a 0°C. 5-metilisoxazol-3-cloruro de carbonilo (0.033 g, 0.23 mmol, 2 equiv) y 4-metilmorfolina (0.025 mL, 0.23 mmol, 2 equiv) fue agregada y la mezcla de reacción fue dejada calentar hasta 23°C. Después de la agitación de 40 min, una mezcla de 10% de $KHSO_4$ y salmuera (1:1, 15 mL) y EtOAc (70 mL) fue agregado. Las fases fueron separadas y la fase orgánica fue lavada con salmuera, secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (50% EtOAc en hexanos) para proporcionar el intermediario del título (0.049 g, 55%): IR (cm-^{1}) 3331, 1678 (br), 1590, 1525; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.58-1.72 (m, 1H), 1.87-2.03 (m, 1H), 2.10-2.26 (m, 2H), 2.48 (s, 3H), 3.15 (dd, 1H.J= 13.7, 7.8), 3.47 (dd, 1H, J== 13.7, 8.1), 4.17 (q, 2H, *J*^ 7.1), 4.43-4.55 (m, 1H), 5.54-5.61 (m, 1H), 5.65 (dd, 1H,J= 15.8,1.5), 6.17 (t, 1H, J= 7.3), 6.45 (s, 1H), 6.65 (dd, 1H,J= 15.8, 5.4), 6.72 (s, 1H), 6.84 (d, 1H, *J*- 8.0). 7.08-7.32 (m., 22 H), 8.35 (dd, 1H, J= 7.3,1.5), 9.49 (s, 1H); Anal. $C_{47}H_{48}N_5O_7$•0.25H_2O: C, H, N.

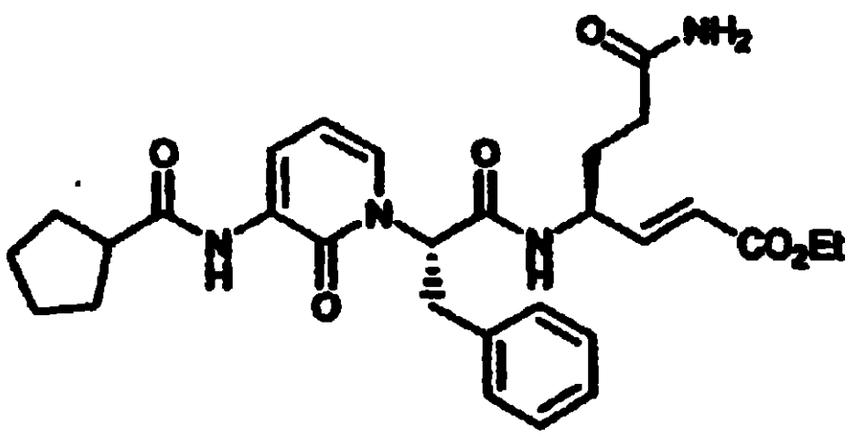
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Preparación del Producto J1 (Compuesto 5)

El intermediario I2 de arriba (0.047 g, 0.059 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (3 mL). Triisopropilsilano (0.036 mL, 0.176 mmol, 3 equiv) y TFA (2 mL) fue agregado. La solución amarilla brillante fue agitada 25 min, entonces diluida con CCl_4 (3 mL) y todos los volátiles fueron evaporados. El residuo fue purificado por cromatografía de columna de destello (3% CH_3OH en CH_2Cl_2) para dar el producto deseado J1 (0.028 g, 85%): IR (cm^{-1}) 3342,1666 (br), 1590,1531,1455; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.17-2.24 (m, 2H), 2.48 (s, 3H), 3.18 (dd, 1H, *J*= 13.7,7.8), 3.50 (dd, 1H, *J*= 13.7,8.1), 4.19 (q, 2H, *J* = 7.1), 4.43-4.54 (m, 1H), 5.68 (dd, 1H, *J* = 15.7,1.3), 5.74-5.82 (m, 1H), 6.00 30 (s, 1H), 6.19 (s, 1H), 6.32 (t, 1H, *J*= 7.3), 6.46 (s, 1H), 6.69 (dd, 1H, *J*= 15.7,5.5), 7.13-7.30(m, 5H), 7.48 (dd, 1H, 7=7.3, 1.6), 7.62(d, 1H,*J*= 7.6), 8.39 (dd, 1H,*J*=7.3, 1.6),9.46(s, 1H); Anal. $C_{28}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 6

Preparación del Compuesto 6: trans-(2'S,4S)-6-Carbamoil-4-{2'-[3''-ciclopentanocarbonilamino-2''-oxo-2''H-piridin-1''-il]-3'-fenilpropionilamino}-hex-2-Ester de Etilo de Acido enóico

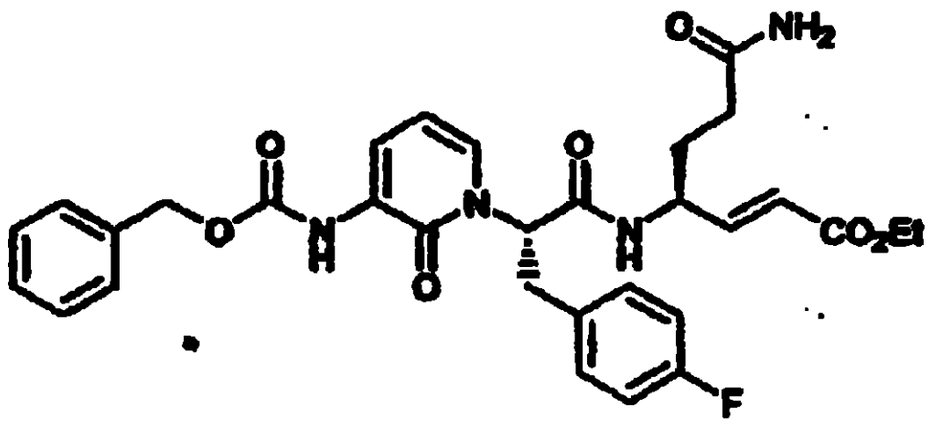


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El compuesto del título fue preparado de I1 (Ejemplo 6) por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando intermediario de cloruro de ciclopentanocarbonilo donde el apropiado: IR(cm^{-1}) 3319, 1713, 1668, 1590, 1514; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, 7= 7.1), 1.55-2.02 (m, 10H), 2.04-2.22 (m, 2H)2.68-2.80 (m, 1H), 3.16 (dd, 1H,J= 13.7,7.7), 3.51 (dd, *J*= 13.7,8.1), 4.19 (q, 2H, *J*= 7.1), 4.45-4.56 (m, 1H), 5.57-5.74 (m, 4H), 6.29 (t, 1H, *J*= 7.4), 6.68 (dd, 1H, *J*= 15.8,5.5), 7.10-7.32 (m. 7H), 8.30(s, IH),8.35(dd, 1H, .7=7.4,1.7); Anal. $C_{29}H_{38}N_4O_6$•0.50H_2O: C, H, N.

EJEMPLO 7

Preparación del Compuesto 7: trans-(2'S,4S)-4-[2'-(3"-Benciloxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3'-(4"'-fluorofenil) propionilamino]-6-carbamoilhex-2-Ester de Etilo de Acido enólico



Preparación del intermediario trans-(2'S,4S)-4-[2'-(3"-Benciloxicarbonylamino-2"-oxo-2"H-piridin-1"-il)-3'-(4"'-fluorofenil)propionilamino]-6-(tritilcarbamoil)hex-2-Ester Etilo de Ácido enólico

El intermediario C1 (Ejemplo 6) fue convertido al intermediario del título por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de C1 a intermediario I1 utilizando S1 (Ejemplo

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22) donde fuere apropiado: IR (cm^{-1}) 3283, 1722, 1651, 1604, 1513; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, *J*= 6.9), 1.62-1.71 (m, 1H), 1.94-2.01 (m, 1H), 2.17-2.24 (m, 2H), 3.06-3.13 (m. 1H), 3.43-3.50 (m, 1H), 4.21 (q, 2H, *J*= 6.9), 4.50-4.57 (m, 1H), 5.16-5.25 (m, 2H), 5.52 (t, 1H, *J*= 8.1), 5.63 (dd, 1H, *J*= 15.6,1.5), 6.18 (t, 1H, *J*= 7.2), 6.65 (s, br. 1H), 6.69 (dd, 1H, *J*= 15.6,5.4), 6.84 (d, 1H, *J*= 8.4), 6.96 (t, 2H, *J*= 8.4), 7.09-7.18 (m, 7H), 7.21-7.33 (m, 12H), 7.38-7.42 (m, 4H), 7.76 (s, br. 1H), 7.99 (d, 1H, *J*= 7.5); Anal. $C_{50}H_{47}N_4O_7 \cdot 0.50H_2O$: C, H, N.

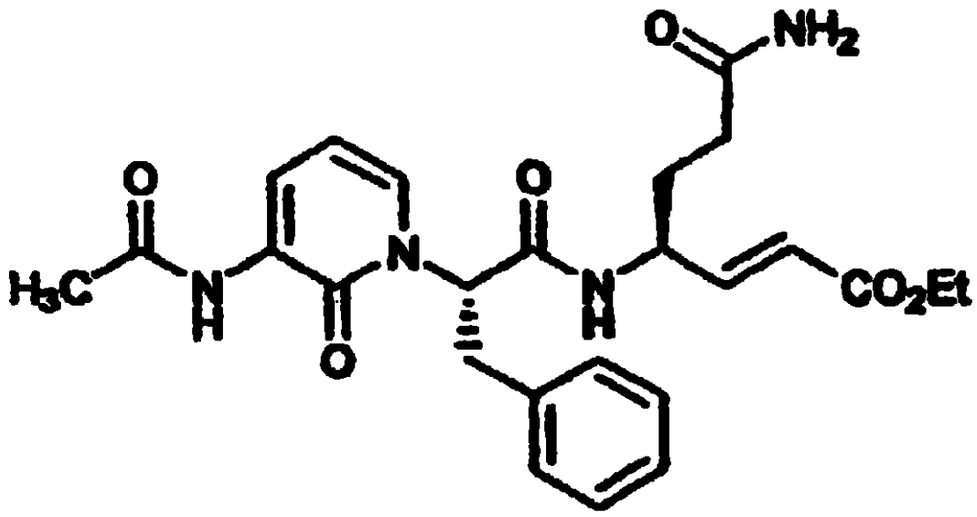
Preparación del Compuesto 7

El intermediario precedente fue convertido a compuesto 7 por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de I2 a producto J1: mp = 99-101 °C; IR (cm^{-1}) 3308, 1714, 1650, 1511, 1199; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, *J*=6.9), 1.72 -1.82 (m, 1H), 1.86-1.96 (m, 1H), 2.10-2.18 (m, 2H), 3.10-3.17 (m, 2H), 3.10-3.17 (m. 2H), 3.46-3.53 (m, 1H), 3.63-3.74 (m, 2H), 4.22 (q, 2H, *J*= 6.9), 4.48-4.57 (m, 1H), 5.21 (s, 2H), 5.58-5.65 .(m, 2H), 5.91-5.97 (m, 1H), 6.19-6.22 (m, 1H), 6.35 (t, 1H, *J*= 7.2), 6.69 (dd, 1H, J= 15.6, 5.1), 6.98 (t, 2H, *J*= 8.7), 7.13-7.18 (m, 2H), 7.36-7.40 (m, 5H), 7.85 (s, br. 1H), 8.06-8.09 (m, 1H); Anal. $C_{33}H_{33}N_4O_7 \cdot 1.25H_2O$: C, H, N.

EJEMPLO 8

Preparación del Compuesto 8: trans-(2'S,4S)-4-[2'-(3"-Acetilamino-2"-oxo-2"H-piridm-1"-il)-3'-fenipropionilamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enoico

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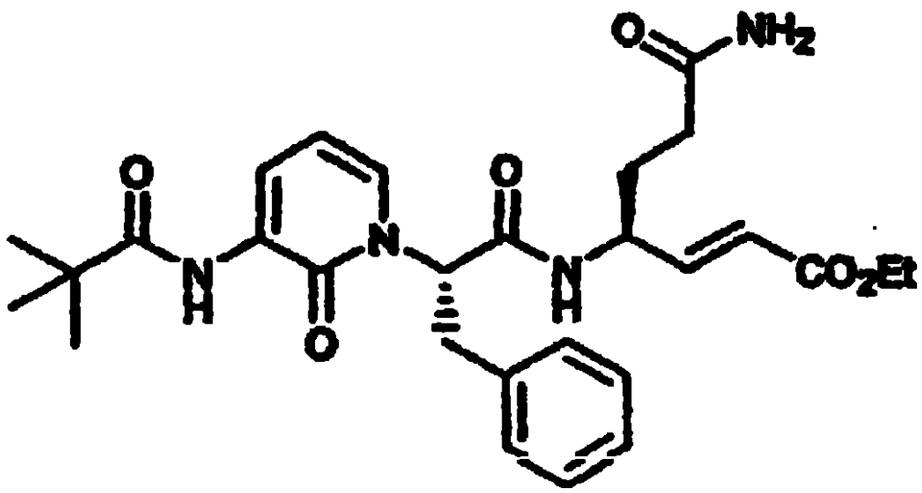


El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a aquel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando intermediario cloruro de acetilo donde fuere apropiado: IR (cm^{-1}) 3307, 1708, 1666, 1643, 1590, 1519; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H,J= 7.1), 1.70-1.86 (m, 2H), 2.05-2.24 (m, 5H), 3.15 (dd, 1H,J= 13.7, 8.1), 3.50 (dd, 1H, J= 13.7,7.8), 4.19 (q, 2H, *J*= 7.1), 4.45-4.56 (m, 1H), 5.66-5.77 (m, 2H), 5.82 (s, 1H), 5.94 (s, 1H), 6.28 (t, 1H, *J*= 7.2), 6.69 (dd, 1H, 7= 15.7,5.6), .7.10-7.29 (m, 5H). 7.32-7.45 (m, 2H), 8.28-8.36 (m, 2H); Anal. $C_{25}H_{30}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 9

Preparación del Compuesto 9: trans-(2'S,4S)-6-Carbamoil-4-{2'-[3"-(2"',2"'-dimetilpropioniiamino)-2"-oxo-2"H-piridin-1"-il]-3'-fenilpro pioniiamino}hex-2-Ester de Etilo de Ácido enóico

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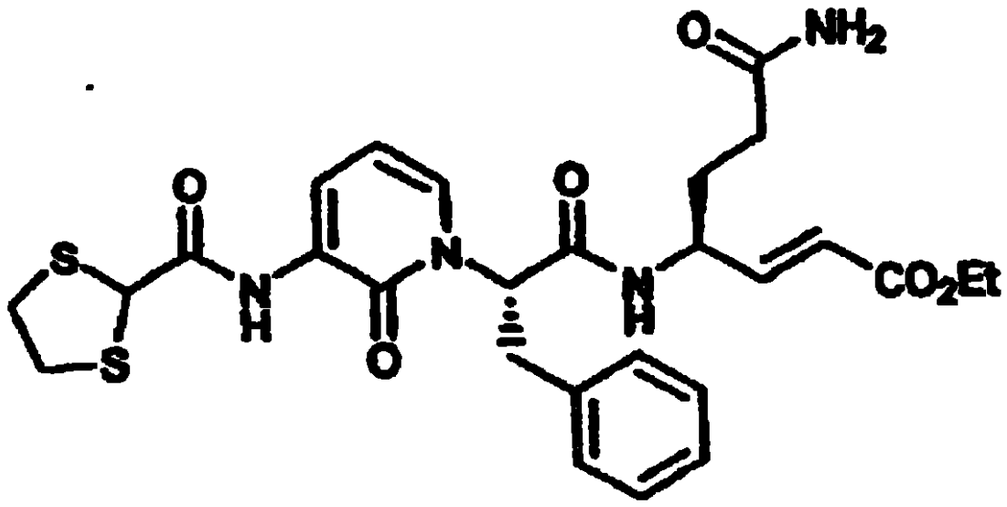


El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a aquel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando intermediario cloruro de 2,2-dimetilpropionilo donde fuere apropiado: IR (cm^{-1}) 3378, 3307, 3213, 1713, 1666, 1643, 1590, 1514, 1273; ^1H NMR ($CDCl_3$) δ 1.18-1.37 (m, 12H), 1.67-1.98 (m, 2H), 2.05-2.20 (m, 2H), 3.17 (dd, 1H,J= 13.6, 7.7), 3.50 (dd, 1H,J= 13.6,8.2), 4.19 (q, 2H,J= 7.1), 4.43-4.54 (m, 1H), 5.62-5.72 (m, 2H), 5.81-5.92 (m, 2H), 6,29 (t, 1H,J= 7.2), 6.66 (dd, 1H, J= 15.8,5.7), 7.13-7.39 (m, 7H), 8.33-8.38 (m, 1H), 8.59 (s, 1H); Anal. $C_{28}H_{36}N_4O_6 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 10

Preparación del Compuesto 10: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3''-[([1''',3''']ditiolano-2'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}-3'-fenilpropioniliamino)hex-2-Ester de Etilo de ácido enóico

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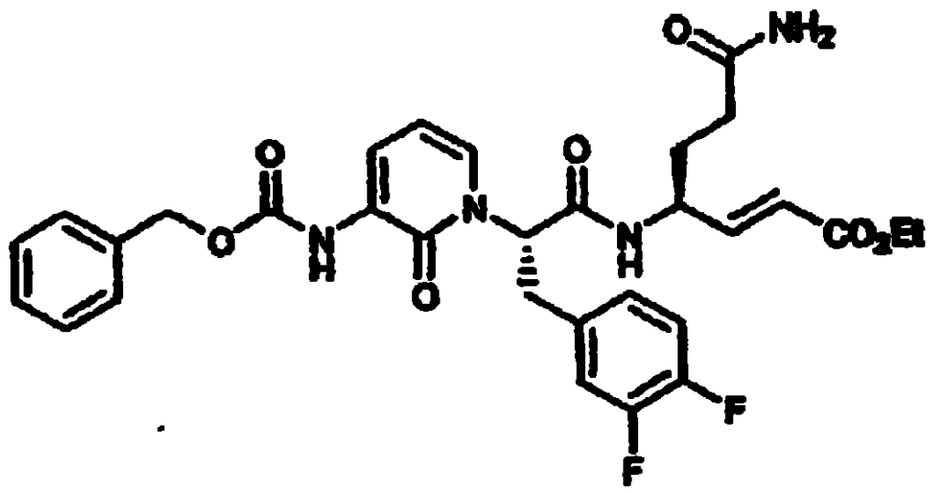


El compuesto del título fue preparado de I1 (Ejemplo 5) por un proceso análogo a quel descrito en el Ejemplo 5 para la conversión de I1 a producto J1 utilizando el intermediario cloruro [1,3]ditiolano-2-carbonilo (preparado tal como se describió en *Helv. Chim. Acta* 1975, *58*, 2509) donde fuere apropiado: IR (cm-I) 3295, 1672 (br), 1590, 1519 (br), 1273; ^{1}HNMR (CDC_3) δ 1.30 (t, 3H, *J*= 7.1), 1.66-2.22 (m, 4H), 3.17 (dd, 1H, *J*= 13.7,7.8), 3.28-3.45 (m, 4H), 3.52 (dd, 1H, *J*= 13.7, 8.1), 4.19 (q, 2H, *J*= 7.1), 4.43-4.55 (m, 1H), 5.01 (s, 1H), 5.66 (dd, 1H, *J*= 15.8,1.5), 5.67 (s, 1H), 5.86 (s, 2H), 6.29 (t, 1H, *J*= 7.3), 6.67 (dd, 1H, *J*= 15.8, 5.5), 7.12-7.40 (m, *7H)*, 8.31 (dd, 1H, *J*= 7.3,1.6), 9.57 (s, 1H); Anal. $C_{27}H_{32}N_4O_7S_4 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 11

Preparación del Compuesto 11: trans-(2'S,4S)-4-[2'-(3"-Benciloxicarbonilamino-2"-oxo-2"H-piridin-1"-il)-3'-(3"',4"'-difluorofenil)propionilamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico

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Preparación del Intermediario (2R)-3-(3',4'-Difluorofenil)-2-Ácido hydroxipropiónico

Boc-D-3,4-Difluorofenilalanina (3.05 g, 11.0 mmol, 1 equiv) fue disuelto en 1,4-dioxano (10 mL), y una solución de HCl en 1,4-dioxano (4.0 M, 10 mL) fue agregada. La reacción fue agitada a 23 °C durante 5 h, entonces el solvente fue removido bajo presión reducida. El residuo fue disuelto en 1 M H_2SO_4 (22 mL), enfriado a 0 °C y 2 N $NaNO_2$ (22 mL) fue agregado via de adición de tunel bajo argón. La mezcla de reacción fue agitada a 0 °C durante 3 h y calentada a temperatura ambiente toda la noche. La mezcla resultante fue extractada con MTBE (3 x 40 mL), secada sobre Na_2SO_4 y concentrada. El residuo fue recristalizado de éter/éter de petróleo para proporcionar el intermediario del título (1.29 g, 58%) como un sólido casi blanco. ^1H NMR (DMSO-d_6) δ 0.82-0.86 (m, 2H), 1.10-1.27 (m, 4H), 1.40-1.48 (m, 2H), 1.63-1.78 (m, 5H), 3.95-4.00 (m, 1H).

Preparación del Compuesto 11

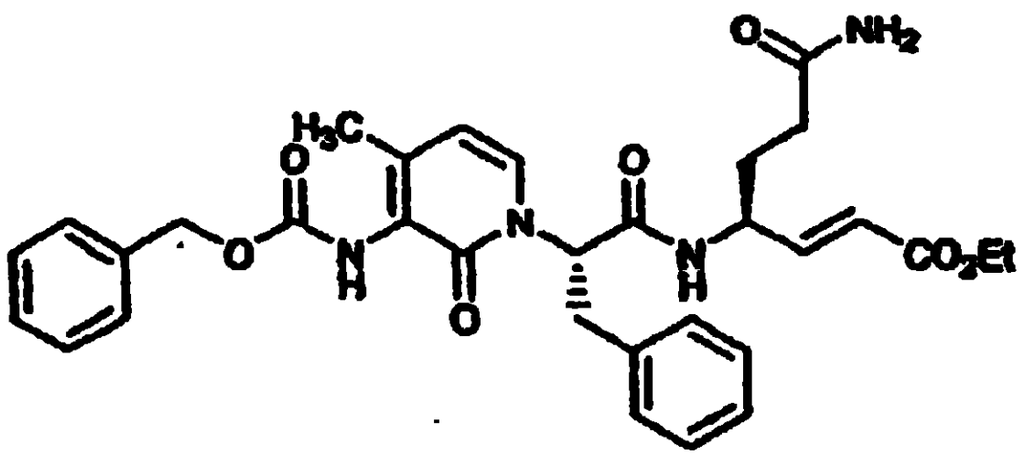
El intermediario C1 (Ejemplo 5) fue convertido a compuesto 11 por un proceso análogo como aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando (2R)-3-(3',4'-difluorofenil)-2-ácido hidroxipropiónico (Ejemplo 11) donde fuere apropiado: mp = 176-178°C; IR (cm^{-1}) 3298, 1661, 1516, 1266; ^{1}HNMR (CDC_3) δ 1.32 (t, 3H,*J*=7.2), 1.74-1.95 (m,2H), 2.12-2.20

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(m,2H), 3.06-3.12 (m, 1H), 3.42-3.50 (m. 1H),4.21 (q,2H,J= 7.2), 4.45-4.56 (m, 1H), 5.21 (s, 2H), 5.58-5.71 (m, 3H), 6.07-6.10 (m, 1H), 6.32-6.34 (m, 1H), 6.71 (dd, 1H, *J*= 15.6, 5.1), 6.88-6.91 (m, 1H), 6.99-7.11 (m, 2H), 7.30-7.33 (m, 1H), 7.36-7.39 (m, 5H), 7.53 (s, br. 1H), 7.86 (s, br. 1H), 8.04 (s, br. 1H); Anal. $C_{31}H_{32}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 12

Preparación del Compuesto 12: trans-(2'S,4S)-4-[2'-(3"-Bencilоxicarboniliamino-4"-metil-2"-oxo-2"H-piridin-1"-il)-3'-fenilpropioniliamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico



Preparación del Intermediario (2-Hidroxi-6-metilfenil)Ester de Bencilo de ácido carbámico

Una suspensión de 10% de paladio sobre carbono (0.045 g) y 2-hidroxi-4-metil-3-nitropiridina (0.600 g, 3.89 mmol, 1 equiv) en EtOH (20 mL) fue sometida a una atmósfera de hidrógeno durante 16 horas. Después de purgar la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-4-metil-3-aminopiridina el cual fue usado sin más purificación. Este material crudo fue agitado en THF (18 mL) a 23°C. Cloroformato de bencilo (0.611 mL, 4.28 mmol, 1.1

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equiv) y Na_2CO_3 (0.907 g, 8.56 mmol, 2.2 equiv) fueron agregados y la mezcla de reacción fue agitada durante 60 h, pero el TLC mostró que la reacción fue solamente 25% completa. La mezcla de reacción fue calentada a reflujo durante 24h. Más cloroformato de bencilo (0.611 mL, 4.28 mmol, 1.1 equiv) y Na_2CO_3 (0.454 g, 4.28 mmol, 1.1 equiv) fue agregado. La mezcla de reacción fue calentada a reflujo durante 24 h más, dejada enfriar, diluida con EtOAc (200 mL, lavada con la mitad de salmuera saturada (2 x 40 mL), secada sobre $MgSO_4$, filtrada y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 3→5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.363 g, 35%) como un sólido blanco: ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 3.3L.3.35 (m, 2H), 5.06 (s, 2H), 6.83 (d, 1H, J= 6.7), 7.17 (d, 1H, J= 6.7), 7.28-7.39 (m, 5H); Anal. $C_{14}H_{14}N_2O_3$: C, H, N.

Preparación del Compuesto 12

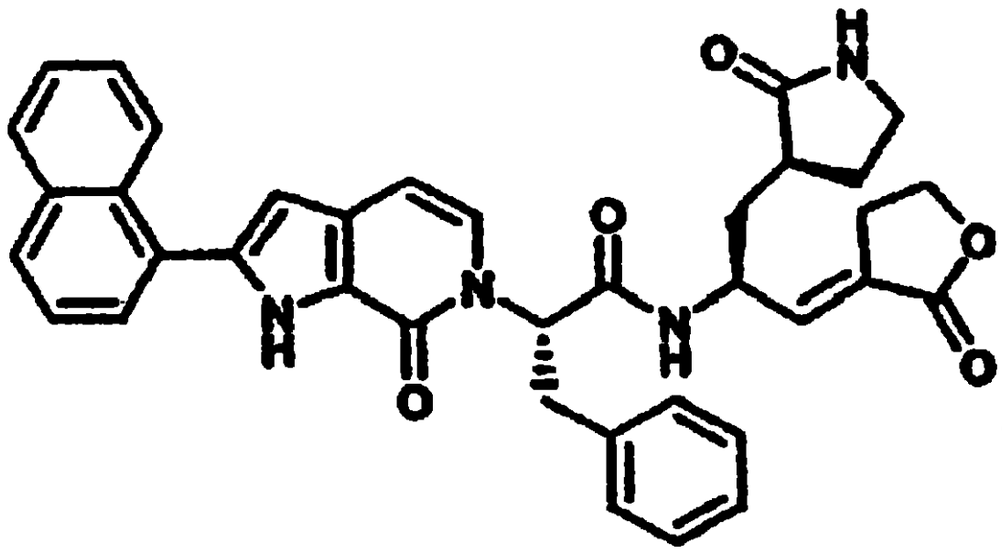
El intermediario precedente fue convertido a compuesto 12 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico y C1 (Ejemplo 5) donde fuere apropiado: IR cm^{-1}) 3284, 1684 (br), 1596, 1327, (br), 1308, 1267, 1237; ^{1}HNMR (CDC_3) δ 1.29 (t, 3H, *J*= 7.1), 1.56-1.68 (m, 1H), 1.82-2.07 (m, 4H), 2.14 (s, 3H), 3.08 (dd, 1H, *J*= 13.6,7.1), 3.47 dd, *J*= 13.6, 8.8), 4.17 (q, 2H, *J*= 7.1), 4.41-4.52 (m, 1H), 5.06 (d, 1H, *J*= 12.3), 5.12 (d, H, *J*= 12.3), 5.59 (dd, 1H, *J*= 15.7,1.6), 5.67-5.74 (m, 1H), 5.90 (s, 1H), 6.02 (s, 1H), 6.17 d, 1H, *J*= 7.3), 6.68 (dd, 1H, *J*= 15.7, 5.1), 7.01 (s, 1H), 7.13-7.38 (m, 10H), 7.48 (d, 1H, *J* = 7.3); Anal. $C_{32}H_{36}N_4O_7 \cdot 0.75H_2O$: C, H, N.

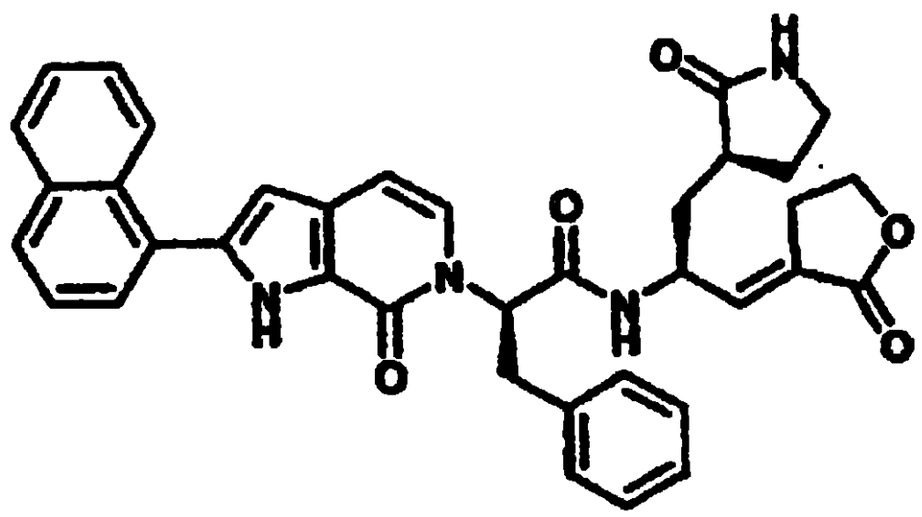
EJEMPLO 13

Preparación de 1:1 mezcla del Compuesto 13: trans-(2S,2''S,3S)-2-(2'-Naftalen-1'-il-7'-oxo-1',7'-dihidropirrolo[2',3'-c]piridin-6'-il)-N-[2''-(2'''-oxodihidrofurán-3'''-ilideno)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]-3-fenilpropionamida y Compuesto 14: trans-

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(2R,2''S,3S)-2-(2'-Naftalen-1'-il-7'-oxo-1',7'-dihidropirrolo[2',3'-c]piridin-6'-il)-N-[2''-(2'''-oxodihidrofurán-3'''-iliden)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]-3-fenilpropionamida





Preparación del intermediario Pirrol-2-Ester de Metilo de Ácido carboxílico

Pirrol-2-ácido carboxílico (10.0 g, 90.0 mmol) en éter de dietilo (200 mL) fue tratado con diazometano (270 mmol, generado de N-nitroso-N-metil úrea), entonces la parte trasera tritada con ácido acético hasta cuando el color amarillo se disipó. La solución

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fue lavada con bicarbonato de sodio acuoso (3 x 20 mL), seguido por salmuera (3 x 20 mL) entonces fue evaporado para obtener 10 g (88%) de producto. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.26-6.29 (m, 1H), 6.91-6.94 (m, 1H), 6.65-6.98 (m, 1H), 9.14 (s, 1H).

Preparación del Intermediario 5-Bromo-1H-pirrol-2-Ester de Metilo de Ácido carboxílico

Una solución del intermediario precedente (10.0 g, 79.9 mmol, 1 equiv) en tetracloruro de carbono (300 mL) fue calentada a 70°C, entonces tratada gota a gota con una solución de bromuro (126.0 mL, 99.9 mmol, 1.25 equiv) en tetracloruro de carbóno (200 mL). La reacción fue iniciada por la adición de yodo (40 mg). Después que la adición estuvo completa, la reacción fue mantenida a 70°C durante 10 min, entonces enfriada a 23°C usando un baño de hielo. La mezcla fue lavada con 10% con carbonato de sodio acuoso (100 mL), seguida por agua (100 mL). Los volátiles fueron evaporados, y el residuo fue purificado por cromatografía de gel de sílice para obtener 4.5 g (27%) de producto: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.23 (dd, 1H, *J*= 3.8,2.6), 6.80 (dd, 1H, *J*= 3.9,2.7), 9.29 (s, 1H).

Preparación del Intermediario 5-Naftalen-1-il-1H-pirrol-2-Ester de Metilo de Ácido carboxílico

Gas de argón fue bombeado durante 15 min a través de una solución del intermediario precedente (2.04 g, 10.0 mmol, 1 equiv) en 2 M de carbonato de sodio acuoso (20 mL), y DMF (150 mL). La mezcla fue tratada con tris(dibencilidienacetona)dipaladio (0) (0.46 g, 0.50 mmol, 0.05 equiv), y trifenilarsina (0.61 g, 2.0 mmol, 0.20 equiv), entonces calentada a reflujo, bajo argón, durante 12 h. La mezcla fue tomada en acetato de etilo (500 mL) y agua (150 mL), entonces filtrada a través de celita. La capa orgánica fue lavada con salmuera (3 x 50 mL), entonces evaporada. La purificación del residuo por cromatografía de gel de sílice rindió 2.05 g (81%) del producto. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.22 (dd, 1H, *J*= 3.8.2.6), 7.50-7.59 (m, 4H), 7.88 (dd, 1H, *J*= 3.9,2.7), 7.89-8.16 (m, 2H), 8.17-8.22 (m, 1H), 9.37 (s. 1H). Este material fue tomado en 1:1

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1,4-dioxano-agua (30 mL), y tratado con hidrato de hidroxido de litio (1.02 g, 24.4 mmol, 2.4 equiv), entonces calentada a reflujo durante 15 min. La solución fue acidificada con 20% ácido cítrico acuoso (30 mL), entonces extractada con acetato de etilo (75 mL). La capa orgánica fue lavada con salmuera (2 x 20 mL), entonces evaporada. El residuo fue tomado en CH_2Cl_2, (30 mL), y tratada con cloruro de oxalilo (2.10 mL, 24.0 mmol, 2.4 equiv), y DMF (una gota), entonces calentada a reflujo durante 30 min. La evaporación rindió 5-naftalen-1-il-1H-pirrol-2-cloruro de ácido carboxílico el cual fue usado en el procedimiento subsiguiente sin purificación adicional.

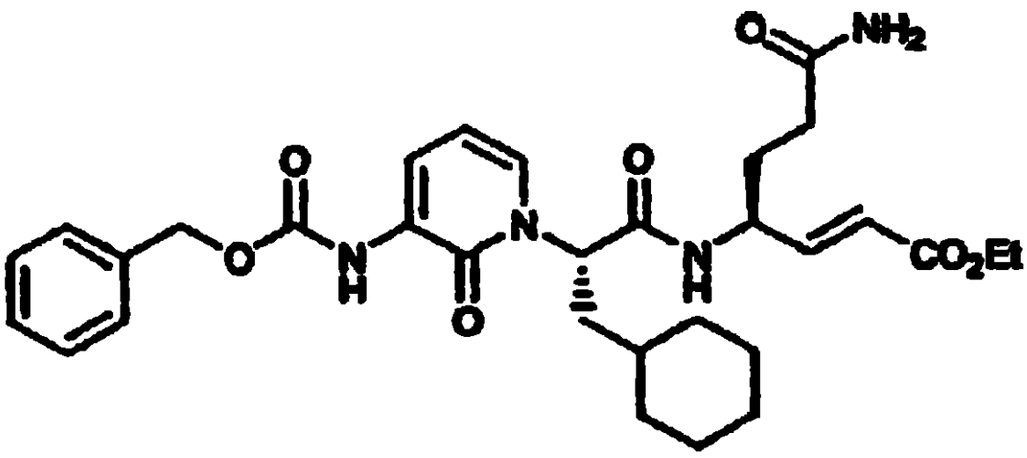
Preparación del Producto 13 y 14

El intermediario precedente fue convertido a una inseparable mezcla de 1:1 de los compuestos del título por un proceso que fue análogo a aquel descrito en el Ejemplo 3 para la conversión de pirrol-2-cloruro de carbonilo a compuestos 3 y 4 y utilizando intermediario Y1 (Ejemplo 22) en lugar deY2 donde fuere apropiado. ^{1}H NMR ($CDCl_3$) δ 1.55-2.00 (m, 6H), 2.50-3.50 (m, 7H), 4.00-4.50 (m, 3H), 4.42-5.80 (m, 1H), 5.90-8.40 (m, 15H), 10.49 (s, 0.5H), 11.54 (s, 0.5H).

EXAMPLE 14

Preparación del Compuesto 15: trans-(2'S,4S)-4-[2'-(3''-Benciloxicarboniiamino-2''-oxo-2''H-piridin-1''-il)-3'-ciclohexilpropioniiamino]-6-carbamoil-hex-2-Ester de Etilo de Ácido enóico

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Preparación del Intermediario (2R)-3-Ciclohexil-2-Ácido hidroxipropiónico

Boc-D-Ciclohexilalanina-OH (3.00 g, 11.1 mmol, 1 equiv) fue disuelto en 1,4-dioxano (10 mL), y una solución de HCl en 1,4-dioxano (4.0 M, 10 mL) fue agregada. La reacción fue agitada a 23 °C durante 5 h, entonces el solvente fue removido bajo presión reducida. El residuo fue disuelto en 1 M H_2SO_2 (22 mL), enfriado hasta O °C y 2 N $NaNO_2$ (22 mL) fue agregado vía tunel de adición bajo argón. La mezcla de reacción fue agitada a O °C durante 3 h y calentada a temperatura ambiente toda la noche. La mezcla resultante fue extractada con MTI (3 x 40 mL), secada sobre Na_2SO_4 y concentrada. El residuo fue triturado con éter de petróleo, filtrado y secado en el aire para proporcionar el intermediario del título (0.6 g, 31%) como un sólido casi blanco. ^1H NMR (DMSO-d_6) δ 3.09-3.24 (m, 2H), 4.20-4.24 (m, 1H), 7.13-7.18 (m, 1H), 7.38-7.47 (m, 2H), 8.49 (s, br. 1H).

Preparación del Compuesto 15

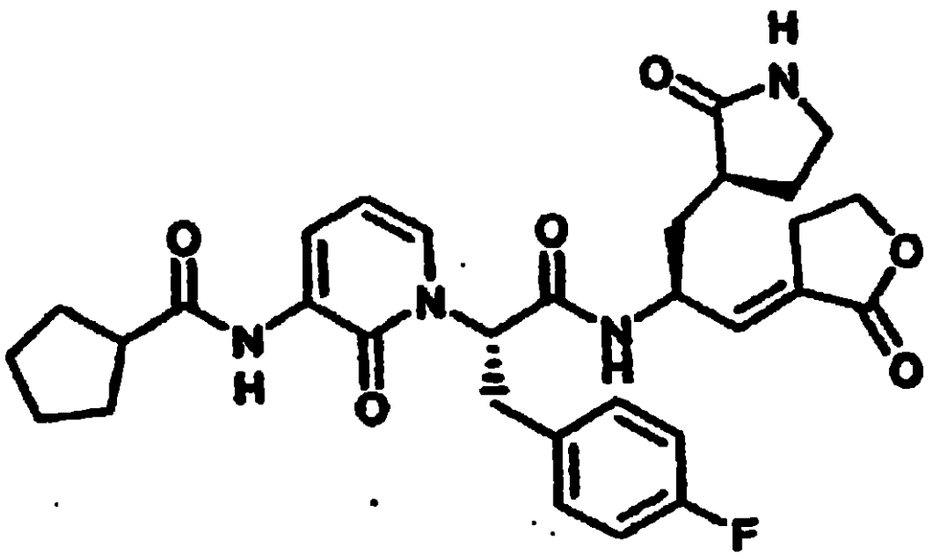
El intermediario C1 (Ejemplo 5) fue convertido a producto 15 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a compuesto 7 utilizando (2R)-3-ciclohexil-2-ácido hidroxipropiónico (Ejemplo 14) donde fuere apropiado: mp = 64-66 ^oC; IR (cm^{-1}) 3302, 2925, 1721, 1651, 1197; ^1H NMR ($CDCl_3$)

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δ 0.93-1.05 (m,2H), 1.18-1.22 (m, 4H), 1.32 (t, 3H, *J*= 7.2), 1.66-1.75 (m, 4H), 1.82-1.91 (m, 2H), 1.94-2.06 (m, 2H), 2.10-2.17 (m, 2H), 2.90-2.92 (m, 2H), 4.23 (q, 2H, *J*= 7.2), 4.52-4.60 (m, 1H), 5.23 (s, 2H), 5.65 (t, 1H,J= 8.1), 5.82-5.86 (m, 1H), 5.62 (dd, 1H, *J*= 15.9,1.8), 6.01-6.05 (m, 1H), 6.37 (t, 1H,7= 7.2), 6.85 (dd, 1H,,*J*= 15.9, 5.7), 7.25-7.29 (m, 1H), 7.36-7.43 (m, 5H), 7.88 (s, br. 1H), 8.09 (d, 1H, J° 6.9); Anal. $C_{31}H_{40}N_4O_7$•1.0H_2O: C, H, N.

EJEMPLO 16

Preparación del Compuesto 16: trans-(2'S,2'''S,3'''''S)-Ácido ciclopentanocarboxílico (l-{2'-(4"-fluorofenil)-1'-[2"-(2'''-oxo-dihidrofurán-3'''-ilideno)-1'''-(2'''''-oxopirrolidin-3'''''-ilmetil) etilcarbamoil]etil}-2-oxo-l ,2-dihidropiridin-3-il)amida



Preparación del intermediario de Ácido Ciclopentanocarboxílico (2-Hidroxipiridin-3-il)amida

Una muestra de 10% Pd sobre C (0.40 g) fue agregada a una solución de 2-hidroxi-3-nitropiridina (3.52 g, 25.0 mmol, 1 equiv) en EtOH. La mezcla de reacción fue agitada a temperatura ambiente

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bajo atmósfera de H_2 (aerostato) toda la noche y entonces fue filtrada a traves de Celite. El filtrado fue concentrado bajo presión reducida. EL residuo fue disuelto en CH_3CN (100 mL), enfriada hasta O ^oC, cloruro de ciclopentanocarbonilo (25 mmol, 3.04 mL, 1 equiv) y NMM (2.75 mL, 25 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla resultante fue agitada a O ^oC durante 20 min, entonces fue partida entre agua (400 mL) y 10% CH_3OH en CH_2Cl_2 (2 x 400 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4, concentrada, y el residuo resultante recristalizado de CH_2Cl_2/hexanos para proporcionar el intermediario del título como un sólido casi blanco (3.36 g, 65%); mp = 242-243 ^oC; IR (cm^{-1}) 3263, 644, 1605, 1521, 1199; ^1H NMR (DMSO-d_6) δ 1.51-1.57 (m,2H), 1.60-1.72(m, 4H), 1.79-1.88 (m, 2H), 2.98-3.08 (m, 1H), 6.20 (t, 1H, J = 6.9), 7.08 (d, 1H, J= 6.6), 8.23 (d, 1H, J= 7.5), 9.02 (s, br. 1H), 11.95 (s, br. 1H); $C_{11}H_{14}N_2O_2$: C, H, N.

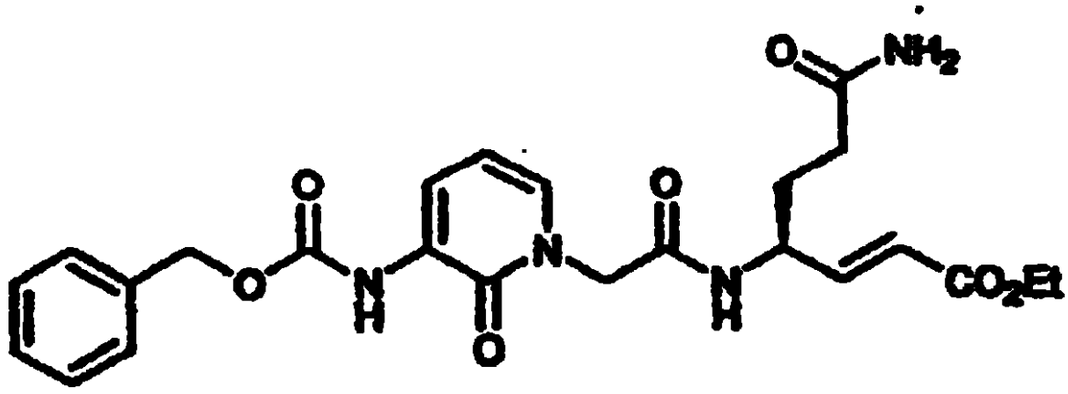
Preparación del Compuesto 16

El intermediario precedente fue convertido a compuesto 16 por un proceso que fue análogo a aquel descrito en el Ejemplo 19 para la conversión de F2 a R1: mp =135-137 °C; IR (cm^{-1}) 3288, 2954, 1754, 1682, 1511, 1219; ^1H NMR ($CDCl_3$) δ 0.84-0.93 (m, 2H), 1.55-1.66 (m, 4H), 1.82-2.02 (m, 5H), 2.27-3.22 (m, 2H), 2.70-2.89 (m, 3H), 3.09-3.17 (m, 1H), 3.20-3.37 (m, 2H), 3.42-3.39 (m, 1H), 5.83 (t, 1H, J= 7.2), 6.03 (s, br. 1H), 6.25-6.35 (m, 2H), 6.94 (t, 2H, J= 8.7), 7.08-7.12 (m, 2H), 7.25 (d, 1H, J= 9.0), 8.30-8.35 (m, 2H), 8.44 (d, 1H, J= 6.0); Anal. $C_{31}H_{36}FN_4O_8 \cdot 1.0H_2O$: C, H, N.

EJEMPLO 18

Preparación del Compuesto 17: trans-(4S)-4-[2'-(3"-Benciloxicarboniiamino-2"-oxo-2"H-piridin-1"-il)acetiiamino]-6-carbamoilhex-2-Ester de Etilo de Ácido enico

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Preparación del intermediario (3-benciloxicarboniiamino-2-oxo-2h-piridin-1-il)ester de tert-butilo de ácido acético

Hidruro de sodio (0.070 g de una suspensión 60% en aceite mienral, 1.75 mmol, 1.0 equiv) fue agregada a una solución de (2-hidroxipiridin-3-il)ester de bencilo de ácido carbámico (preparado tal como se describió en el Ejemplo 1) (0.415 g, 1.70 mmol, 1 equiv) en THF (20 mL) a O °C. La mezcla de reacción fue agitada durante 20 min a O °C, entonces bromoacetato de tert-butilo (0.275 mL, 1.86 mmol, 1.1 equiv) fue agregado. La reacción de mezcla fue calentada a 23 °C durante 45 min, entonces fue particionada entre 0.5 M HC1 (150 mL) and EtOAc (2 x 100 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4 y fueron concentradas. Purificación del residuo por comratografía de columna de destello (30% EtOAc en hexanos) proporciona el compuesto del título (0.485 g, 85%) como un sólido casi blanco: mp=88-90°C; IR (cm^{-1}) 3380, 1739, 1652, 1604; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 4.57 (s, 2H), 5.20 (s, 2H), 6.25 (t, 1H, *J*= 7.1), 6.87 (dd, 1H, *J*= 6.9,1.7), 7 27-7.41 (m, 5H), 7.86 (s, br, 1H), 8.05 (d, br, 1H J= 6.8); Anal. $C_{19}H_{22}N_2O_5$: C, H, N.

Preparación del intermediario (3-Benciloxicarboniiamino- 2-oxo-2H-piridin-1 -il)Ácido acético

(3-Benciloxicarboniiamino-2-oxo-2H-piridin-1-il) éster de tert-butilo de ácido acético (0,485 g, 1.35 mmol) fue agitada de una mezcla 1:1 de ácido trifluoroacético and CH_2Cl_2 a 23 °C durante 1

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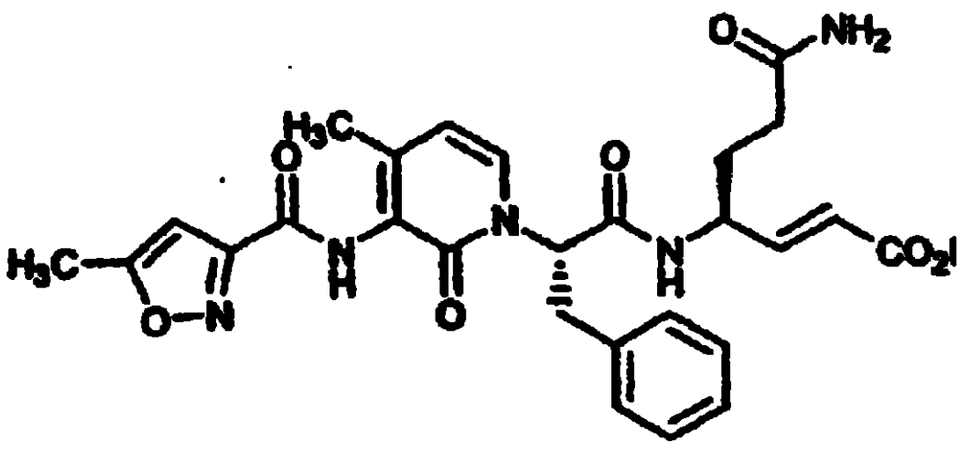
h. Los volátiles entonces fueron removidos bajo presión reducida y el residuo fue triturado con Et_2O (40 mL). El sólido resultante fuefiltrado a través de una firtura media, lavada con Et_2O (20 mL) y secada al aire para dar el intermediario del título (0.315 g, 77%): mp =171-173 °C; ^1H NMR (DMSO-d_6) δ 4.67 (s, 2H), 5.15 (s, 2H), 6.28 (t, *IH*,*J*= 7.1), 7.29-7.43 (m, 7H), 7.85 (dd, 1H,J= 7.4,1.7), 8.47 (s, 1H).

Preparation of Compound 17

El intermediario precedente fue convertido a compuesto 17 por un proceso análogo a aquel descrito en el Ejemplo 23 para la conversión de W2 a J2: mp = 169-174 °C; IR (cm^{-1}) 3273, 1719, 1649; ^1H NMR (DMSO-d_6) δ 1.19 (t,3H,J= 7.1), 1.64-1.85 (m,2H), 2.10(t, 2H,J=7.6),4.11 (q,2H,J=7.J), 4.38-4.41 (m, IH),4.60(d, 1H,^= 15.5), 4.67 (d, 1H, *J*=15.5),5.15 (s, 2H), 5.92 (dd, 1H, *J*=15.8,1.3), 6.26 (t, 1H,J= 7.1), 6.76-6.83 (m,2H), 7.09-7.42 (m, 7H), 7.84 (d, 1H, *J*=7.3), 8.41-8.44 (m, 2H); Anal. $C_{24}H_{26}N_4O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 17

Preparación del Compuesto 18: trans-(2'S,4S)-6-Carbamoil-4-(2'-{4"-metil-3"-[5"'-metilisoxazol-3""-carbonil)amino]-2"-oxo-2"H-piridin-1"-il}-3'- fenilpropioniiamino)hex-2-Ester de Etilo de Ácido enóico



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Preparación del intermediario 5-Metilisoxazol-3-Ácido carboxílico (2' -hidroxi-4'-metilpiridin-3' -il)amide

Una muestra de 10% Pd sobre C (0.35g) fue agregada a una solución de 2-hidroxi-3-nitropiridina (2.03 g, 14.5 mmol, 1 equiv) en EtOH. La mezcla de reacción fue agitada a temperatura ambiente bajo atmósfera H_2 (aerostato) toda la noche y entonces fue filtrada a través de Celita. El filtrado fue concentrado bajo presion reducida. El residuo fue disuelto en CH_3CN (100 mL), enfirada a °C, y 5-metilisoxazol-3-cloruro de carbonilo (2.11 g, 14.5 mmol, 1 equiv) y NMM (1.51 mL, 14.5 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla resultante fue agitada a O °C durante 20 min, y entonces fue partida por medio de agua (400 mL) y 10% CH_3OH en CH_2Cl_2 (2 x 400 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4, concentrada y el residuo resultante fue recristalizado de CH_2Cl_2/hexanos para proporcionar el intermediario del título como un sólido casi blanco (2.42 g, 76%): IR (cm^{-1}) 3330, 1650, 1536; ^1H NMR (DMSO-d_6) δ 3.34 (s, 3H). 6.31 (t, 1H, *J*=6.6), 6.73 (s, 1H), 7.21 (d, 1H, *J*= 7.2), 8.29 (s, 1H, *J*=7.2), 9.46 (s, br. 1H), 12.23 (s, br. 1H).

Preparación del Compuesto 18

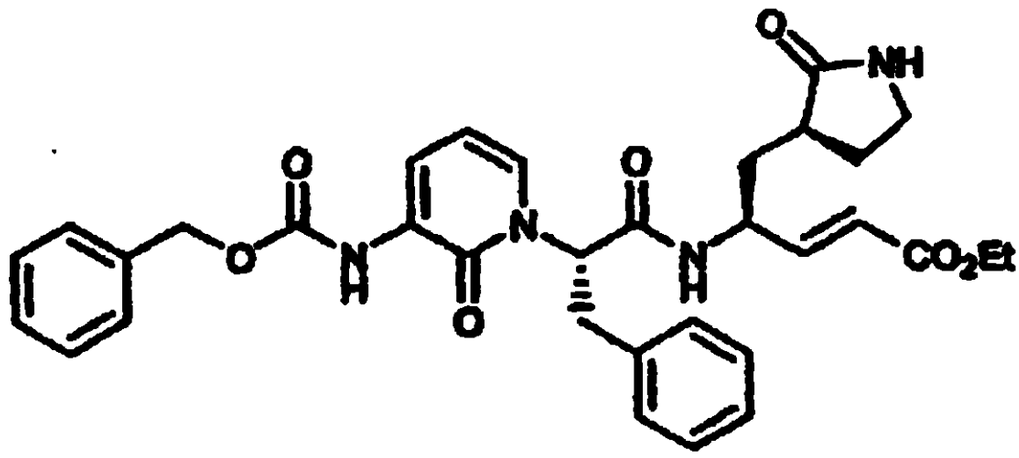
El intermediario precedente fue converrtido a compuesto 18 por un proceso análogo a aquel descrito en el Ejemplo 7 para la conversión de C1 a Compuesto 7 utilizando (2R)-2-hidroxi-3-ácido fenilpropiónico donde fuere apropiado: mp = 138-141°C; IR (cm^{-1}) 3289, 1663, 1542, 1203; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, *J*=7.2), 1.62-1.89 (m, 2H), 1.99 (s, 3H), 2.02-2.07 (m, 1H), 2.47 (s, 3H), 3.03-3.39 (m, 5H), 4.12 (q, 2H,*J*= 7.2), 4.32-4.41 (m, 1H), 5.76 (dd, 1H, *J*=15.6,1.5), 5.80-5.83 (m, 1H), 6.13 (d, 1H, *J*=7.5), 6.60 (s, br. 1H), 6.75 (dd, 1H, *J*=15.6,5.4), 7.15-7.24 (m, 5H), 7.76 (d, 1H, *J*= 7.2), 8.65 (d, 1H, *J*=7.8), 9.59 (s, br. 1H); $C_{29}H_{33}N_5O_7$•1.5TFA: C, H, N.

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EJEMPLO 18

Preparación del Compuesto 18: trans-(2'S,3'''S,4S)-4-[2'- (3''-Benciloxi- carbonilamino-2''-oxo-2''H-piridin-1'' -il)-3'-fenilpro pionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Ácido enóico



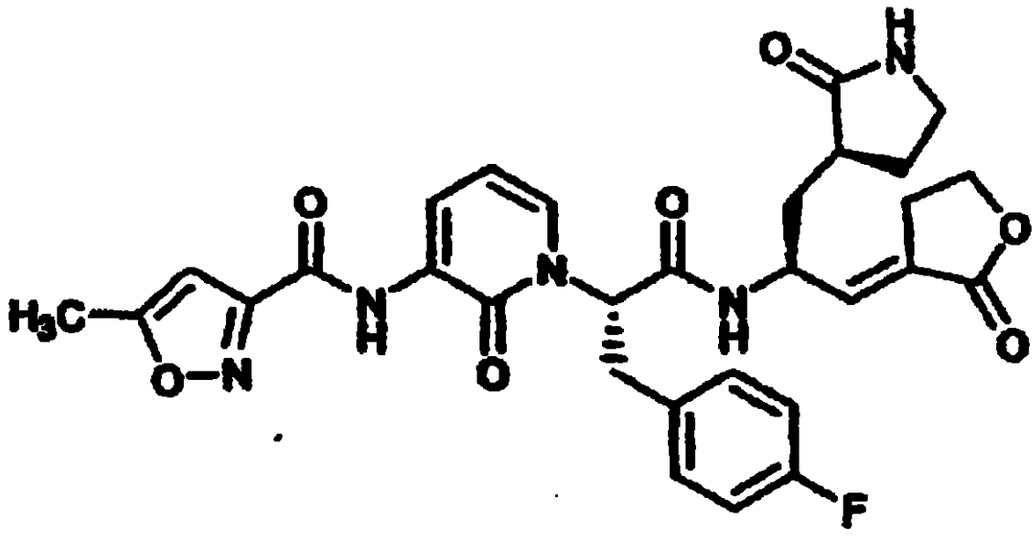
El compuesto del título fue preparado de K1 (Ejemplo 19) por un proceso análogo a aquel descrito en el Ejemplo 19 para la conversión de K1 a R1 utilizando el comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico, (2-hidroxipyridin-3-il)éster de bencilo de ácido carbámico (Ejemplo 2), y el comercialmente disponible (carbetoximetileno)-trifenilfosforano donde fuere apropiado: IR (cm^{-1}) 3272, 1684 (br), 1590, 1514, 1273, 1196; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.42-1.55 (m, 1H), 1.59-1.75 (m, 1H), 2.00-2.27 (m, 3H), 3.07-3.28 (m, 3H), 3.43 (dd, 1H, *J*= 13.7,7.3), 4.19 (q, 2H, *J*= 7.1), 4.36-4.47 (m, 1H), 5.12-5.21 (m, 2H), 5.75 (dd, 1H, *J*= 15.6,1.2), 5.85-5.94 (m, 1H), 6.26 (t, 1H, *J*= 7.2), 6.58 (s, 1H), 6.70 (dd, 1H, *J*= 15.6, 5.7), 7.10-7.41 (m, 10H), 7.44-7.50 (m, 1H), 7.71 (s, 1H), 7.97 (d, 1H *J*= 6.2), 8.28 (d, 1H, *J*= 6.8); Anal. $C_{33}H_{38}N_4O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 19

Preparación del Compuesto 20: trans-(2''S,2''''S,3''''''S)-Metilisoxazol-3- Ácido carboxílico(1'-{2''-(4''''-fluorofenil)-1''-[2''''-

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(2''''''-oxodihidrofurán-3''''''-ilideno)-1''''-(2''''''-oxopirrolidin-3''''''-ilmetil)etilcarbamoil]etil}-2'-oxo-1',2'-dihidropiridin-3'-il)amida (R1)



Preparación del Intermediario (1S,3'S)-{2-(tert-Butildifenilsilaniloxi)-1-[1'-(2'',4''-dimetoxibencil-2'-oxopirrolidin-3'-ilmetil]etil} Ester de tert-Butilo de Ácido carbámico (L1)

El intermediario K1 (4.41 g, 10.8 mmol, 1 equiv) fue agitado en CH_2Cl_2 (50 mL) y la mezcla fue congelada a 0°C. Trietilamino (7.52 mL, 54.0 mmol, 5 equiv), tert-butilclorodifenilsilano (5.53 mL, 21.6 mmol, 2 equiv) y 4-(dimetilamino)piridina (0.330 g, 2.70 mmol, 0.25 equiv) fueron agregados sucesivamente. La mezcla fue dejada calentar a 23 °C y fue agitado durante 2 h. Este fue entonces diluido con MTBE (400 mL), lavada con salmuera (2 x 100 mL), secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello para proporcionar el intermediario del título (3.51 g, 50%) como una espuma blanca: IR (cm^{-1}) 3319, 1678, 1508; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.42 (s, 9H), 1.44-1.65 (m, 2H), 2.05-2.17 (m, 1H), 2.23-2.35 (m, 1H), 2.44-2.56 (m, 1H), 3.14-3.21 (m, 2H), 3.55-3.68 (m, 2H), 3.69-3.81 (m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 4.42 (s, 2H), 4.77 (d, 1H, J=9.3), 6.41-6.46 (m, 2H), 7.09-7.13 (m, 1H), 7.34-7.46 (m, 6H), 7.61-7.67 (m. 4H); Anal. $C_{37}H_{50}N_2O_6Si$: C, H, N.

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Preparación del intermediario (1'S,2R,3"S)-N-{2'-(tert-Butildifenilsilanilioxi)-1'- [1"-(2"',4"'-dimetoxibencil)-2"-oxopirrolidin -3"-ilmetil]etil} -2-hidroxi-3-(4""-fluorofenil)propionamida (M1)

El intermediario L1 de arriba (3.4 g, 5.26 mmol, 1 equiv) fue disuelto en 1,4-dioxano (20 mL) a 23°C. Una solución de HCl en el mismo solvente (4.0 M, 20 mL) fue agregada. Después de la agitación de 75 min, los volátiles fueron evaporados para proporcionar un residuo el cual fue disuelto en CH_3CN (25 mL) y enfriado a 0°C. (2R)-3-(4'-Fluorofenil)-2-ácido hidroxipropiónico (intermediario S1, ver abajo, 0.968 g, 5.26 mmol, 1 equiv), 4-metilmorfolina (1.91 mL, 17.4 mmol, 3.3 equiv) y HATU (2.20 g, 5.79 mmol, 1.1 equiv) fueron agregados sucesivamente y la mezcla de reacción fue dejado calentar a 23°C y agitada 2.5 h. Esta fue entonces diluida con EtOAc (500 mL) y lavada con una mezzcla de salmuera y 10% $KHSO_4$ (3:1,100 mL) y una mezcla de salmuera $NaHCO_3$ (1:1,100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (primero en 5% CH_3OH en CH_2Cl_2, entonces en 3% CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.90 g,51%) como una espuma blanca: IR (cm^{-1}) 3389, 3319, 1660, 1508; ^1H NMR ($CDCl_3$) δ 1.04(s, 9H), 1.52-1.66 (m, 2H), 2.02-2.13 (m, 2H), 2.20-2.39 (m, 2H), 2.77-2.86 (m, 1H), 3.07-3.23 (m, 3H), 3.47 (dd, 1H, *J*=9.9,5.9), 3.59 (dd, 1H, *J*=9.9,3.6), 3.77 (s, 3H), 3.78 (s, 3H), 3.99-4.11 (m, 1H), 4.22-4.29 (m, 1H), 4.31-4.41 (m, 2H), 6.36-6.45 (m, 2H), 6.81-6.89 (m, 2H), 7.05 (d, 1H, *J*= 8.0), 7.13-7.22 (m, 3H), 7.34-7.46 (m, 6H), 7.59-7.67 (m, 4H); Anal. $C_{41}H_{49}FN_2O_6Si \cdot 0.25H_2O$: C, H, N.

Preparación del intermediario (1'S,2R,3"S)-Ácido de Metanosulfónico 1-*[2'-tert-* butildifenilsilanilioxi)-1'-[1"-(2"',4"'-dimetoxibencil)-2"-oxopirrolidin-3"- ilmetil]etilcarbamoil}-2-(4""-fluorofenil)Ester de etilo (N1)

El intermediario M1 de arriba (2.13 g, 2.99 mmol, 1 equiv) y IPr_2NEt (0.729 mL, 4.19 mmol, 1.4 equiv) fueron disueltos en CH_2C_2

(35 mL) y enfriados a -10°C. Cloruro de metanosulfónico (0.277 mL, 3.58 mmol, 1.2 equiv) fue agregado gota a gota, lentamente, con agitación vigorosa. Después de 30 min, la mezcla de reacción fue diluida con with MTBE (500 mL), lavada con una mezcla de salmuera y 10% $KHSO_4$ (2:1,100 mL) y salmuera (100 mL), secada sobre Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario 5-Metilisoxazol-3-Ácido carboxílico(2'-hidroxipiridin-3'-il)amida (F2)

Una suspensión de 10% paladio sobre carbono (0.45 g) y 2-hidroxi-3-nitropiridina (7.00 g, 50.0 mmol, 1 equiv) en EtOH (210 mL) fue sometido a una atmósfera de hidrógeno durante 16 horas. Después de la purgación la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-3-aminopiridina el cual fue usado sin más purificación. Este material crudo fue suspendido en CH_3CN (170 mL) y enfriada a 0°C. 5-Metilisoxazol-3-cloruro de carbonilo (8.00 g, 55.0 mmol, 1 equiv) fue agregada en una parte. Después de 25 min a 0°C, la mezcla de reacción fue dejada calentar a 23 °C y agitada durante unos 75 min adicionales. La mezcla espesa fue entonces vertida dentro de dilución HCl (0.02 M, 150 mL) y mezclada vigorosamente. El sólido sin indiluir fue recogido por filtración y lavado con H_2O (2 x 20 mL) entonces secado bajo vacio toda la noche para proporcionar el intermediario del título (7.1 g, 66%): ^1H NMR (DMSO-d_6) δ 6 2.48 (s, 3H), 6.29 (dd, 1H, *J*= 7.2, 6.6), 6.69 (s, 1H), 7.19 (dd, 1H, *J*= 6.6, 1.8), 8.26 (dd, 1H.*J*= 7.2, 1.8), 9.43 (s, 1H), 12.20 (s, 1H).

Preparación del intermediario (1'''S,2''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-{2'''-(terl-butildifenilsilaniloxi)-1'''-[1''''-(2''''',4''''''-dimetoxibencil)-2''''-oxopirrolidin-3''''- ilmetil]etilcarbamoil}-2''-(4'''''-fluorofenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (O1)

El intermediario F2 de arriba (1.11 g, 5.06 mmol, 1.7 equiv) fue agitada en THF (14 mL). Hidruro de sodio (60% de dispersión de aceite mineral, 0.173 g, 4.32 mmol, 1.45 equiv) fue agregado. Despues de la agitación de 30 min, una solución del intermediario N1 de arriba (1 equiv basada sobre M1) en THF (11 mL) fue agregada. La mezcla resultante fue calentada a reflujo toda la noche, entonces diluida con EtOAc (500 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (3:1,100 mL) y salmuera y $NaHCO_3$ (3:1,100 mL). La fase orgánica fue secada bajo Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH en CH_2Cl_2) para proporcionar el intermediario deseado O1 como una espuma blanca (2.58 g, 95%): IR (cm^{-1}) 3331, 3284, 1666, 1596, 1631, 1455; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.46-1.71 (m, 2H), 1.94-2.32 (m, 3H), 2.52 (s, 3H), 3.07-3.19 (m, 3H), 3.42-3.52 (m, 2H), 3.67-3.74 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.99-4.10 (m, 1H), 430 (d, 1H, *J*= 14.6), 4.39 (d, 1H, *J*=14.6), 5.54-5.63 (m, 1H), 6.25 (t, 1H, *J*=7.3), 6.42-6.50 (m, 3H), 6.81-6.88 (m, 2H), 7.04-7.13 (m, 3H), 7.20-7.26 (m, 1H), 7.36-7.48 (m, 7H), 7.60-7.68 (m, 4H), 8.40 (dd, 1H, *J*= 7.3, 1.6), 9.60 (s, 1H); Anal. $C_{61}H_{58}FN_5O_8Si$: C, H, N.

Preparation of Intermediate (2''S,2'''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-{1'''-[1''''-(2''''',4''''')-dimetoxibencil)-2''''-oxopirrolidin-3''''-ilmetil]-2'''-hidroxietilcarbamoil}-2''-(4'''''-fluoro fenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (PI)

El intermediario O1 de arriba (2.51 g, 2.75 mmol, 1 equiv) fue disuelto en una mezcla de CH_3CN (30 mL) y H_2O (1 mL) en un tubo plástico. Ácido hidrofluórico (48%, 5 mL) fue agregado gota a gota. Después de 1 h y 1.5 h, más ácido hidrofluórico (2.5 mL y 2 mL respectivamente) fue agregado. Después de 3.5 h total, la mezcla de reacción fue vertida dentro de $NaHCO_3$ (250 mL) acuoso saturado, extractado con CH_2Cl_2 (3 x 400 mL), secado bajo Na_2SO_4 y evaporado. El residuo fue purificado por cromatografía de columna de destello (5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (1.84 g, 99%) como una espuma blanca: IR

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(cm^{-1}) 3401 (br), 3331, 1655, 1590, 1531, 1508, 1455, 1208; ^1H NMR ($CDCl_3$) δ 1.47-1.63 (m, 2H), 1.87-1.99 (m, 1H), 2.07-2.18 (m, 1H), 2.33-2.44 (m, 1H), 2.49 (s, 3H), 3.10-3.24 (m, 3H), 3.46-3.56 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.84-3.89 (m, 1H), 3.92-4.03 (m, 1H), 4.19 (d, 1H, *J*= 14.5), 4.39 (d, 1H, *J*= 14.5), 5.54-5.61 (m, 1H), 6.22 (t. 1H, *J*= 7.2), 6.38-6.48 (m, 3H), 6.85-6.93 (m, 2H), 6.99-7.04 (m, 1H), 7.06-7.13 (m, 2H), 7.24 (dd, 1H. .7= 7.2,1.7), 8.33 (d, 1H, .7= 7.3), 8.38 (dd, 1H, *J*=7.2,1.7), 9.54 (s, 1H); Anal. $C_{35}H_{38}FN_5O_8 \cdot 0.5H_2O$: C, H, N.

Preparación del Intermediario trans-(2''S,2'''S,3''''S)-5-Metilisoxazol-3-Ácido carboxílico{1'-[1''-[1'''-[1''''-(2''''',4''''')-dimetoxibencil)-2''''-oxopirrolidin-3''''-ilmetil]-2'''-(2-oxociclopentilideno)etilcarbamoil]-2''-(4'''''-fluorofenil)etil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (QI)

El intermediario P1 de arriba (1.76 g, 2.60 mmol, 1 equiv) y comercialmente disponible de Dess-Martin periodinano (1.11 g, 2.60 mmol, 1 equiv) fueron combinados en CH_2Cl_2 (20 mL) a 23 °C y agitados 2 h. Los volátiles fueron evaporados. El residuo fue suspendido en tolueno y concentrados secos (2 x 25 mL). El residuo resultante fue disuelto en una mezcla de éter de dimetil deglicol de etileno y DMF (5:1,24 mL). 3-(trifenil-λ^5-fosfanilideno)-dihidrofurán-2-ona (preparado en una manera análoga a aquel descrito en Baldwin y otros, *J. Org. Chem.* 1971, vol. 36,1441) (0.902 g, 2.60 mmol, 1 equiv) fue agregado y la mezcla de reacción dejada enfriar, diluida con EtOAc (500 mL), lavada con salmuera (200 mL, 100 mL), secada bajo $MgSO_4$ y evaporada. El residuo fue cromatografiado (elución de gradiente, 2→3% CH_3OH en CH_2Cl_2) entonces recromatografiado (50% EtOAc in CH_2Cl_2) para dar el intermediario del título (1.46 g) contenido con óxido de trifenilfosfina (aproximadamente 35% por peso): ^1H NMR ($CDCl_3$) δ 1.47-1.62 (m, 2H), 1.87-1.98 (m, 1H), 2.21-2.31 (m, 1H), 2.38-2.52 (m, 1H), 2.50 (s, 3H), 2.81-2.93 (m, 1H), 3.10-3.33 (m, 4H), 3.50 (dd, 1H, *J*= 14.1, 7.0), 3.76 (s, 3H), 3.77 (s, 3H), 4.19 (d, 1H, *J*= 14.3), 4.29-4.62 (m, 3H), 4.38 (d, 1H, *J*= 14.3), 5.42-5.49 (m, 1H), 6.23 (t, 1H, *J*=- 7.2),

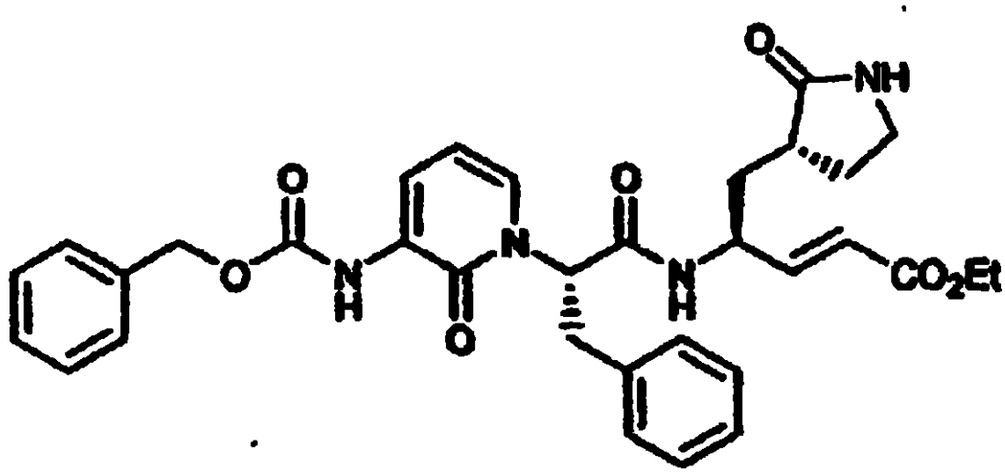
6.27-6.33 (m, 1H), 6.40-6.48 (m, 3H), 10 6.90-6.97 (m, 2H), 7.00-7.12 (m, 3H), 7.15 (dd, 1H, *J*= 7.2,1.6), 8.39 (dd, 1H, *J*= 7.2,1.6), 8.83 (d, 1H, *J*= 5.7), 9.56 (s, 1H).

Preparación del Producto R1 (Compound 20)

El intermediario Q1, preparado arriba, fue disuelto en una mezcla de $CHCl_3$ (30 mL) y 15 H_2O (3 mL). DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue agregado y la mezcla de reacción fue calentada en solución de aceite a 60 °C durante 1.5 h. Más DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue agregado y la vasija de reacción fue conservado en una solución de aceite a 60 °C durante 1.5 h más. DDQ (0.390 g, 1.72 mmol, 1.4 equiv) fue nuevamente agregado. Despues de la agitación 2 h más, la mezcla de reacción fue dejada enfriar, diluida con CH_2Cl_2 (250 mL), y lavada secuencialmente con una mezcla de salmuera y 20 1 N HCl (2:1,80 mL), una mezcla de salmuera y $NaHCO_3$ (2:1,80 mL) y salmuera (80 mL). La fase orgánica fue secada bajo $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (2.5% CH_3OH in CH_2Cl_2) para proporcionar el producto deseado (0.530 g, 73%) como un sólido amorfo casi blanco: IR (cm^{-1}) 3336, 1750, 1682, 1530; ^1H NMR ($CDCl_3$) δ 1.39-1.49 (m, 1H), 1.63-1.80 (m, 1H), 2.09-2.37 (m, 3H), 2.49 (s, 3H), 2.74-2.86 (m, 1H), 25 3.11 (dd, 1H, *J*=13.8,8.5), 3.14-3.38 (m, 3H), 3.39 (dd, 1H, *J*= 13.8, 7.5), 4.30-4.46 (m, 3H), 5.72-5.79 (m, 1H), 6.29 (t, 1H, *J*=7.2), 6.30-6.36 (m, 1H), 6.44-6.47 (m, 1H), 6.77 (s, 1H), 6.88-6.97 (m, 2H), 7.04-7.11 (m, 2H), 7.44-7.50 (m. 1H), 8.37 (dd, 1H, *J*=7.2, 1.6), 8.66 (d, 1H, *J*=6.2), 9.47 (s, 1H); Anal. $C_{30}H_{30}FN_5O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 20

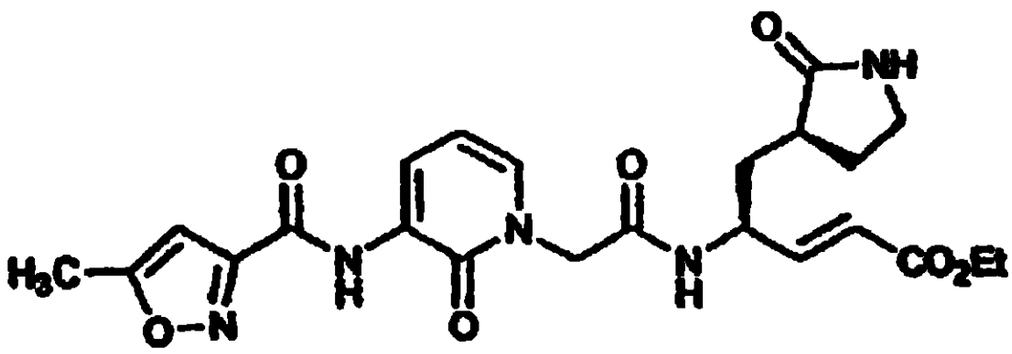
Preparación del Compuesto 21: *trans*-(2'S,3'''R,4S)-4-[2'-(3''-Benciloxicarbonilamino-2''-oxo-2''H-piridin-1''-il)-3'-fenilpropionilamino]-5-(2'''-oxopirrolidin-3'''-il)pent-2-Ester de Etilo de Ácido enóico



El compuesto del título fue preparado de (2S,3'R)-{1-[1'-(2'',4''-dimetoxibencil)-2'-oxopirrolidin-3'-ilmetil]-2-hidroxietil}éster de terl-butilo de ácido carbámico (preparado tal como se describio en Dragovich, et al. *J. Med. Chem.* 1999, *42*, 1213) por un proceso análogo a aquel descrito en el Ejemplo 19 para la conversión de K1 a R1 utilizando el comercialmente disponible (2R)-2-hidroxi-3-ácido fenilpropiónico, (2-hidroxipiridin-3-il)éster de bencilo de ácido carbámico (Ejemplo 2), y el comercialmente disponible (trifenil-λ^5-fosfanilideno)éster de etilo de ácido acético donde fuere apropiado: IR (cm^{-1}) 3483, 3272, 1684 (br), 1514, 1267, 1196; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*=7.1), 1.48-1.79 (m, 2H), 2.02-2.24 (m, 2H), 2.27-2.39 (m, 1H), 3.12 (dd, 1H, *J*= 13.7, 8.2), 3.19-3.34 (m, 2H), 3.48 (dd, 1H, *J*=13.7, 7.8), 4.19 (q, 2H, *J*=7.1), 4.43-4.53 (m, 1H), 5.17 (s, 2H), 5.73 (dd, 1H, *J*=15.6, 1.3), 5.90-5.98 (m, 1H), 6.27 (t, 1H, *J*=7.1), 6.63 (dd, 1H, *J*=15.6, 6.0), 6.65-6.71 (m, 1H), 7.13-7.27 (m, 6H), 7.31-7.40 (m, 4H), 7.50 (dd, 1H, *J*=7.1, 1.6), 7.75 (s, 1H), 7.97 (d, 1H,J= 6.6), 8.69 (d, 1H, *J*=7.0); Anal. $C_{33}H_{38}N_4O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 21

Preparación del Compuesto 22: trans-(4S,3''''S)-4-(2'-{3''-[(5''''-Metilisoxazol-3''''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}acetilamino)-5-(2''''-oxopirrilidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico



Preparación del Intermediario {3-[(5'-Metilisoxazol-3'-carbonil)amino]- 2-oxo-2H-piridin-1-il}Ester de tert-butilo de Ácido acético

Para una solución de 5-metilisoxazol-3-ácido carboxílico (2'-hidroxi-4'-metilpiridin-3'-il)amida (F2, Ejemplo 19) (0.520 g, 2.37 mmol, 1 equiv) en THF (20 mL) a 0 °C fue agregado NaH (0.095 g, 2.37 mmol, 1.0 equiv). La mezcla resultante fue agitada a 0 °C durante 20 min, y entonces bromoacetato de t-butilo (0.385 mL, 2.61 mmol, 1.1 equiv) fue agregado. La mezcla de reacción fue agitada y calentada a temperatura ambiente durante 30 min, entonces fue partida por medio de 0.5 N HCl (100 mL) y EtOAc (2 x 100 mL). Las capas orgánicas combinadas fueron secadas bajo Na_2SO_4 y fueron concentradas. La purificación del residuo por cormatografía de columna de destello (30% EtOAc en hexanos) proporcionando el intermediario del título (0.628 g, 79%) como un sólido blanco: IR (cm^{-1}) 3343, 1743, 1651, 1581, 1156; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.53 (s, 3H), 4.65 (s, 2H), 6.32 (t, 1H, *J*= 7.2), 6.51 (s, 1H), 7.01 (dd, 1H, *J*=6.9,1.8), 8.50 (dd, 1H, *J*=7.5,1.8), 9.63 (s, br. 1H); Anal. $C_{18}H_{19}N_3O_5$: C, H, N.

Preparación del Compuesto 22

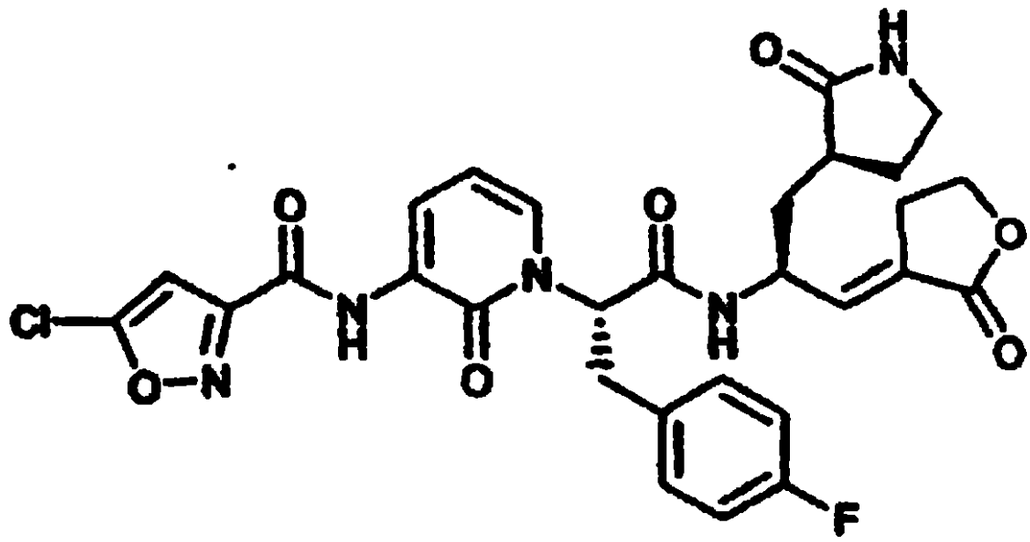
El intermediario precedente fue transformado en Compuesto 22 por un proceso que fue análogo a aquel descrito en el Ejemplo 25 por la transformación de V3 a producto R3: mp = 102-106°C; IR (cm^{-1}) 3336, 1684, 1634, 1457; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*=7.2), 1.67-1.75 (m, 1H). 1.98-2.09 (m, 1H), 2.37-2.48 (m, 1H),

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2.53 (s, 3H), 2.55-2.61 (m, 1H), 3.34-3.46 (m, 2H), 3.51-3.52 (m, IH), 4.17 (q, 2H, *J*=7.2), 4.61-4.78 (m, 3H). 5.98 (dd, 1H, *J*=15.6, 1.5), 6.20 (s, br. 1H), 6.35 (t, 1H, *J*= 7.8), 6.51 (s, IH), 6.85 (dd, 1H, *J*= 15.6, 5.1), 7.17 (d, 1H, *J*= 7.2), 8.33 (d, 1H, *J*= 7.2), 8.49 (d, 1H, *J*= 7.5), 9.57 (s, br. 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 22

Preparación del Compuesto 23: trans-(2''S,2''''S,3''''''S)-5-Cloroisoxazol- 3-Ácido carboxílico (1'-{2''-(4'''-fluorofenil)-1''-[2''''-oxodihidrofurán-3''''-ilideno)-1''''-(2''''''-oxopirrolidin-3''''''-ilmetil) etilcarbamoil]etil}-2'-oxo-1',2'-dihidropiridin-3'-il)amida (R2)



Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ácido hidroxipropiónico (S1)

Este intermediario fue preparado de acuerdo a el método revelado en la solicitud co-pendiente, Solicitud de Patentes Provisional de los E.U. No. 60/150,365, presentada en Agosto 24 de 1999.

Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ester de Metilo de Ácido hidroxipropiónico (T1)

Este intermediario fue preparado tal como se describió en la Solicitud de Patente Provisional co-pendiente de los E.U. No. 60/150,365, presentada en Agosto 24 de 1999.

Preparación del Intermediario (2R)-3-(4-Fluorofenil)-2-trifluoro metano- Ester de Metilo de Ácido sulfoniloxipropiónico (U1)

El intermediario T1 de arriba (0.198 g, 1.00 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (6 mL) y enfriada en una solución helada. 2,6-Lutidino (0.198 mL, 1.70 mmol, 1.7 equiv) y anhidrido de trifluorometanosulfónico (0.269 mL, 1.60 mmol, 1.6 equiv) fueron agregados y la mezcla de reacción fue agitada 30 min. Esta fue entonces diluida con MTBE (200 mL), lavada con una mezcla de salmuera y 1 N HCl (2:1, 75 mL) y salmuera (75 mL), secada bajo Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación .

Preparación del Intermediario 5-Cloroisoxazol-3-Ester de Etilo de Ácido caroxílico

A una solución de clorooximidoacetato (11.0 g, 72.6 mmol, 1 equiv) en 1,1-dicloroetileno (350 mL) fue agregado Et_3N (25.3 mL, 181 mmol, 2.5 equiv) en 1,1-dicloroetileno (100 mL) vía de tunel de adición sobre 30 min. La mezcla de reacción fue agitado a temperatura ambiente durante 23 h, entonces fue partida por medio de agua (150 mL) y CH_2Cl_2 (2x150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas. El residuo fue purificado por cromatografía de columna de destello (10% EtOAc en hexanos) para dar el intermediario del título (4.49 g, 35%) como un aceite amarillo pálido: IR (cm^{-1}) 1735, 1436, 1253; ^1H NMR ($CDCl_3$) δ 1.46 (t,3H, *J*=7.2), 4.49 (q, 2H, *J*=7.2), 7.29 (s, 1H).

Preparación del Intermediario 5-Cloroisoxazol-3-Ácido carboxílico

Una solución acuosa de LiOH (2.0 M, 22.5 mL, 45.0 mmol, 2.0 equiv) fue agregada a una solución del intermediario precendente (3.95 g, 22.5 mmol, 1 equiv) en EtOH (80 mL) a 23 °C. La mezcla

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resultante fue agitada a temperatura ambiente durante 45 min, entonces los volátiles fueron removidos bajo presión reducida. El residuo humeante obtenido fue partido por medio de 1.0 N HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas para dar el intermediario del título (crudo) (2.84 g, 86%) como un sólido casi blanco el cual fue usado sin más purificación: ^1H NMR (DMSO-d_6) δ 7.15 (s, 1H).

Preparación del intermediario 5-Cloroisoxazol-3-Cloruro de carbonilo

Una solución 5-cloroisoxazol-3-ácido carboxílico (0.750 g, 4.32 mmol, 1 equiv) y cloruro de tionilo (9.0 mL, 120 mmol, 28 equiv) en CH_2Cl_2 (21 mL) fue calentado a reflujo durante 28 h. Los volátiles fueron evaporados para proporcionar un residuo el cual fue disuelto en benceno (40 mL), el cual fue subseguientemente evaporado para dar el intermediario del título como un aciete amarillo el cual fue usado sin más purificación.

Preparación del intermediario 5-Cloroisoxazol-3-Ácido carboxílico (2'-hidroxipiridin-3'-il)amida (F3)

Una suspensión de 10% paladio sobre carbono (0.15 g) y 2-hidroxi-3-nitropiridina (1.70 g, 12.1 mmol, 2.8 equiv) en EtOH (60 mL) fue sometido a una atmósfera de hidrógeno durante 16 horas. Después del purgamiento la vasija de reacción con argón, la mezcla fue filtrada a través de papel Whatman #3 y el filtrado fue evaporado para dar 2-hidroxi-3-aminopiridina (1.33 g, 99%) el cual fue usado sin más purificación. Una parte de este material (0.524 g, 4.76 mmoL 1.1 equiv) fue combinado con el 5-cloroisoxazol-3-cloruro de carbonilo preparado arriba (4.32 mmol, 1 equiv basado sobre rendimiento teórico) en THF (50 mL) y agitada 60 min. Los volátiles fueron evaporados y el residuo fue agitado en saturación media $NaHCO_3$ (20 mL) durante 30 min. El sólido sin diluir fue recogido por filtración, lavada con H_2O (3 x 5 mL) y secado bajo vacío toda la noche para proporcionar el intermediario del título

(0.900 g, 87%) como un sólido tostado el cual fue usado sin más purificación. ^{1}H NMR (DMSO-d_6) δ 6.30 (t, 1H, *J*=6.9), 7.22 (dd, 1H, *J*=6.9, 1.7), 7.25 (s, 1H), 8.24 (dd, 1H, *J*=6.9, 1.7), 9.47 (s, 1H), 12.22 (s, 1H).

Preparación del Intermediario (2R)-2-{3'-[(5"-Cloroisoxazol-3"-carbonyl)amino]-2'-oxo-2'H-piridin-1'-il}-3-(4"'-fluorofenil) Ester de Metilo de Ácido propiónico (V1)

El intermediario F3 de arriba (0.280 g, 1.17 mmol, 1.17 equiv) fue suspendido en THF (7 mL). Hidruro de sodio (60% de dispersión en aceite mineral, 0.044 g, 1.1 mmol, 1.1 equiv) fue agregada en una parte. Después de la agitación 30 min, una solución del intermediario U1 de arriba (1.00 mmol, 1 equiv, basado sobre T1) en THF (10 mL) fue agregado gota a gota. La mezcla resultante fue agitada 16 horas, entonces diluida con MTBE (250 mL) y lavada con salmuera (2 x 80 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado cromatografía de columna de destello (33% EtOAc in hexanos) para proporcionar el intermediario del título (0.316 g, 75%) tal como una espuma blanca: IR (cm^{-1}) 3331 1743, 1690, 1643, 602, 1531,1437; ^{1}H NMR ($CDCl_3$) δ 3.33 (dd, 1H, *J*=14.5, 10.3), 3.53 (dd, 1H, *J*=14.5, 5.5), 3.78 (s, 3H), 5.36 (dd, 1H, *J*= 10.3, 5.5), 6.18 (t, 1H, *J*=7.2), 6.67 (s, 1H), 6.82 (dd, 1H, *J*= 7.2, 1.7). 6.89-6.97 (m, 2H), 7.01-7.07 (m, 2H), 8.38 (dd, 1H, *J*=7.2, 1.7), 9.52 (s, 1H); Anal. $C_{18}H_{15}ClFN_3O_5$: C, H, N.

Preparation of Intermediate (2R)-2-{3'-[(5"-Cloroisoxazol-3"-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}-3-(4"'-fluorofenil)Ácido propiónico (W1)

El intermediario V1 de arriba (0.445 g, 1.06 mmol, 1 equiv) fue disuelto en CH_3OH (10 mL). Una solución acuosa de NaOH (1.0 M, 4.2 mL, 4.2 mmol, 4 equiv) fue agregado gota a gota. La mezcla de reacción fue agitada 2 h, entonces vertido dentro de una mezcla de salmuera y 10% $KHSO_4$ (1:1, 50 mL) y extractada con

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CH_2Cl_2 (3 x 100 mL). Las fases orgánicas combinadas fueron secadas sobre $MgSO_4$ y evaporada para proporcionar el intermediario del título como una espuma amarilla el cual fue usado sin más purificación.

Preparation of Intermediate trans-(2'S,3''S)-3-[2'-Amino-3'- (2''-oxodihidrofurán-3' '-ilideno)propil]pirrolidin-2-ona (Yl)

El intermediario X1 (preparada en una manera análogo a aquel descrito en Baldwin y otros, J *Org. Chem.* 1971, *36*, 1441) (0.413 g, 1.27 mmol, 1.2 equiv) fue agitado deurante 45 min en una mezcla de TFA (5 mL) en CH_2Cl_2 (10 mL). Entonces los volátiles fueron evaporados para porporcionar el intermediario del título el cual fue usado sin más purificación.

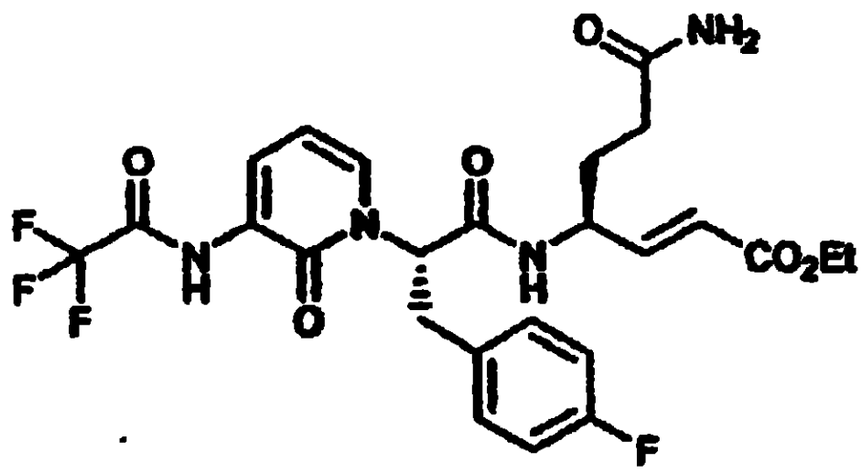
Preparación del Producto R2 (Compuesto 23)

Los intermediario W1 (1.06 mmol, 1 equiv based on Vi) y Y1 (1.27 mmol, 1.2 equiv basada sobre X1) fueron combinados en CH_3CN (14 mL) y enfriada en un baño de hielo. 4-Metilmorfolina (0.583 mL, 5.30 mmol, 5 equiv) y HATU (0.403 g. 1.06 mmol, 1 equiv) fueron agregados y la mezcla de reacción fue dejada calentar a 23 °C y agitada a 1.5 h. Este fue entonces diluido con EtOAc (500 mL) y lavado con una mezcla de salmuera y 10% $KHSO_4$ (3:1, 80 mL), una mezcla de salmuera y $NaHCO_3$ (3:1, 80 mL) y salmuera (80 mL). La fase orgánica fue secada sobre Na_2SO_4 y evaporada. El residuo fue cromatografiado (5% CH_3OH in CH_2Cl_2) entonces recromatografiado (2.5% CH_3OH en CH_2Cl_2) para proporcionar el residuo deseado R2 (0.418 g, 64%) contaminado con un diastereomero (aproximadamente 30%, presumiblemente 2''R epimero): ^1H NMR ($CDCl_3$) (mezcla de isómeros) δ 1.33-1.51 (m), 1.62-1.88 (m), 2.06-2.39 (m), 2.73-2.88 (m), 2.98-3.45 (m), 4.27-4.44 (m), 5.71-5.88 (m), 6.27-6.43 (m), 6.66 (s), 6.68 (s), 6.81 (s), 6.88-6.98 (m), 7.03-7.24 (m), 7.48 (d, *J*= 7.3), 7.55-7.62 (m), 8.34-8.42 (m), 8.65 (d, J= 6.2), 8.77 (d, J= 7.0), 9.41-9.48 (m).

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EJEMPLO 23

Preparación del Compuesto 24: trans-(2'S,4S)-6-Carbamoil-4-{3'-(4''-fluorofenil)-2'-[2'''-oxo-3'''-(2'''',2'''',2''''-trifluoroacetilamino)-2'''H-piridin-1'''-il]propionilamino}hex-2-Ester de Etilo de Ácido enóico (J2)



Preparación del Intermediario (2R)-3-(4'-Fluorofenil)-2-Ester de Bencilo de Ácido hidroxipropiónico (T2)

El intermediario S1 (1.00 g, 5.43 mmol, 1 equiv) fue disuelto en CH_3CN (8 mL). 1,8-Diazabiciclo[5.4.0]undec-7-eno (0.812 mL, 5.43 mmol, 1 equiv) y bromuro de bencilo (0.646 mL, 5.43 mmol, 1 equiv) fueron agregados sucesivamente. La solución resultante fue agitada 40 h, entonces diluida con MTBE (250 mL) y lavada con 5% $KHSO_4$ y salmuera (75 mL cada una). La fase orgánica fue secada sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (1.25 g, 84%) como un aceite sin color el cual se solidifica sobre varios días: IR (cm^{-1}) 3450, 1954, 1890, 1725, 1602; ^1H NMR ($CDCl_3$) δ 2.76-2.81 (m. 1H), 2.94 (dd, 1H, *J*= 14.1,6.2), 3.08 (dd, 1H. *J*=14.1, 4.6), 4.42-4.49 (m, 1H), 5.14 (d, 1H, *J*= 12.1), 5.21 (d, 1H, *J*= 12.1), 6.86-6.94 (m, 2H), 7.03-7.11 (m, 2H), 7.29-7.42 (m, 5H); Anal. $C_{16}H_{15}FO_3$: C, H.

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Preparación del Intermediario (2R)-3-(4-Fluorofenil)-2-trifluorometano- Ester de Bencilo de Ácido sulfoniloxipropiónico (U2)

El intermediario T2 de arriba (0.134 g, 0.489 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (5 mL) y enfriada en un baño helado. 2,6-Lutidina (0.114 mL, 0.979 mmol, 2 equiv) y anhídrido de trifluorometanosulfónico (0.156 mL, 0.927 mmol, 1.9 equiv) fueron agregados y la mezcla de reacción fue agitada 30 min. Este fue entonces diluido con MTBE (150 mL), lavado con una mezcla de salmuera y 1 N HCl (2:1,75 mL) y salmuera (50 mL), secada sobre Na_2SO_4 y evaporada para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario 2,2,2-Trifluoro-N- (2'-hidroxipiridin-3' -il)acetamida (F4)

TFA (4 mL) fue agregado a una solución de intermediario F1 (0.700 g, 3.33 mmol, 1 equiv) en CH_2Cl_2 (6 mL). Después de la agitación de 30 min, los volátiles fueron evaporados. El residuo fue suspendido en tolueno y concentrado menos seco para proporcionar crudo 2-hidroxi-3-aminopiridina el cual fue (sin más purificación) suspendido en CH_2Cl_2 (14 mL) y enfriado en un baño helado. 4-Metilmorfolina (1.10 mL, 10.0 mmol, 3 equiv) y anhídrido trifluoroacético (0.471 mL, 3.33 mmol, 1 equiv) fueron agregados sucesivamente. Después 30 min, más 4-metilmorfolina (0.550 mL, 5 mmol, 1.5 equiv) fue agregado. La mezcla de reacción fue agitada un adicional 1.5 h, entonces diluida con EtOAc (250 mL) y lavada con salmuera, H20 y salmuera (25 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (5% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.173 g, 25%) tal como un sólido amorfo blanco: ^1H NMR (DMSO-d_6) δ 6.27 (t, 1H, J= 6.9), 7.32 (dd, 1H, J=6.9, 1.8), 7.94 (dd, 1H, J=6.9, 1.8), 10.16 (s, 1H), 12.20 (s, 1H); Anal. $C_7H_5F_3N_2O_2$; C, H, N.

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Preparación del intermediario (2S)-3-(4'-Fluorofenil)-2-[2''-oxo-3''-(2''',2''',2'''- trifluoroacetilamino)-2''H-piridin-1''-il]Ester de Bencilo de Ácido propiónico (V2)

El intermediario F4 de arriba (0.111 g, 0.539 mmol, 1.1 equiv) fue suspendido en THF (3 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.020 g, 0.50 mmol, 1 equiv) fue agregado en una parte. Después de la agitación 30 min, una solución del intermediario U2 (0.489 mmol, 1 equiv, basado sobre T2) en THF (5 mL) fue agregado gota a gota. La mezcla resultante fue agitada 2 horas, entonces diluida con MTBE (150 mL) y lavada con salmuera (2 x 50 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (0.190 g. 84%) como un aceite delgado: IR (cm^{-1}) 3343, 1743, 1727, 1655, 1602, 1296, 1214, 1161; ^1H NMR ($CDCl_3$) δ 3.31 (dd, 1H, *J*=14.4, 10.0). 3.52 (dd, 1H, *J*=14.4, 5.4), 5.21 (s, 2H), 5.39 (dd, 1H, *J*=10.0, 5.4), 6.18 (t, 1H, *J*=7.3), 6.85 (dd, 1H, *J*=7.3, 1.7), 6.87-7-04 (m, 4H), 7.25-7.38 (m, 5H), 8.31 (dd, 1H, *J*=7.3, 1.7), 9.03 (s, 1H); Anal. $C_{23}H_{18}F_4N_2O_4$: C, H, N.

Preparación del intermediario (2S)-3-(4'-Fluorofenil)-2-[2''-oxo-3''-(2''',2''',2'''-trifluoroacetilammo)-2''H-piridin-1''-il]Ácido propiónico (W2)

Una suspensión de 10% paladio sobre carbono (0.030 g) e intermediario V2 de arriba (0.151 g, 0.327 mmol, 1 equiv) en EtOH (5 mL) fue sometido para una atmósfera de hidrógeno durante 16 horas. Después del purgamiento la vasija de reacción con argón, la mezcla fue filtrado a través del papel Whatman #3 y el filtrado fue evaporado para dar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario trans-(4S)-4-Amino-6-(tritilcarbamoil)hex-2-Ester de Etilo de Ácido enóico (AA1)

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El intermediario Z1 (preparado de acuerdo a Dragovich, y otros, J. *Med Chem.* 1998, *41*, 2806) (0.177 g, 0.326 mmol, 1 equiv) fue agitado durante 2 h en una solución de HCl en 1,4-dioxano (2.0 M, 8 mL). Entonces los volátiles fueron evaporados para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del Intermediario trans-(2'S,4S)-4-{3'-(4"-Fluorofenil)-2'-[2"'-oxo-3"'-(2"",2"",2"",2""-trifluoroacetilamino)-2"'H-piridin-1"'-il]propioniIamino}-6-(tritilcarbamoil)hex-2-Ester de Etilo de Ácido enóico (I3)

Los intermediarios W2 y AA1 (preparado tal como arriba) fueron combinado en CH_2Cl_2 (5 mL) y enfriado en un baño helado. HOBt (0.049 g, 0.36 mmol, 1.1 equiv), iPr_2NEt (0.171 mL, 0.982 mmol, 3 equiv) y EDC (0.063 g, 0.33 mmol, 1 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejado calentar a 23 °C toda la noche, entonces diluida con EtOAc (200 mL) y lavado con 5% $KHSO_4$ y salmuera (50 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (44% EtOAc en hexanos) para proporcionar el intermediario del título (0.138 g, 53%) como un sólido blanco amorfo: ^1H NMR (DMSO-d_6) δ 1.30 (t, 3H, *J*=7.1), 1.70-1.84 (m, 1H), 1.85-1.99 (m, 1H), 2.26-2.34 (m, 2H), 3.01-3.10 (m, 1H), 3.31-3.40 (m, 1H), 4.19 (q, 2H, *J*=7.1), 4.46-4.56 (m, 1H), 5.42-5.49 (m, 1H), 5.63 (dd, 1H, *J*=15.7, 1.6), 6.18 (t, 1H, *J*=7.1), 6.62-6.71 (m, 2H), 6.88-6.96 (m, 2H), 7.00-7.06 (m, 2H), 7.10-7.34 (m, 17H), 8.25 (dd, 1H, *J*=7.3, 1.6), 9.02 (s, 1H); Anal. $C_{44}H_{40}F_4N_4O_6$: C, H, N..

Preparación del Producto J2 (Compuesto 24)

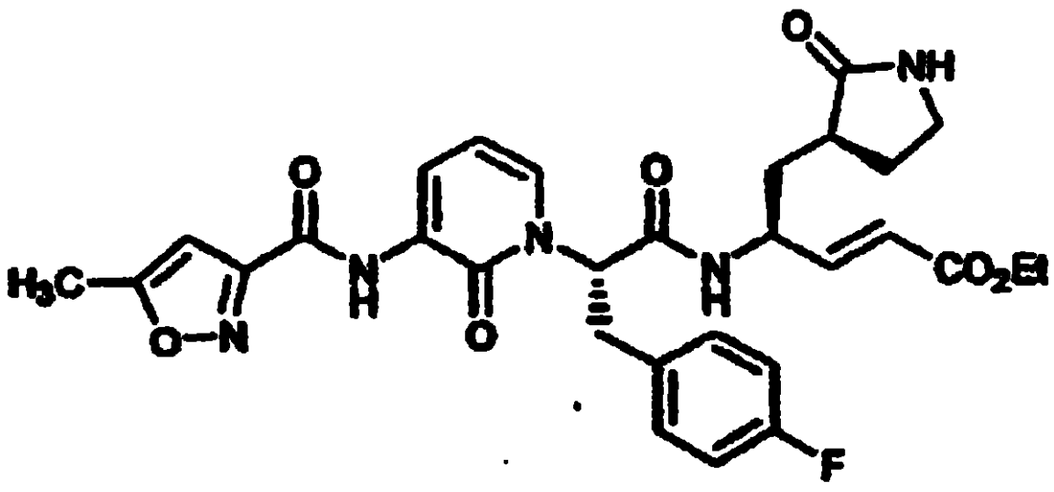
El intermediario I3 de arriba (0.112 g, 0.141 mmol, 1 equiv) y triisopropilsilano (0.086 mL, 0.420 mmol, 3 equiv) fueron combinados en CH_2Cl_2 (4 mL). TFA (2 mL) fue agregado. Después de la agitación 30 min, CCl_4 (4 mL) fue agregado y los volátiles fueron evaporados. El residuo fue purificado por cromatografía de

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columna de destello (5% CH3OH in CH_2Cl_2) para proporcionar el producto deseado (0.078 g, 100%) como un polvo amorfo tostado: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*=7.1), 1.75-1.96 (m, 2H), 2.13-2.30 (m, 2H), 3.12 (dd, 1H, *J*=13.7, 7.5), 3.46 (dd, 1H, *J*=13.7, 8.5), 4.20 (d, 2H, *J*=7.1), 4.45-4.55 (m, 1H), 5.63 (dd, 1H, *J*=15.7, 1.6), 5.66-5.74 (m, 1H), 5.92 (s, 1H), 6.28 (s, 1H), 6.37 (t, 1H, *J*=7.3), 6.87 (dd, 1H, *J*=15.7, 5.7), 6.92-7.00 (m, 2H), 7.09-7.17 (m, 2H), 7.54 (dd, 1H, *J*=7.3, 1.6), 7.60 (d, 1H, *J*=7.5), 8.34 (dd, 1H, *J*=7.3, 1.6), 9.04 (s, 1H); Anal. $C_{25}H_{26}F_4N_4O_6 \cdot 1.25H_2O$: C, H, N.

EJEMPLO 24

Preparación del Compuesto 25: trans-(2'S,3''''S,4S)-4-(3'-(4''-Fluorofenil)-2'-{3'''-[(5''''-metilisoxazol-3''''-carbonil)amino]-2'''-oxo-2'''H-piridin-1'''-il}propionilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico



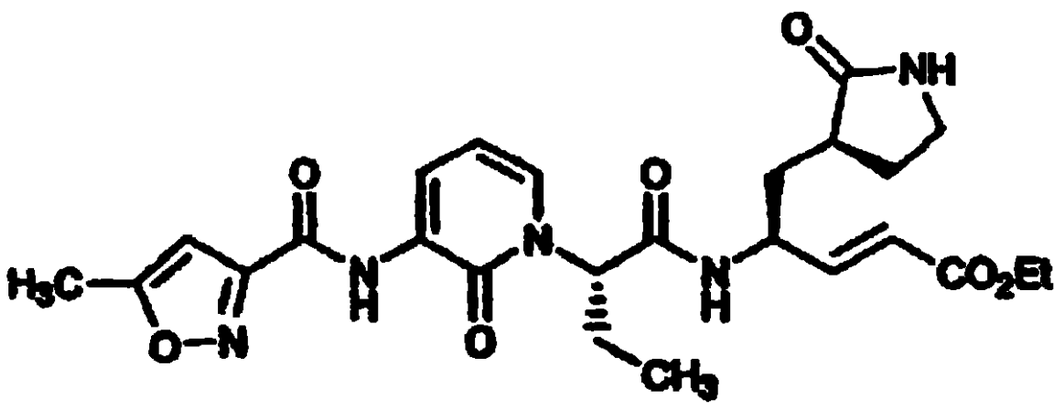
El compuesto del título fue preparado de F2 (Ejemplo 19) en una manera análoga a aquella descrita para la conversión de U2 a I3 en el Ejemplo 23 utilizando intermediario Y2 (Ejemplo 25) donde fuere apropiado: IR(cm^{-1}) 3331, 1690, 1590, 1531, 1455; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.0), 1.45-1.55 (m, 1H), 1.64-1.75 (m, 1H), 2.03-2.31 (m, 3H), 2.49 (s, 3H), 3.10 (dd, 1H, *J*=13.7, 7.9), 3.20-3.46 (m, 3H), 4.20 (q, 2H, *J*=7.0), 4.36-4.47 (m, 1H), 5.67 (dd, 1H, *J*=15.7, 1.4), 5.85-5.92 (m, 1H), 6.28 (t, 1H, *J*=7.2), 6.45 (s, 1H),

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6.70 (dd, 1H, *J*=15.7,5.7), 6.86 (s, 1H), 6.90-6.97 (m, 2H), 7.10-7.16 (m, 2H), 7.60 (dd, 1H, *J*=7.2, 1.6), 8.37 (dd, 1H, *J*=7.2, 1.6), 8.51 (d, 1H, *J*=6.6), 9.47 (s, 1H).

EJEMPLO 26

Preparación del Compuesto 26: *trans*-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metil-isoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}butiril amino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico (R3)



Preparación del intermediario (2R)-2-Trifluorometanosulfonil-ester de tert-butilo de ácido oxibutírico (U3)

Comercialmente disponible T3 (0.575 g, 3.59 mmol, 1 equiv) fue disuelto en CH_2Cl_2 (25 mL) y enfriada en un baño helado. 2,6-Lutidina (0.836 mL, 7.18 mmol, 2 equiv) anhídrido trifluorometanosulfónico (1.15 mL, 6.84 mmol, 1.9 equiv) fue agregados y la mezcla de reacción fue agitada 30 min. Esta entonces fue diluida con MTBE (400 mL), lavada con una mezcla de salmuera y 1 N HCl (2:1,100 mL) y salmuera (100 mL), secado sobre Na_2SO_4 y evaporado para proporcionar el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario (2S)-2-{3'-[(5''-Metilisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ester de tert-Butilo de Ácido butírico (V3)

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El intermediario F2 de arriba (0.200 g, 0-912 mmol, 1.1 equiv) fue suspendido en THF (6 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.0332 g, 0.830 mmol, 1 equiv) fue agregado en una parte. Después de la agitación 30 min, una solución del intermediario U3 (0.830 mmol, 1 equiv, basado en T3) en THF (7 mL) fue agregado gota a gota. La mezcla resultante fue agitada 2 horas, entonces diluida con EtOAc (200 mL) y lavada con salmuera (2 x 50 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (25% EtOAc en hexanos) para proporcionar el intermediario del título (0.178 g, 59%) como un aceite: R*f*=0.30 (25% EtOAc en hexanos); IR (cm^{-1}) 3331, 1731, 1690, 1649, 1602, 1531; ^1H NMR ($CDCl_3$) δ 50.93 (t, 3H, *J*=7.3), 1.45 (s, 9H), 1.83-2.01 (m, 1H), 2.17-2.31 (m, 1H), 2.50 (s,3H), 5.44-5.51 (m, 1H), 6.32(t, 1H, *J*=7.2), 6.48 (s, 1H), 7.10 (dd, 1H, *J*=7.2, 1.8), 8.45 (dd, 1H, *J*=7.2, 1.8), 9.64 (s, 1H); Anal. $C_{18}H_{23}N_3O_5$: C, H, N.

Preparación del intermediario (2R)-2-{3'-[(5"-Metilisoxazol-3"-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ácido butírico (W3)

El intermediario V3 de arriba (0.143 g, 0.397 mmol, 1 equiv) fue agitado durante 1 h en una solución TFA (2 mL) en CH_2Cl_2 (3 mL). Los volátiles fueron evaporados. El residuo fue suspendido en tolueno (10 mL) y concentrado menos seco, proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario trans-(3'S,4S)-4-Amino-5-(2'-oxopirrolidin-3'-il)pent-2-Ester de Etilo de Ácido enóico (Y2)

El intermediario X2, preparado de acuerdo a el método revelado en la solicitud copendiente, Solicitud de Patente Provisional de los E.U. No. 60/150,358, presentada en Agosto 24 de 1999 (0.130 g, 0.398 mmol, 1 equiv), fue agitado durante 30 min en una solución de TFA (2 mL) en CH_2Cl_2 (3 mL). Los volátiles fueron evaporados. El residuo fue suspendido en tolueno (10 mL) y

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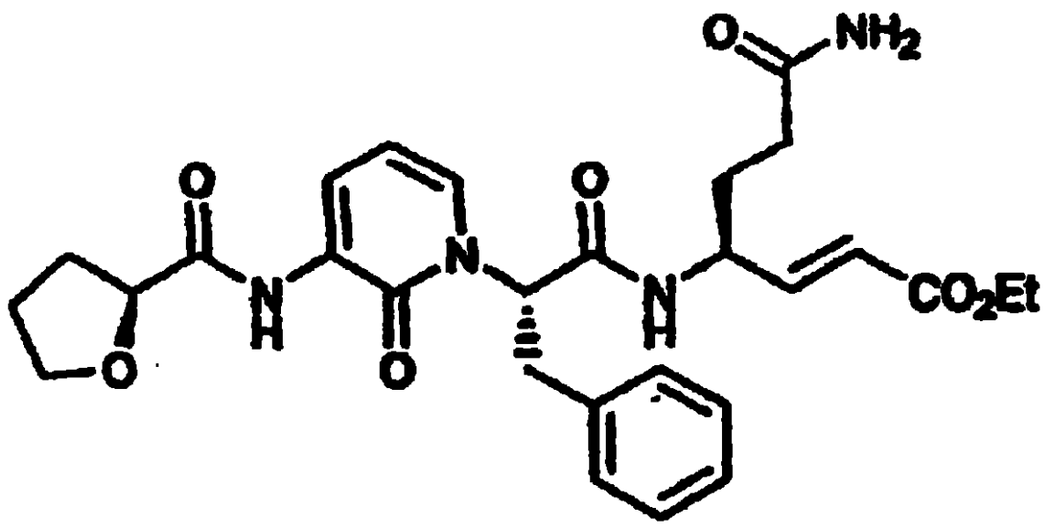
concentrado menos seco, proporcionando el intermediario del título el cual fue usado sin más purificación.

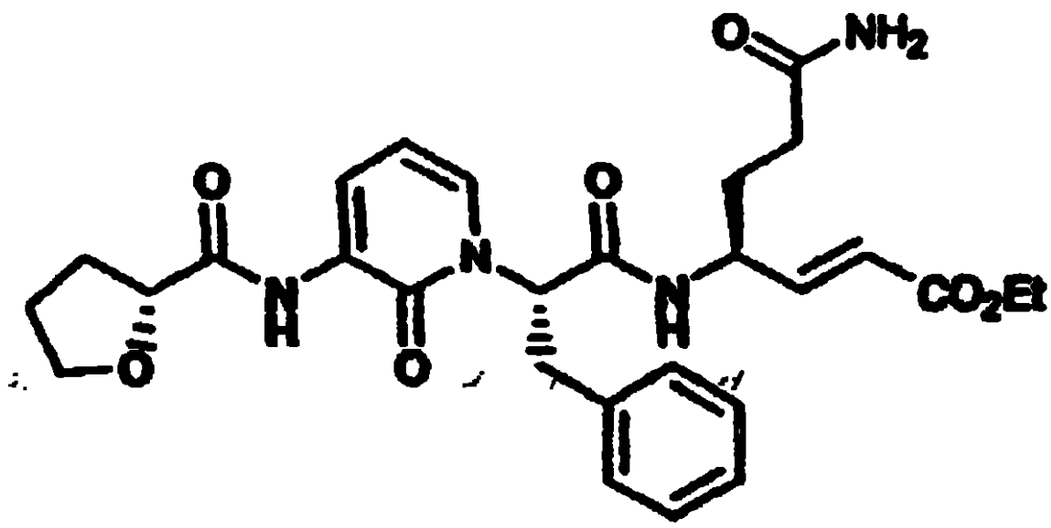
Preparación del Compuesto R3 (Compuesto 26)

Los intermediarios W3 y Y2 (como preparados arriba) fueron combinados en CH_2Cl_2 (7 mL) y enfriada en un baño helado. HOBt (0.064 g, 0.47 mmol, 1.2 equiv), iPr_2NEt (0.484 mL, 2.78 mmol, 7 equiv) y EDC (0.084 g, 0.44 mmol, 1.1 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejada calentar a 23 °C toda la noche, entonces diluida con EtOAc (500 mL) y lavada con 5% $KHSO_4$, saturado por medio de $NaHCO_3$, y salmuera (100 mL cada una). La fase orgánica fue secada sobre $MgSO_4$ y evpaorada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.119 g, 58%) como una espuma blanca: IR (cm^{-1}) 3331. 1684, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.3), 1.28 (t, 3H, *J* = 7.1), 1.47-1.58 (m, 1H), 1.62-1.77 (m, 1H), 1.86-2.00 (m, 1H), 2.08-2.33 (m, 4H), 2.49 (s, 3H), 3.25-3.42 (m, 2H), 4.19 (q, 2H, *J* = 7.1), 4.39-4.50 (m, 1H), 5.73 (dd, 1H, *J* = 8.8,6.8), 5.97 (dd, 1H, *J* = 15.7,1.4), 6.34 (t, 1H, *J*= 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J* = 15.7,5.9). 7.18 (s, 1H), 7.59 (dd, 1H, *J* = 7.2,1.8), 8.42 (dd, 1H, *J* = 7.2,1.8), 8.58-8.62 (m, 1H), 9.56 (s, 1); Anal. $C_{25}H_{31}N_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 26

Preparación de una 1:1 Mezcla del Compuesto 27: trans-(2'S,2'''S,4S)-6-Carbamoil-4-(2'-{2''-oxo-3''-[(tetrahidrofurán-2'''-carbonil)amino]-2''H-piridin-1''-il}-3'-fenilpropioniliamino)hex-2-Ester de Etilo de Ácido enóico y Compuesto 28: trans-(2'S,2'''R,4S)-6-Carbamoil-4-(2'-{2''-oxo-3''-[(tetrahidrofurán-2'''-carbonil)amino]-2''H-piridin-1''-il}-3'-fenilpropioniliamino)hex-2-Ester de Etilo de Ácido enóico



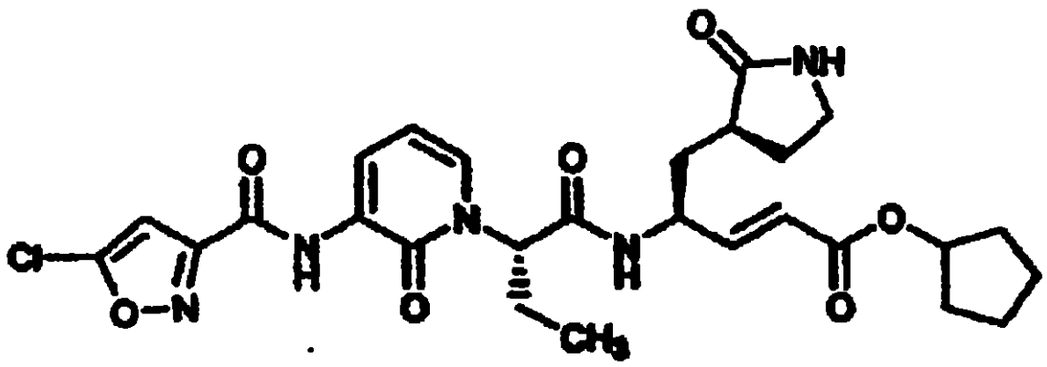


Los compuestos del título fueron preparados de I1 (Ejemplo 5) por un proceso análogo a aquel descrito en el Ejemplo 6 para la conversiónn de I1 a J1 utilizando el intermediario tetrahidrofurán-2-cloruro de carbonilo (racemic, Aldrich) donde fuere apropiado: IR (cm^{-1}) 3344, 1646, 1519, 1178; ^1H NMR ($CDCl_3$) δ 1.34(t, 3H, *J*=7.2), 1.72-1.82 (m, 1H), 1.95-2.04 (m, 2H), 2.16-2.23 (m, 2H), 2.32-2.43 (m, 1H), 3.18-3.27 (m, 1H), 3.51-3.60 (m, 5H), 3.93-4.00 (m, 1H), 4.05-4.12 (m, 1H), 4.22 (q, 2H,J= 7.20, 4.46-4.55 (m, 2H), 5.54-5.69 (m, 2H), 6.34-6.41 (m, 2H), 6.68 (dd, 1H,J= 15.6,5.4), 6.86-6.93 (m, 1H), 7.17-7.41 (m, 5H), 8.42-8.45 (m, 1H), 9.37 (d, 1H,7= 10.2); Anal. $C_{28}H_{34}N_4O_7 \cdot 1.5TFA$: C, H, N.

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EJEMPLO 27

Preparación del Compuesto 29: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Cloroisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}butirilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Ciclopentilo de Ácido enóico (R4)



Preparación del Intermediario (2S)-2-{3'-[(5''-Cloroisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ester de tert-Butilo de Ácido butírico (V4)

El intermediario F3 de arriba (0.781 g, 3.26 mmol, 1.1 equiv) fue suspendido en THF (10 mL). Hidruro de sodio (60% dispersión en aceite mineral, 0.119 g, 2.98 mmol, 1 equiv) fue agregado en una parte. Despues de agitación 30 min, una solución del intermediario U3 (2.96 mmol, 1 equiv, basado sobre T3) en THF (15 mL) fue por jeringa. La mezcla resultante fue agitada 2 horas, entonces diluida con EtOAc (500 mL) y lavada con salmuera (2 x 100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporado. El residuo fue purificado por cromatografía de columna de destello (20% EtOAc en hexanos) para proporcionar el intermediario del título (0.834 g, 74%): R_f = 0.33 (20% EtOAc en hexanos); IR (cm^{-1}) 3334, 1732, 1694, 1650, 1603, 1537; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J*=7.4), 1.46 (s, 9H), 1.85-2.00 (m, 1H), 2.17-2.32 (m, 1H), 5.44-5.50 (m, 1H), 6.33 (t, 1H, *J*=7.3), 6.88 (s, 1H), 7.12 (dd, 1H, *J*=73,1.7), 8.43 (dd, 1H, *J*=7.3, 1.7), 9.61 (s, 1H); Anal. $C_{17}H_{20}ClN_3O_5$: C, H, N.

Preparación del Intermediario (2S)-2-{3'-[(''-Cloroisoxazol-3''-carbonil)amino]-2'-oxo-2'H-piridin-1'-il}Ácido butírico (W4)

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El intermediario V4 de arriba (0.544 g, 1.42 mmol, 1 equiv) fue agitado durante 1 h en una mezcla de TFA (9 mL) y CH_2Cl_2 (9 mL). Los volátiles fueron evaporados. El residuo fue suspendido en CCU y concentrado menos seco (2 x 10 mL), proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del intermediario trans-(3'S,4S)-4-tert-Butoxicarbonilamino-5-[1'-(2",4"-dimetoxibencil)-2'-oxopirrolidin-3'-il]pent-2-Ester de Ciclopentilo de Ácido enóico (X3)

El intermediario K1 (preparado de acuerdo a Dragovich, y otros, J. *Med. Chem.* 1999, *42*, 1213) (2.00 g, 4.90 mmoL 1 equiv) y el comercialmente disponible Dess-Martin "periodinane" (2.30 g, 5.38 mmol, 1.1 equiv) fueron combinados CH_2Cl_2 (50 mL) y agitada 2 h. El solvente fue evaporado y el residuo fue suspendido en y entonces evaporado de tolueno (2 x 25 mL). El residuo resultante fue siduelto en (100 mL). (Trifenil-P-fosfanilideno)éster de ciclopentil de ácido acético (preparado en una manera análoga a aquella descrita en Baldwin, y otros *J. Org, Chem.* 1971, *36*, 1441) (2.28 g, 5.87 mmol, 1.2 equiv) fue agregado. La mezcla de reacción fue calentado a reflujo durante 100 min, dejada enfriar, diluida con EtOAc (300 mL) y lavada con una mezcla de salmuera y $NaHCO_3$ (1:1, 100 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 44→50% EtOAc en hexanos) para proporcionar el intermediario del título (1.68 g, 62%) como una espuma: IR (cm^{-1}) 3307, 1708, 1678,1508; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.50-1.93 (m, 10H), 1.97-2.08 (m, 1H), 2.21-2.33 (m, 1H), 2.48-2.60 (m, 1H), 3.17-3.23 (m, 2H), 3.80 (s, 6H), 4.26-4.40 (m, 1H). 4.41 (s, 2H), 5.18-5.24 (m, 1H), 5.26-5.33 (m, 1H), 5.92 (dd, 1H, *J*=15.6, 1.6), 6.41-6.47 (m, 2H), 6.82 (dd, 1H, *J*=15.6, 5.2), 7.08-7.13 (m, 1H); Anal. $C_{28}H_{40}N_2O_7 \cdot 0.75H_2O$: C, H, N.

Preparación del intermediario trans-(3'S,4S)-4-tert-Butoxicarbonilamino-5-(2'-oxopirrolidin-3'-il)pent-2-Ester de Ciclopentilo de Ácido enócio (X4)

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El intermediario X3 de arriba (1.54 g, 2.98 mmol, 1 equiv) fue disuelto en una mezcla de H_2O (5 mL) y $CHCl_3$ (50 mL). DDQ (0.947 g, 4.17 mmol, 1.4 equiv) fue agregado y la mezcla de reacción fue calentada en un baño de aceite a 60 °C durante 1.5 h. Más DDQ (0.90 g, 3.96 mmol, 1.3 equiv) fue agregado y calentado a 60 °C fue continuada durante 2 h más. Después del agitamiento a 23 °C, la mezcla de reacción fue diluida con CH_2Cl_2 (600 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (1:1,150 mL) y una mezcla de salmuera y $NaHCO_3$ (2 x 200 mL). La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El residuo fue purificado por cromatografía de columna de destello (elución de gradiente, 2→3% CH_3OH in CH_2Cl_2) para proporcionar el intermediario del título (0.850 g, 78%) como una espuma color canela: IR (cm^{-1}) 3305, 1698, 1522, 1279, 1165; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.52-2.05 (m, 1H), 2.38-2.54 (m, 2H), 3.29-3.40 (m, 2H), 4.29-4.41 (m, 1H), 5.17-5.27 (m, 2H), 5.93 (dd, 1H, *J*=15.7, 1.6), 5.98-6.40 (m, 1H), 6.82 (dd, 1H, *J*=15.7, 5.3); Anal. $C_{19}H_{30}N_2O_5 \cdot 0.30H_2O$: C, H, N.

Preparación del Intermediario trans-(3'S,4S)-4-Amino-5-(2'-oxo-pirrolidin-3'-il)pent-2-Ester de Ciclopentilo de ácido enóico (Y3)

El intermediario X4 (0.522 g, 1.42 mmol, 1 equiv) fue agitado durante 40 min en una solución de TFA (7 mL) in CH_2Cl_2 (10 mL). Los volátiles fueron evaporados. El residuo fue suspendido en CCU y concentrado menos seco (2 x 20 mL), proporcionando el intermediario del título el cual fue usado sin más purificación.

Preparación del Producto R4 (Compuesto 29)

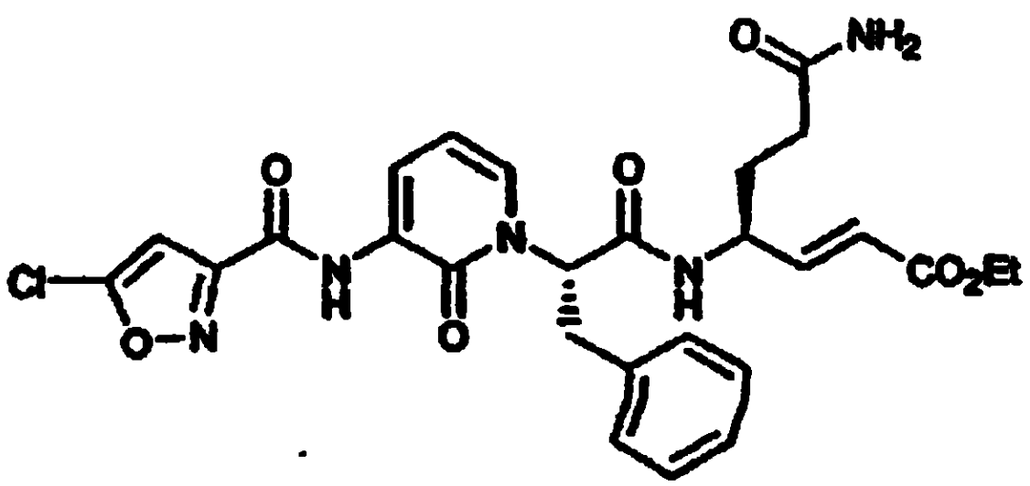
Los intermediarios W4 y Y3 (como preparado arriba) fueron combinados en CH_2Cl_2 (25 mL) y enfriado en una baño helado. HOBt (0.269 g, 1.99 mmol, 1.4 equiv), IPr2NEt (1.74 mL, 9.99 mmol, 7 equiv) y EDC (0.341 g, 0.1.78 mmol, 1.25 equiv) fueron agregados secuencialmente. La mezcla de reacción fue dejada calentar a 23 °C durante el fin de semana. Esta fue entonces diluida con EtOAc (500 mL) y lavada con una mezcla de salmuera y 10% $KHSO_4$ (1:1,100 mL) y salmuera (100 mL). La fase orgánica fue secada

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sobre Na_2SO_4 y evaporada. El residuo fue purificado por cromatografía de columna de destello (2% CH_3OH en CH_2Cl_2) para proporcionar el intermediario del título (0.590 g, 72%) como una espuma blanca: IR (cm^{-1}) 3295, 1690, 1649, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.3), 1.50-2.02 (m, 10H), 2.11-2.37 (m, 4H), 3.25.3.44 (m, 2H), 3.64-3.74 (m, 1H), 4.41-4.52 (m, 1H), 5.18-5.24 (m, 1H), 5.69 (dd, 1H, *J* = 9.0,6.6), 5.94 (dd, 1H, *J* = 15.6, 1.4), 6.36 (t, 1H, *J* = 7.3), 6.67 (s, 1H), 6.82 (dd, 1H, *J* = 15.6,5.9), 7.15 (s, 1H). 7.58 (dd, 1H, *J* = 7.3,1.7), 8.42 (dd, 1H, *J* = 7.3, 1.7). 8.49 (m, 1H), 9.52 (s, 1H); Anal. $C_{27}H_{32}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 28

Preparación del Compuesto 30: trans-(2'S,4S)-6-Carbamoil-4-(2'-{3''-[(5'''-cloroisoxazol-3''' -carbonil)amino]-2''-oxo-2''H-piridin-1''-il}-3'-fenilpropioniamino)hex-2- Ester de Etilo de Ácido enóico



Preparación del intermediario (1'S,4''S)-5-Cloroisoxazol-3-Ácido carboxílico {1'-[1''-Bencil-4''-(tert-butildimetilsilaniloximetil)-2''-oxo-6'-(tritilcarbamoil)hexil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida

A una solución de 5-cloroisoxazol-3-ácido carboxílico (Ejemplo 22, 0.253 g, 1.71 mmol, 2.0 equiv) en $CHCl_3$ (21 mL) fue agregada $SOCl_2$ (9 mL). La mezcla de reacción fue calentada a reflujo durnate 26 h. Los volátiles fueron removidos bajo presión reducida para dar 5-cloroisoxazol-3-cloruro de carbonilo crudo.

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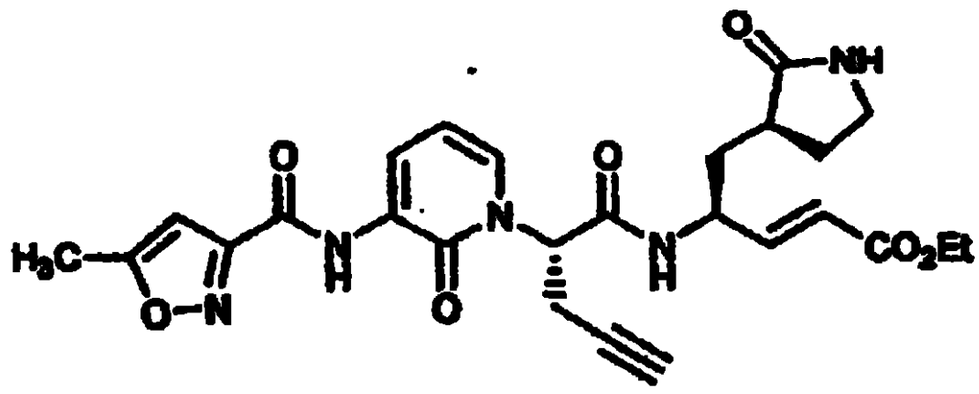
Una muestra de 10% Pd sobre C (0.070 g) fue agregada a una solución de (1'S,4"S)-5-cloroisoxazol-3-ácido carboxílico {1'-[1"-Bencil-4-(tert-butildimetilsilaniloxi-metil)-2"-oxo-6"-(tritilcarbamoil) hexil]-2'-oxo-1',2'-dihidropiridin-3'-il}amida (Ejemplo 1, 0.74 g, 0.855 mmol, 1 equiv) en EtOAc (15 mL). La mezcla de reacción fue agitada a temepratura ambiente bajo atmósfera H2 (aeróstato) durante 4 h, y entonces fue filtrada a través de Celita. El filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en THF (15 mL), enfriada a 0 °C, y 5-cloroisoxazol-3-cloruro de carbonilo (1.71 mmol, 2.0 equiv) y NMM (0.188 mL, 1.71 mmol, 2.0 equiv) fueron agregados secuencialmente. La mezcla de reacción fue agitada a 0 °C durante 1 h, entonces fue partida por medio de agua (100 mL) y EtOAc (2 x 100 mL). Las capas orgánicas fueron secadas bajo Na_2SO_4 y concentradas. El residuo fue purificado por cromatografía de columna de destello (35% EtOAc en hexanos) para proporcionar el intermediario del título (0.666 g, 90%): IR (cm^{-1}) 3332, 1684, 1531; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.60-1,71 (m, 1H), 1.80-1.83 (m, 1H), 2.12-2.16 (m, 2H), 3.16-3.23 (m, 1H), 3.36-3.41 (m, 1H), 3.47-3.55 (m, 2H), 3.81-3.90 (m, 1H), 5.64-5.70 (m, 1H), 6.26 (t, 1H, *J*= 7.2), 6.47 (d, 1H, *J*= 8.7), 6.70 (s, 1H), 7.02 (s, br. 1 H), 7.17-7.33 (m, 20H), 7.37 (d, 1H, *J*= 7.2), 8.40 (d, *J*= 7.8), 9.56 (s, br. 1H).

Preparación del Compuesto 30

El intermediario precedente fue convertido en compuesto 30 por un proceso que fue análogo a aquel descrito en el Ejemplo 7 para la conversión del intermediario C1 a compuesto 7: mp = 163-165 °C; IR (cm^{-1}) 3335, 1648, 1533, 1179; ^1H NMR ($CDCl_3$) δ 0.34 (t, 3H, *J*=7.2), 1.76-1.86 (m, 1H), 1.94-2.00 (m, 1H), 2.23 (t, 2H, *J*= 6.9), 3.20-3.27 (m, 1H), 3.35-3.42 (m, 2H), 3.51-3.58 (m, 1H), 4.22 (q, 2H, *J*= 7.2), 4.52-4.57 (m, 1H), 5.69 (dd, 1H, *J*= 15.6, 1.5), 6.70 (s, br. 1H), 6.14 (s, br. 1H), 6.32 (s, br. 1H), 6.39 (t, 1H, J = 7.2), 6.69 (dd, 1H, *J*= 15.6, 5.4), 7.21-7.33 (m, 4H), 7.47 (d, 1H, *J*= 7.2), 8.44 (d, 1H, *J*= 7.5), 9.47 (s, br. 1H); Anal. $C_{27}H_{28}ClN_5O_7 \cdot 0.6H_2O$: C, H, N.

EJEMPLO 29

Preparación del Compuesto 31: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}pent-4'-inoil-amino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Etilo de Ácido enóico

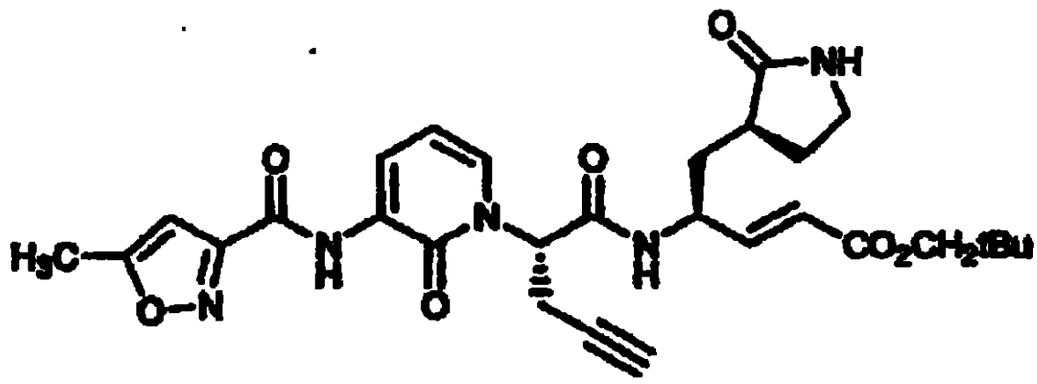


El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito en el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando el intermediario F2 y Y2 y una desprotección alternada del intermediario correspondiente a VI (LII en piridina) donde fuere apropiado: IR (cm^{-1}) 3295, 1684, 1648, 1596, 1531; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*= 7.1), 1.52-1.62 (m, 1H), 1.64-1.80 (m, 1H), 2.04 (t, 1H, *J*= 2.6), 2.08-2.38 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, *J*= 17.0, 8.4,2.6), 3.01 (ddd, 1H, J= 17.0,6.8,2.6), 3.22-3.39 (m, 2H), 4.18 (q, 2H, *J*= 7.1), 4.44-4.55 (m, 1H), 5.71-5.78 (m, 1H), 6.03 (dd, 1H, *J*= 15.6, 1.5), 6.32 (t, 1H, .7= 7.2), 6.46 (s, 1H), 6.85 (dd, 1H, *J*= 15.6, 5.4), 6.89 (s, 1H), 7.49 (dd, 1H, *J*= 7.2, 1.7) 8.41 (dd, 1H, *J*= 7-2, 1.7), 8.69 (d, 1H, *J*= 6.6), 9.52 (s, 1H); Anal. $C_{28}H_{29}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 30

Preparación del Compuesto 32: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil)amino]-2''-oxo-2''H-piridin-1''-il}-pent-4'-inoilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester 2,2-Dimetilpropilo de Ácido enóico

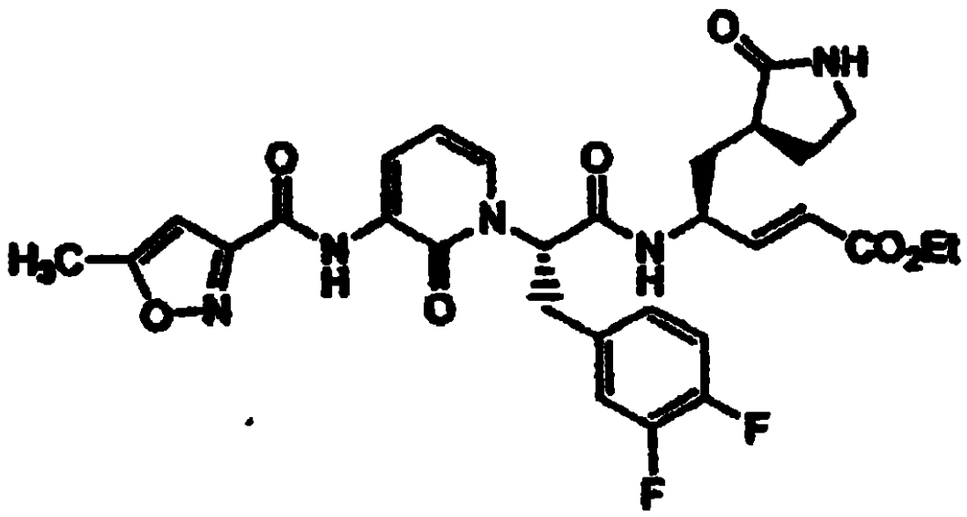
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El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito ene el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando intermediarios F2 y trans-(3'S,4S)4-tert-butoxicarbonilamino-5-(2'-oxopirrolidin-3'-il)pent-2-éster de 2,2-dimetilpropilo de ácido enóico (preparado de K1 en una manera similar a aquella descrita para la preparación del X4 en el Ejemplo 27). y una desprotección alternada del intermediario correspondiente a V1 (Lil en piridina) donde fuere apropiado: IR (cm^{-1}) 3295, 1690, 1649, 1596, 1531; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.54-1.80 (m, 2H), 2.05 (t, 1H, *J*= 2.6), 2.10-2.39 (m, 3H), 2.49 (s, 3H), 2.91 (ddd, 1H, *J*= 17.0, 8.2,2.6), 3.01 (ddd, 1H, *J*= 17.0, 6.8,2.6), 3.22-3.38 (m, 2H), 3.62 (s, 2H), 4.45-4.56 (m, 1H), 5.72-5.79 (m, 1H), 6.06 (dd, 1H, *J*= 15.7,1.5), 6.33 (t, 1H, *J*= 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J*= 15.7,5.4), 6.93 (s, 1H), 7.51 (dd, 1H, *J*= 7.2,1.7), 8.41 (dd, 1H, J= 7.2,1.7), 8.69 (d, 1H, *J*= 6.6), 9.52 (s, 1H); Anal. $C_{29}H_{35}N_5O_7 \cdot 0.25H_2O$: C, H, N.

EJEMPLO 31

Preparación del Compuesto 33: trans-(2'S,3''''S,4S)-4-(3'-(3'',4''-Difluorofenil)-2'-{3'''-[(5''''-metilisoxazol-3''''-carbonil)amino]-2'''-oxo-2'''H-piridin-1'''-il}propionilamino)-5-(2'''''-oxopirrolidin-3'''''-il)pent-2-Eester de Etilo de Ácido enóico

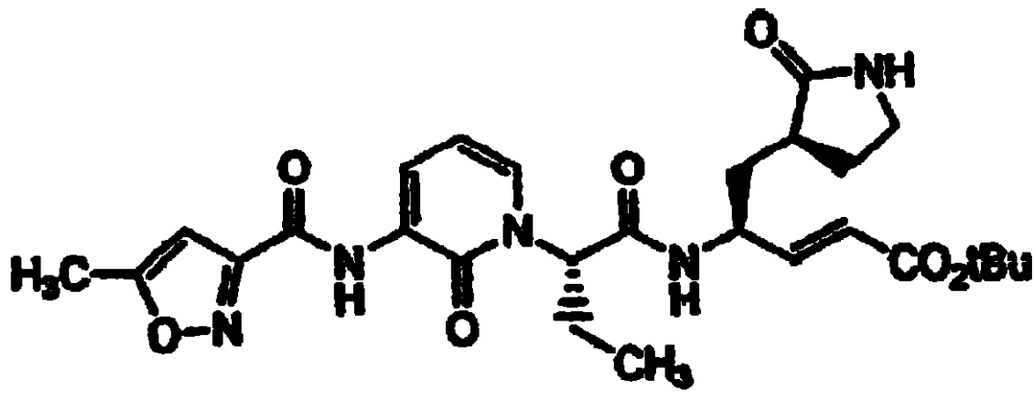


El compuesto del título fue preparado por un un método análogo a aquel descrito en el Ejemplo 19 para la preparación del intermediario específico R1 utilizando (2R)-3-(3',4'-difluorofenil)-2-ácido hidroxipropiónico (sintetizado de (2R)-2-terc-butoxicarbonilamino-3-(3',4'-difluorofenil)ácido propiónico en analogía a la preparación del intermediario S1 descrito en el Ejemplo 22) y trietilfosfonoacetato donde fuere apropiado: IR(cm^{-1}) 3331, 1690, 1649, 1598, 1531, 1455, 1278; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*= 7.1), 1.44-1.54 (m, 1H), 1.63-1.78 (m, 1H), 2.08-2.9 (m, 3H), 2.49 (d, 3H, *J*= 0.9), 3.05 (dd, 1H, *J*= 13.6,7.5), 3.20-3.42 (m, 3H), 4.19 (dq, 2H, *J*= 7.1,1.7), 4.34-4.45 (m, 1H), 5.64 (dd, 1H, *J*= 15.7,1.4), 6.00 (t, 1H, *J*= 7.8), 6.32 (t, 1H, *J*= 7.3), 6.45 (s, 1H), 6.71 (dd, 1H, *J*= 15.7,5.6), 6.86-6.91 (m, 1H), 6.98-7.08 (m, 2H), 7.15 (s, 1H), 7.68 (dd, 1H, *J*=7.3, 1.7), 8.39 (dd, 1H, *J*= 7.3,1.7), 8.65 (d, 1H, .7= 6.8). 9.46 (s, 1H); Anal. $C_{30}H_{31}F_2N_5O_7$: C, H, N.

EJEMPLO 32

Preparación del Compuesto 34: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil) amino]-2''-oxo-2''H-piridin-1''-il}butirilamino)-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de tert-Butilo de Ácido enoico

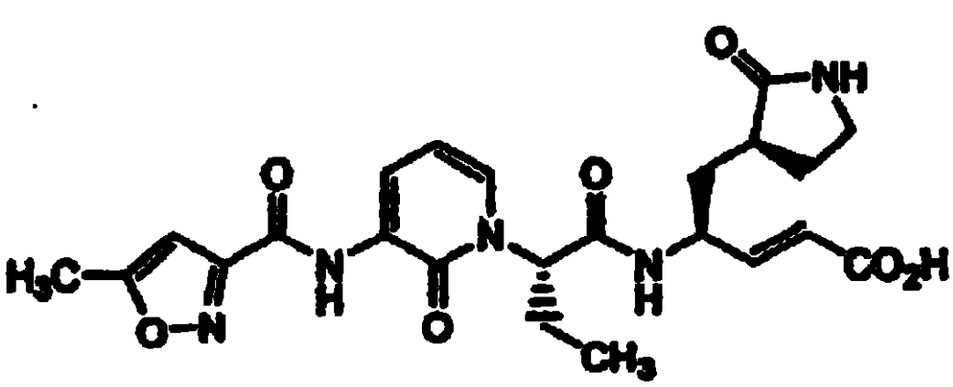
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El compuesto del título fue preparado por un método análogo a aquel descrito para la síntesis del compuesto R3 en el Ejemplo 25: IR (cm^{-1}) 3331, 3295, 1690, 1649, 1590, 1531, 1455, 1155; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J*= 7.3), 1.40-1.60 (m, 1H), 1.49 (s, 9H), 1.62-1.78 (m, 1H), 1.87-2.02 (m, 1H), 2.09-2.36 (m, 4H), 2.50 (s, 3H), 3.26-3.43 (m, 2H), 4.39-4.50 (m, 1H), 5.78 (dd, 1H, .7= 8.9, 6.7), 5.89 (dd, 1H, *J*= 15.7, 1.3), 6.35 (t, 1H, *J*= 7.3), 6.47 (s, 1H), 6.76 (dd, 1H, *J*= 15.7,5.9), 7.33 (s, 1H), 7.64 (dd, 1H, *J*= 7.3, 1.8), 8.43 (dd, 1H, *J*= 7.3, 1.8), 8.59 (d, 1H, *J*= 6.8), 9.57 (s, 1H); Anal. $C_{27}H_{35}N_5O_7 \cdot 0.5H_2O$: C, H, N.

EJEMPLO 33

Preparación del Compuesto 35: trans-(2'S,3''''S,4S)-4-(2'-{3''-[(5'''-Metilisoxazol-3'''-carbonil) amino]-2''-oxo-2''H-piridin-1'' -il} butirilamino)-5-(2'''' -oxopirrolidin-3''''-il)pent-2-Ácido enóico

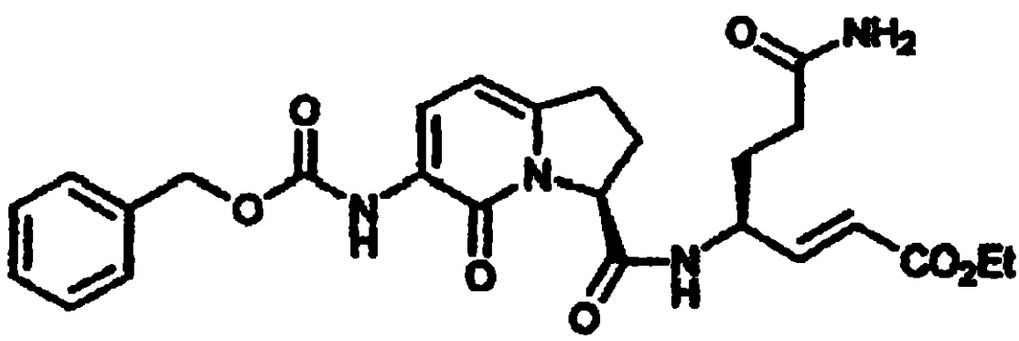


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El compuesto del título fue preparado del compuesto 34 por desprotección acídica de la mitad de éster de terl-butilo presente en aquel compuesto (procedimientos de literatura normales siguientes): IR (cm^{-1}) 3319, 1678, 1643, 1590, 1531; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J*= 7.2), 1.61-1.99 (m, 3H), 2.08-2.32 (m, 3H), 2.40-2.54 (m, 1H), 2.49 (s, 3H), 3.25-3.41 (m, 2H), 4.58-4.69 (m, 1H), 5.56-5.64 (m, 1H), 5.98 (d, 1H, *J*= 15.6), 6.21 (br, 1H), 6.37 (t, 1H, *J*= 7.3), 6.47 (s, 1H), 6.96 (dd, 1H, *J*= 15.6, 6.6), 7.50 (dd, 1H, *J*= 7.3, 1.6), 7.52 (s, 1H), 8.26 (d, 1H, *J*= 7.7), 8.44 (dd, 1H, *J*= 7.3, 1.6), 8.62 (s, 1H); Anal. $C_{23}H_{27}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 34

Preparación del Compuesto 36: trans-(3'S,4S)-4-[(6'-Benciloxicarboniiamino-5'-oxo-1',2',3',5'-tetrahidroindolizina-3'- carbonil)amino]-6-carbamoilhex-2-Ester de Etilo de Ácido enóico



Preparación del Intermediario 6-But-3-enil-2-hidroxinicotinonitrilo (a1)

n-Butillitio (100 mL de una solución de 1.6 M en hexanos, 160 mmol, 2.5 equiv) fue agregada vía cánula más de 10 min a una solución de diisopropilamina (22.4 mL, 160 mmol, 2.5 equiv) en THF (600 mL) a -78 °C. La solución amarilla pálido resultante fue agitada a -78 °C durante 5 min, entonces fue calentada a 0 °C durante un adicional de 5 min. 2-Hidroxi-6-metilnicotinonitrilo (8) (8.58 g, 64.0 mmol, 1 equiv) fue agregado como un sólido en pequeñas partes más de 15 min y la solución anaranjada intensa así obtenida fue agitada durante 1 h a 0 °C. Bromuro de alilo (8.31 mL,

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96.0 mmol, 1.5 equiv) fue entonces agregado y la mezcla de reacción fue calentada a 23 °C, mantenida a aquella temperatura durante for 30 min, y fue partida por medio de 1.0 M HCl (300 mL) y EtOAc (2 x 250 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. El sólido naranja resultante fue triturado con cocción de Et_2O (100 mL) y subsiguientemente enfriado a 23 °C, entonces fue filtrada a través de un derretimiento medio, lavado con Et_2O (2 x 50 mL) y secado al aire para dar a1 (6.42 g, 58%) como un sólido tostado: mp = 122-125 °C; IR (pildora KBr, cm^{-1}) 2223, 1654; ^1H NMR (DMSO-d_6) δ 2.32-2.37 (m, 2H), 2.62 (t, 2H, *J*= 7.6), 4.96-5.06 (m, 2H), 5.69-5.83 (m, 1H), 6.23 (d, 1H, *J*= 7.3), 8.03 (d, 1H, *J*= 7.3), 12.55 (s, br, 1H); Anal. $C_{10}H_{10}N_2O \cdot 0.10H_2O$: C, H, N.

Preparación del Intermediario 6-But-3-enil-2-hidroxinicotinamida (b1)

Peroxido de hidrógeno (30 wt. % solución en agua, 45 mL) fue agregada a una solución de a1 (12.13 g, 70.2 mmol) en una mezcla de EtOH (150 mL) y 10% NaOH acuoso (280 mL) a 23 °C. La mezcla resultante fue calentada a 50 °C for 18 h, entonces fue enfriada a 23 °C y los volátiles fueron removidos bajo presión reducida. El residuo fue acidificado con 12 M HCl a pH 2-3, y el precipitado resultante fue filtrado, lavado con agua (2 x 50 mL), y secado al aire para proporcionar b1 como un sólido amarillo (13.48 g, 100%): mp = 196-198 °C; IR (cm^{-1}) 3329, 3134, 1688, 1642; ^1H NMR (DMSO-d_6) δ 2.31-2.38 (m, 2H), 2.64 (t, 2H, *J*= 7.6), 4.96-5.05 (m, 2H), 5.71-5.84 (m, 1H), 6.29 (d, 1H, *J*= 7.3), 7.45 (s, br, 1H), 8.21 (d. 1H, *J*= 7.3), 9.00 (s, br, 1H), 12.37 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparación del Intermediario 6-But-3-enil-2-Ácido hidroxinicotínico (c1)

Una solución de b1 (12.38 g, 70.1 mmol) en 10% KOH acuoso (350 mL) fue calentado a reflujo durante 20 h y subsiguientemente enfriada a temperatura ambiente. La mezcla de reacción fue

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acidificada con 12 M HCl a pH 2-3, y el precipitado resultante fue filtrado, lavado con agua (2 x 50 mL), y secado bajo vacio para proporcionar c1 como un sólido amarillo (12.46 g, 92%): mp = 151-155 °C; IR (cm^{-1}) 2905 (br), 1736, 1652; ^1H NMR (DMSO-d_6) δ 2.34-2.29 (m, 2H), 2.73 (t, 2H, *J*= 7.6), 4.96-5.07 (m, 2H), 5.72-5.85 (m, 1H), 6.56 (d, 1H, J= 7.5), 8.28 (d, 1H, *J*= 7.5), 13.26 (s, br, 1H), 14.64 (s, br, 1H); Anal. $C_{10}H_{11}NO_3 \cdot 0.10H_2O$: C, H, N.

Preparación del Intermendiario (6-But-3-enil-2-hidroxipiridin-3-il)Ester de Bencilo de Ácido carbámico (d1)

Trietilamino (13.9 mL, 99.7 mmol, 2.0 equiv) y ácido de difenilfosforilo (16.1 mL, 74.7 mmol, 1.5 equiv) fueron agregados secuencialmente a una supensión de c1 (9.63 g, 49.8 mmol, 1 equiv) en 1,4-dioxano (450 mL) a 23 °C. La solución resultante fue calentada a reflujo durante 7.5 h, entonces alcohol de bencilo (10.5 mL, 99.5 mmol, 2.0 equiv) fue agregado y el reflujo fue continuado durante un adicional de 16 h. La mezcla de reacción café obscura fue enfriada a 23 °C y los volátiles fueron removidos bajo presión reducida. El aceite café obscuro resultante fue partida por medio de agua (300 mL) y EtOAc (2 x 250 mL) y las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y conccentrada. El sólido así obtenido fue triturado con Et_2O (150 mL) y filtrado a través de derretimiento medio, lavado con Et_2O (2 x 50 mL)y secado al aire para dar d1 (7.34 g, 49%) como un polvo casi blanco: mp = 179-180 °C; IR (cm^{-1}) 3386, 1727, 1645; ^1H NMR ($CDCl_3$) δ 2.39-2.46 (m, 2H), 2.65 (t, 2H, *J*= 7.5), 4.97-5.07 (m, 2H), 5.21 (s, 2H), 5.73-5.87 (m, 1H), 6.10 (d, 1H, *J* = 7.5), 7.32-7.44 (m, 5H), 7.68 (s, br, 1H), 8.06 (s, br, 1H), 12.74 (s, br, 1H); $C_{17}H_{18}N_2O_3$: C, H, N.

Preparación del Intermendiario (6-But-3-enil-2-metoxipiridin-3-il)Ester de Bencilo de Ácido carbámico (e1)

Tetrafluoroborato de trimetiloxinio (2.0 g, 13.5 mmol, 1.2 equiv) y 2,6-di-tert-butilpiridina (1.52 mL, 6.76 mmol, 0.6 equiv) fueron agregados a una solución de d1 (3.36 g, 11.26 mmol, 1 equiv) en CH_2Cl_2 (80 mL) a 23 °C. La mezcla de reacción fue

agitada a aquella temperatura durnate 65 h, entonces fue partida por medio de agua (2 x 50 mL) y CH_2Cl_2 (2 x 200 mL) y capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas. El residuo fue purificado por cromatografía de columna de destello (5% EtOAc en hexanos) para proporcionar e1 (3.19 g, 91%) como un aceite descolorido: IR (cm^{-1}) 3432, 1733; ^1H NMR ($CDCl_3$) δ 2.42-2.49 (m, 2H), 2.73 (t, 2H, *J*= 7.6), 3.96 (s, 3H), 4.94-5.07 (m, 2H), 5.20 (s, 2H), 5.80-5.94 (m, 1H), 6.71 (d, 1H, *J*= 7.8), 7.11 (s, br, 1H), 7.32-7.43 (m, 5H), 8.16 (s, br, 1H); Anal. $C_{18}H_{20}N_2O_3$: C, H, N.

Preparación del intermediario (3'R)-[6-(3',4'-Dihidroxibutil)-2-metoxipiridin-3-il]Ester de Bencilo de Ácido carbámico (f1)

A una mezcla de 1:1 t-BuOH y agua (300 mL) a O °C fue agregado $(DHQD)_2AQN$ (0.148 g, 0.164 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (16.2 g, 49.2 mmol, 3 equiv), K_2CO_3 (6.8 g, 49.2 mmol, 3 equiv), dihidrato de osmato de potasio (0.024 g, 0.066 mmol, 0.004 equiv), y entonces e1 en t-BuOH (25 mL), secuencialmente. La mezcla resultante fue agitada a O °C durante 20 h, entonces calentada a temperatura ambiente y Na_2SO_3 (30 g) fue agregado cuidadosamente. La mezcla fue agitada a temperatura ambiente durante 2 h, entonces los volátiles fueron removidos bajo presión reducida. El residuo fue partido por medio de agua (200 mL) y EtOAc (3 x 200 mL) y las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas. El residuo fue purificado por cromaografía de columna de destello (2% CH_3OH en CH_2Cl_2) pafra proporcionar f1 (5.57 g, 98%) como un aceite amarillo pálido: IR (cm^{-1}) 3427(br), 1731; ^1H NMR ($CDCl_3$) δ 1.76-1.87 (m, 2H), 2.07-2.11 (m, 1H), 2.80-2.89 (m, 2H), 3.46-3.53 (m, 1H), 3.60-3.67 (m, 1H), 3.71-3.77 (m, 1H), 3.96 (s, 3H), 4.64 (d, 1H, *J*= 3.2), 5.21 (s, 2H), 6.76 (d, 1H, *J*= 7.8), 7.12 (s, br, 1H), 7.34-7.43 (m, 5H), 8.22 (s, br, 1H); Anal. $C_{18}H_{22}N_2O_5$: C, H, N.

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Preparación del intermediario (3'R)-{6-[4'-(tert-Butil-dimetil-silanilioxi)-3'-hidroxibutil]-2-metoxipiridin-3-il}Ester de Bencilo de Ácido carbámico (g1)

Trietilamino (1.55 mL, 11.1 mmol, 2.5 equiv), cloruro de tert-butildimetilsililo (1.07 g, 7.10 mmol, 1.6 equiv), y 4-dimetilaminopiridina (0.025 g, 0.20 mmol, 0.045 equiv) fueron agregados secuencialmente a una solución de f1 (1.54 g, 4.45 mmol, 1 equiv) en CH_2Cl_2 (50 mL) a 23 °C. La mezcla de reacción fue agitada durante 19 h a 23 °C, entonces fue partida por medio de 0.5 M HCl (150 mL) y una mezcla 1:1 de EtOAc y hexanos (2 x 150 mL). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y fueron concentradas. Purificación del residuo por cromatografía de columna de destello (20% EtOAc en hexanos) proporciona g1 (1.69 g, 82%) como un aceite descolorido: IR (cm^{-1}) 3436, 1734; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.72-1.94 (m, 2H), 2.72-2.88 m, 2H), 3.26 (d, 1H, *J*= 3.1), 3.50 (dd, 1H, *J*= 9.8,6.9), 3.58-3.63 (m, 1H), 3.65-3.70 (m, 1H), 3.95 (s, 3H), 5.20 (s. 2H), 6.75 (d, 1H, *J*= 8.1), 7.11 (s, br, 1H), 7.33-7.43 (m, 5H), 8.20 (s, br, 1H); Anal. $C_{24}H_{38}N_2O_5Si$: C, H, N.

Preparación del intermediario (3S)-(3-Hidroximetil-5-oxo- 1,2,3,5-tetrahidroindolizin-6-il)-Ester de Bencilo de Ácido Carbámico (h1)

2,6-Lutidina (2.43 mL, 20.84 mmol, 4.0 equiv) y anhídrido de trifluorometanesulfónico (1.31 mL, 7.82 mmol, 1.5 equiv) fueron agregados secuencialmente a una solución de g1 (2.4 g, 5.21 mmol, 1 equiv) en CH_2Cl_2 (100 mL) a -78 °C. La mezcla de reacción descolorida fue agitada a -78 °C durante 45 min, calentada a 23 °C durante un adicional de 15 min, entonces fue partida por medio de 0.5 M HCl (150 mL) y CH_2Cl_2 (2x150 mL). La capa orgánica fue secada sobre Na_2SO_4 y fue concentrada. El residuo así obtenido fue disuelto en THF (120 mL) a 23 °C fluoruro de tetrabutilamonio (15.63 mL a una solución 1:0 M en THF, 15.63 mmol, 3.0 equiv) fue agregado. La mezcla de reacción fue agitado a aquella temperatura durante 1 h, entonces fue partida por medio de 0.5 M HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas fueron secadas sobre

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Na_2SO_4 y concentradas. El residuo así obtenido fue purificado por cromatografía de columna de destello (80% EtOAc en hexanos) para dar h1 (0.953 g, 58%) como un aceite descolorido: IR (cm^{-1}) 3379 (br), 1727, 1649; ^1H NMR ($CDCl_3$) δ 1.86-1.97 (m, 1H), 2.29-2.41 (m, 1H), 2.90-3.15 (m, 2H), 3.80-3.93 (m, 2H), 4.78-4.86 (m, 1H), 5.11-5.15 (m, 1H), 5.20 (s, 2H), 6.20 (d, 1H, *J*= 7.5), 7.30-7.41 (m, 5H), 7.75 (s, br, 1H), 8.07 (d, IH,^ 7.5); Anal $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

Preparación del Intermediario (3S)-6-Benciloxicarboniiamino-5-oxo-l,2,3,5-tetrahidroindolizina-3-Ácido carboxílico (I1)

Dimetilsulfixido (0.522 mL, 7.36 mmol, 2.6 equiv) fue agregado gota/ a gota a una solución de cloruro de oxalilo (0.321 mL, 3.68 mmol, 1.3 equiv) en CH_2Cl_2 (80 mL) a -78 °C. La mezcla de reacción fue agitada durante 20 min a aquella temperatura, entonces una solución de h1 (0.890 g, 2.83 mmol, 1 equiv) en CH_2Cl_2 (20 mL) fue agregada vía cánula. Después de la agitación un adicional de 20 min a -78 °C, trietilamino (1.97 mL, 14.15 mmol, 5.0 equiv) fue agregado gota a gota. La mezcla de reacción fue mantenida a -78 °C durante 1.5 h, entonces ácido acético (15.57 mmol, 0.891 mL, 5.5 equiv) fue agregado. La mezcla de reacción fue calentada a O °C durante 5 min, entonces fue lavada con agua (50 mL), saturada $NaHCO_3$ (50 mL) y salmuera (50 mL). La capa orgánica fue secada sobre Na_2SO_4 y concentrada para proporcionar el producto de aldehido crudo como una espuma casi blanca. Este material fue utilizado sin más purificación.

Una solución de $NaClO_2$ (2.88 g, 25.47 mmol, 9.0 equiv) y NaH_2PO_4 (2.73 g, 19.81 mmol, 7.0 equiv) en agua (60 mL) fue agregada gota a gota para una solución del aldehido crudo precedente (2.83 mmol, 1 equiv) en una mezcla de tBuOH (60 mL) y 2-metil-2-buteno (10 mL) sobre 15 min a 23 °C. La mezcla resultante fue agitada a temperatura ambiente durante 1 h, entonces, los volátiles fueron removidos bajo presión reducida. El residuo así obtenido fue partido por medio de 0.5 M HCl (150 mL) y

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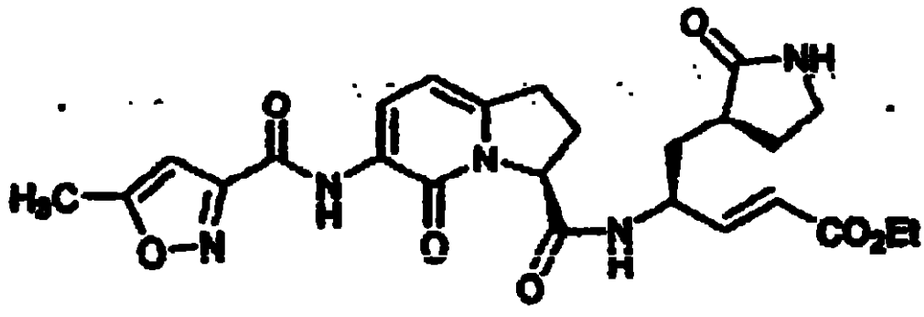
10% CH_3OH en CH_2Cl_2 (2 x 150 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. El residuo resultante fue purificado por cromatografía de columna de destello (10% CH_3OH en CH_2Cl_2). Para dar I1 (0346 g, 37%) como un sólido casi blanco: mp = 204-206 °C; IR (cm^{-1}) 3298, 1722, 1564, 1208; ^1H NMR (DMSO-d_6) δ 2.17-2.55 (m, 2H), 2.45-2.59 (m, 2H), 4.98 (dd, 1H, *J*= 9.6,2.7), 5.16 (s, 2H), 6.23 (d, 1H, *J*= 7.5), 7.34-7.45 (m, 5H), 7.83 (d, 1H, *J*= 7.5), 8.34 (s, 1H); Anal. $C_{17}H_{18}N_2O_5$: C, H, N.

Preparación del Producto k1 (Compuesto 36)

El intermediario I1 fue transformado en compuesto 36 (vía acoplamiento con el intermediario AA1) por un proceso que fue análogo a aquel en el Ejemplo 23 para la transformación de W2 a producto J2: ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, *J*= 7.1), 1.64-1.84 (m,2H), 2.01-2.16 (m,2H), 2.41-2.50 (m, 1H), 3.01-3.06 (m,2H), 4.11 (q, 2H, *J*= 7.1), 4.41 (m, br, 1H), 5.01 (dd, 1H, *J*= 9.2, 2.7), 5.14 (s,2H), 5.87 (dd, 1H, *J*= 1.4), 6.20 (d, 1H, *J*= 7.6), 6.75 (s, br, 1H), 6.82 (dd, 1H, *J*= 15.8,5.0), 7.09-7.42 (m, 7H), 7.81 (d, 1H, *J*= 7.6), 8.38 (s, 1H), 8.55 (d, 1H, *J*= 8.4).

EJEMPLO 38

Preparación del Compuesto 37: trans-(3'S,3'''S,4S)-4-({6'-[(5''-Metilisoxazol-3''-carbonil)amino]-5'-oxo-1',2',3',5'-tetrahidroindolizina-3'-carbonil}amino-5-(2'''-oxopirrolidin-3'''-il)-pent-2-Ester de Etilo Ácido de enóico



Preparación del intermediario (3"R)-(5-Metilisoxazol-3-Ácido carboxílico-{6'-[4"-(tert-butildimetilsilaniloxi)-3"-hidroxibutilo] 2'-metoxipiridin-3'-il}amida (g2)

Una suspensión del intermediario g1 (preparada como se describió en el Ejemplo 34) (4.21 g, 9.14 mmol, 1 equiv) y Pd en C (10%, 0.375 g) en EtOAc (120 mL) fue agitado bajo una atmósfera H_2 (aerostato) a 23°C durante 1 h. La mezcla de reacción fue filtrada a través de Celita y el filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en CH_3CN (120 mL), enfriada a 0 °C, y NMM (1.00 mL, 9.10 mmol, 1.0 equiv) y 5-metilisoxazol-3-cloruro de carbonilo (1.33 g, 9.14 mmol, 1.0 equiv) fue agregado secuencialmente. La mezcla de reacción fue agitada a 0 °C durante 1 h, entonces fue partida por medio de 0.5 M HCl (150 mL) y EtOAc (2 x 150 mL). Las capas orgánicas fueron secadas sobre Na_2SO_4 y fueron concentradas. La trituración del residuo con una mezcla de 1:3 de Et_2O y hexanos (130 mL) proporciona un sólido blanco el cual fue recogido por filtración, lavado con hexanos (25 mL), y secado al aire (2.61 g, 66%): mp = 100-102°C; IR (cm^{-1}) 3390, 1696, 1593, 1536; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.78-1.95 (m, 2H), 2.52 (s, 3H), 2.78-2.90 (m, 2H), 3.45-3.53 (m, 2H), 3.60-3.74 (m, 2H), 4.03 (s, 3H), 6.51 (s, 1H), 6.79 (d, 1H, *J*= 7.9), 8.55 (d, 1H, *J*= 7.9), 8.95 (s, 1H); Anal. $C_{21}H_{33}N_3O_5Si$: C, H, N.

Preparación de los intermediarios (3S)-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5'-oxo-1,2,3,5-tetrahidro indolizina-3-Ácido carbo xílico (i2) y (3S)-8-Cloro-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5'-oxo-1,2,3,5-tetrahidroindolizina-3-Ácido carboxílico (i3)

El intermediario precedente (g2) fue transformado en una mezcla 1:4 de los intermediarios i2 y i3 por un proceso aue fue análogo a aquel descrito en el Ejemplo 34 por la transformación de g1 a i1: (i2) IR (cm^{-1}) 3343, 2977 (br), 1741, 1688, 1648; ^1H NMR ($CDCl_3$) δ 2.28-2.74 (m, 2H), 2.50 (s, 3H), 3.04-3.32 (m, 2H), 5.31 (d, 1H, *J*= 7.9), 6.36 (d, 1H, *J*= 7.7), 6.48 (s, 1H), 8.58 (d, 1H, *J*= 7.7), 9.40 (s, 1H); (i3) IR (cm^{-1}) 2240, 1652, 1532, 1260; ^1H NMR

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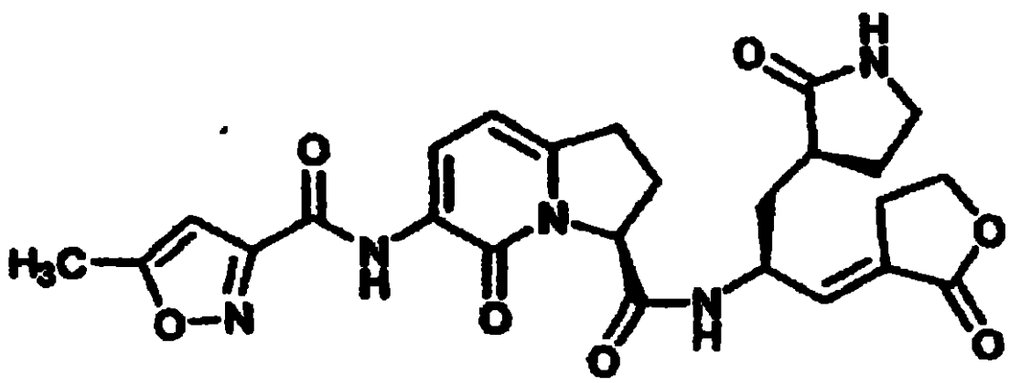
(DMSO-d_6) δ 1.53-1.63 (m, 2H), 3.11-3.20 (m, 2H), 5.14 (dd, 1H, *J* = 6.9, 2.7), 6.75 (s, 1H), 8.32 (s, 1H), 9.41 (s, br. 1H).

Preparación del Producto I1 (Compuesto 37)

El intermediario I2 fue transformado en compuesto 37 (vía acoplamiento con el intermediario Y2) por un proceso que fue análogo a aquel descrito en el Ejemplo 25 para la transformación de W3 a producto R3: IR (cm^{-1}) 3336, 1684, 1651, 1596, 1536; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 7.1), 1.63-1.89 (m, 2H), 2.04-2.15 (m, 1H), 2.38-2.64 (m, 3H), 2.50 (s, 3H), 2.98-3.06 (m, 1H), 3.26-3.42 (m, 4H), 4.19 (q, 2H, *J*= 7.1), 4.63-4.65 (m, 1H), 5.15 (dd, 1H, *J*= 8.3,2.7), 5.97-6.05 (m, 2H), 6.21 (d, 1H, *J*= 7.3), 6.48 (s, 1H), 6.89 (dd, 1H, J= 15.6, 5.5), 8.44-8.52 (m, 2H), 9.40 (s, 1H); Anal. $C_7H_{18}N_2O_4 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 38

Preparación del Compuesto 38: trans-(2''S,3S,3''''S)-6-[(5'-Metilisoxazol-3'-carbonil)amino]-5-oxo-1,2,3,5-tetrahidroindolizina-3-Ácido carboxílico [2''-(2'''-oxodihi drofurán-3'''-ilideno)-1''-(2''''-oxopirrolidin-3''''-ilmetil)etil]amida

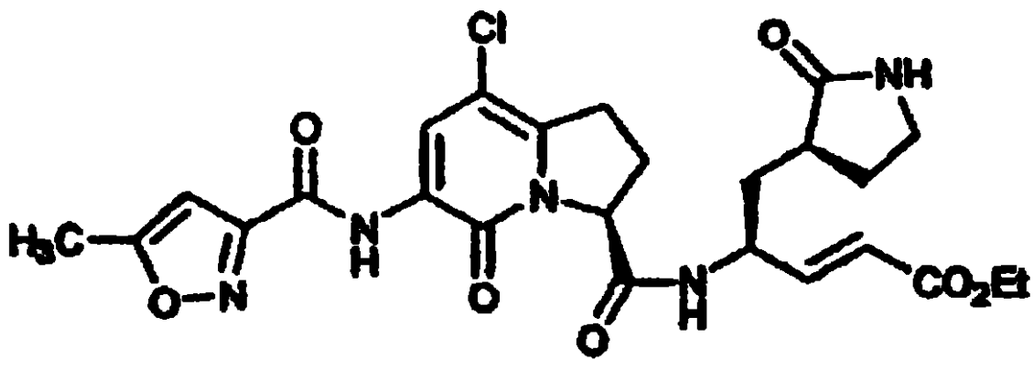


El compuesto del intermediario fue preparado del intermediario i2 (vía acoplamiento con intermediario Yl) por un proceso que fue análogo a aquel descrito en el Ejemplo 22 por la transformación de W1 a producto R2: IR (cm^{-1}) 3336, 1752, 1686, 1651, 1594, 1535; ^1H NMR ($CDCl_3$) δ 1.59-1.68 (m, 1H), 1.77-1.81 (m, 1H), 2.09-1.81 (m, 1H), 2.37-2.45 (m, 2H), 2.50 (s, 3H), 2.58-

2.66 (m, 1H), 2.91-3.05 (m, 2H), 3.23-3.44 (m, 4H), 4.39 (t, 2H, *J*= 7.2), 4.60-4.67 (m, 1H), 5.10-5.13 (m, 1H), 6.09 (s, 1H), 6.21 (d, 1H, *J*= 7.9), 6.41-6.48 (m, 2H), 8.45-8.50 (m, 2H), 8.77 (d, 1H, *J*= 6.2), 9.39 (s, 1H).

EJEMPLO 37

Preparación del Compuesto 39: trans-(3'S,3'''S,4S)-({8'-Cloro-6'-[(5''-metilisoxazol-3''-carbonil)amino]-5'-oxo-1',2',3',5,- tetrahidroindolizina-3'-carbonil}amino)-5-(2'''-oxopirrolidin-3'''-il)-pent-2-Ester de Etilo de Ácido enóico



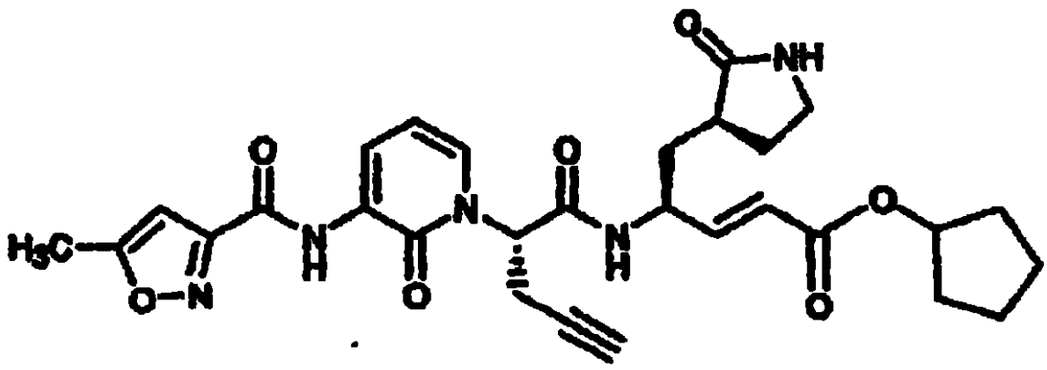
El compuesto del título fue preparado del intermediario I3 (vía acoplamiento con el intermediario Y2) por un proceso qu fue análogo a aquel descrito en el Ejemplo 25 para la transforamción de W3 a producto R3: IR (ccm^{-1}) 3334, 1683, 1532; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, *J*= 7.2), 1.66-1.89 (m, 4H), 233-2.50 (m, 1H), 2.53 (s, 3H), 2.67-2.72 (m, 1H), 3.04-3.20 (m, 2H), 3.27-3.48 (m, 2H), 4.21 (q, 2H, J= 7.2), 4.62-4.64 (m, 1H), 5.16-5.20 (m, 1H), 5.94 (s, br. 1H), 5.99 (dd, 1H,J= 15.6, 1.5), 6.51 (s, 1H), 6.89 (dd, 1H, *J*= 15.6, 5.7), 8.52 (s, 1H), 8.56 (s, br. 1H), 9.41 (s, br. 1H); Anal. $C_{25}H_{28}ClN_5O_7 \cdot 0.50H_2O$: C, H, N.

EJEMPLO 38

Compuesto 40: trans-(2'S,3''''S,4S)-4-[2'-(3''-{[1'''-(5''''-Metilisoxazol-3'''-il)metanoil]amino}-2'''-oxo-2'''H-piridin-1'''-il)pent-

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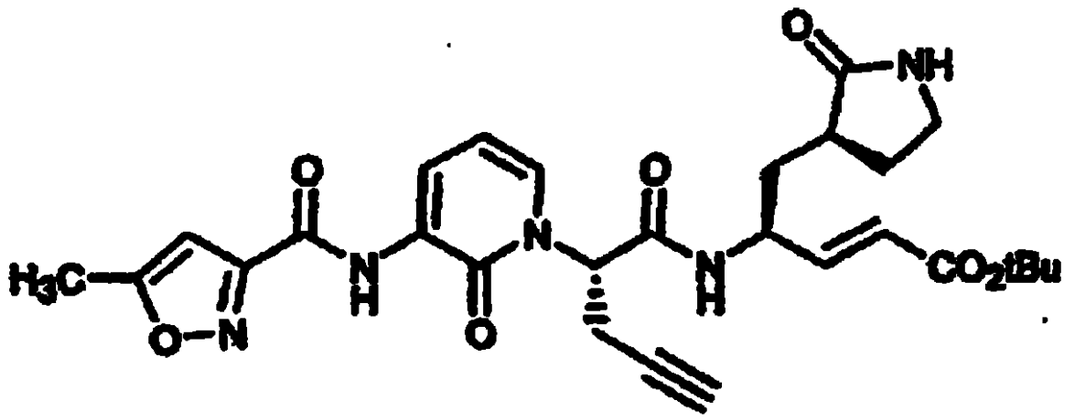
4''-inoilamino]-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de Ciclopentilo de Ácido enfoco



El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito en el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando intermediarios F2 y Y3 y una desprotección alternada del intermediario correspondiente a VI (LiI en piridina) donde fuere apropiado: IR (cm^{-1}) 3302, 1690, 1649, 1632; ^1H NMR ($CDCl_3$) δ 1.62-1.80 (m, 7H), 1.87-1.92 (m, 2H), 2.01-2.12 (m, 2H), 2.26-2.40 (m, 2H), 2.53 (s, 3H), 2.95-3.12 (m, 2H), 3.26-3.36 (m, 2H), 4.50-4.53 (m, 1H), 5.20-5.25 (m, 1H), 5.54-5.60 (m, 1H), 6.01 (dd, 1H, *J*= 15.6, 1.5), 6.31 (t, 2H, .7= 7.2), 6.40 (s, br, 1H), 6.49 (s, 1H), 6.83 (dd, 1H, *J*= 15.6, 5.4), 7.43 (dd, 1H, *J*= 6.9, 1.8) 8.44 (dd, 1H, *J*= 6.9, 1.5), 8.58 (d, 1H, *J*= 6.6), 9.56 (s, 1H); Anal. $C_{29}H_{33}N_5O_7 \cdot 0.75H_2O$: C, H, N.

EJEMPLO 39

Preparación del Compuesto 41: trans-(2'S,3''''S,4S)-4-[2'-(3''-{[1'''-(5''''-Metilisoxazol-3'''-il)metanoil]amino}-2'''-oxo-2'''H-piridin-1'''-il)pent-4''-inoilamino]-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de tert-Butilo de Ácido enóico

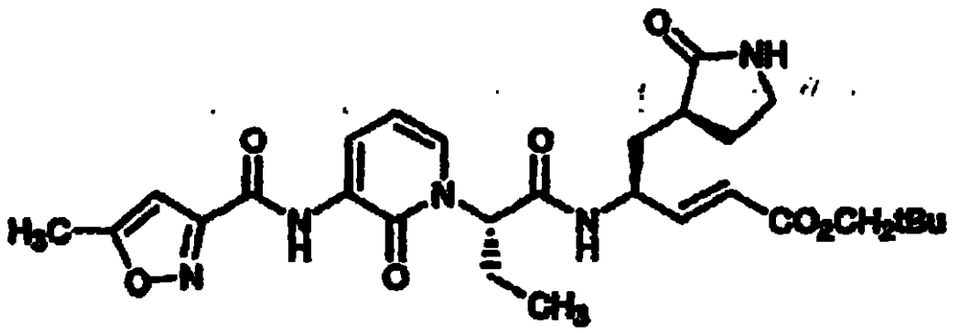


El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito en el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando intermediarios F2, K1, y (trifenil-λ^5-fosfanilideno)-ester de terf-butilo de ácido acético y una desprotección alternada del intermediario correspondiente a VI (LiI en piridina) donde fuere apropiado: mp = 195°C, dec.; IR (cm^{-1}) 3295, 1690, 1649; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.50-1.79 (m, 2H), 2.04 (t, 1H, *J*=2.6), 2.05-2.37 (m, 3H), 2.49 (s, 3H), 2.92 (ddd, 1H, *J*= 17.0, 8.6, 2.6), 3.02 (ddd, 1H, *J*= 17.0, 6.7, 2.6), 3.20-3.37 (m, 2H), 4.41-4.52 (m, 1H), 5.65-5.73 (m, 1H), 5.94 (dd, 1H, *J*= 15.6, 1.4), 6.33 (t, 1H, *J*= 7.3), 6.46 (s, 1H), 6.70 (s, 1H), 6.73 (dd, 1H, *J*=15.6, 5.3), 7.48 (dd, 1H, *J*= 7.3, 1.7), 8.41 (dd, 1H, *J*= 7.3, 1.7), 8.62 (d, 1H, *J*= 6.6), 9.53 (s, 1H); Anal. ($C_{28}H_{33}N_5O_7$) C, H, N.

EJEMPLO 40

Preparación del Compuesto 42: trans-(2'S,3''''S,4S)-4-[2'-(3''-{[1'''-(5''''-Metilisoxazol-3'''-il)metanoil]amino}-2'''-oxo-2'''H-piridin-1'''-il)butanoilamino]-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ester de 2,2-Dimetilpropil de Ácido enóico

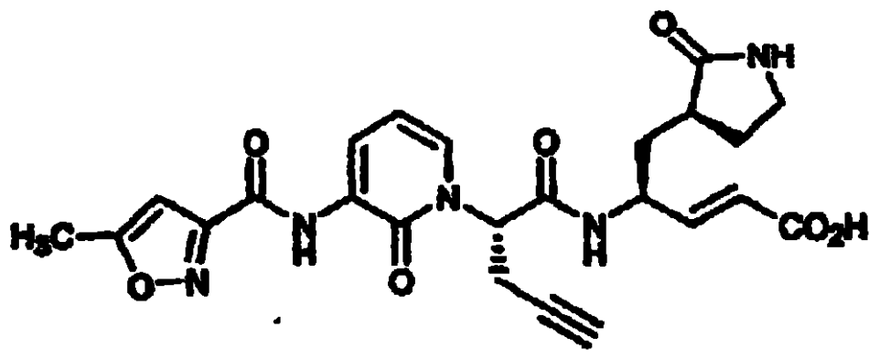
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El compuesto del título fue preparado por un método análogo a aquel descrito en el Ejemplo 25 para la preparación del intermediario específico R3 utilizando trans-(3'S,4S)4-terc-butoxycarbonilamino-5-(2'-oxopirrolidin-3'-il)pent-2-ácido enóico 2,2- éster dimetilpropil (preparado de K1 en una manera similar a aquella descrita para la prepración de X4 en el Ejemplo 27) donde fuere apropiado: IR (cm^{-1}) 3331, 3295, 1690, 1649; ^1H NMR ($CDCl_3$) δ 0.87-0.99 (m, 12H), 1.51-1.61 (m, 1H), 1.64-1.79 (m, 1H), 1.83-2.00 (m, 1H), 2.10-2.37 (m, 4H), 2.49 (s, 3H), 3.26-3.43 (m, 2H), 3.83 (s, 2H), 4.43-4.54 (m, 1H), 5.71 (dd, 1H, *J* = 8.7,6.9), 6.00 (dd, 1H, *J*= 15.7,1.3), 6.35 (t, 1H, *J* = 7.2), 6.46 (s, 1H), 6.86 (dd, 1H, *J* = 15.7,5.9), 7.39 (s, 1H), 7.58 (dd, 1H, J= 7.2,1.7), 8.42 (dd, 1H, *J* = 7.2,1.7), 8.53 (d, 1H, *J*= 7.0), 9.55 (s, 1H); Anal. ($C_{28}H_{33}N_5O_7 \cdot 0.5H_2O$) C, H. N.

EJEMPLO 41

Preparación del Compuesto 43: trans-(2'S,3''''S,4S)-4-[2'-(3''-{[1'''-(5''''-Metilisoxazol-3''''-il)metanoil]amino}-2'''-oxo-2'''H-piridin-1'''-il) pent-4''-inoilamino]-5-(2''''-oxopirrolidin-3''''-il)pent-2-Ácido enóico

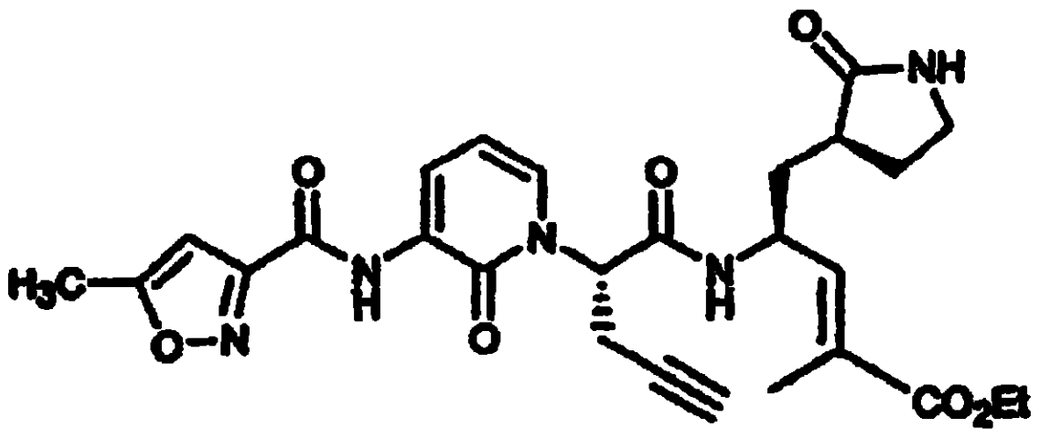


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El compuesto del título fue preparado del compuesto 41 por desprotección acídica de la mitad de éster de tert-butilo presente en aquel compuesto (procedimientos literarios normales siguientes): R*f* = 0.37 (10% CH_3OH en $CHCl_3$); IR (cm^{-1}) 3295, 2950 (br), 1696, 1649; ^1H NMR ($CDCl_3$) δ 1.62-1.85 (m, 2H), 2.05-2.16 (m, 2H), 2.24-2.36 (m, 1H), 2.43-2.56 (m, 1H), 2.52 (s, 3H), 2.92-3.11 (m, 2H), 3.30-3.42 (m, 2H), 4.60-4.71 (m, 1H), 5.65-5.73 (m, 1H), 6.03 (d, 1H, *J*= 15.6), 6.37 (t, 1H, *J*= 7.2), 6.50 (s, 1H), 6.94 (dd, 1H, *J* = 15.6, 6.0), 7.24 (s, 1H), 7.47 (dd, 1H, *J*= 7.2,1.3), 8.31 (d, 1H, *J*= 7.5), 8.45 (dd, 1H, *J* = 7.2, 1.3), 9.53 (s. 1H); Anal. ($C_{24}H_{25}N_5O_7 \cdot 0.5H_2O$) C, H. N.

EJEMPLO 42

Compuesto 44: trans-(2'S,3''''S,4S)-2-metilo-4-[2'-(3''-{[1'''-(5''''-Metilisoxazol-3''''-il)metanoil]amino}-2'''-oxo-2'''H-piridin-1'''-il) pent-4''-inoilamino]-5-(2''''-oxopirrolidin-3''''-il)pent-2-Éster de Etilo de Ácido enóico



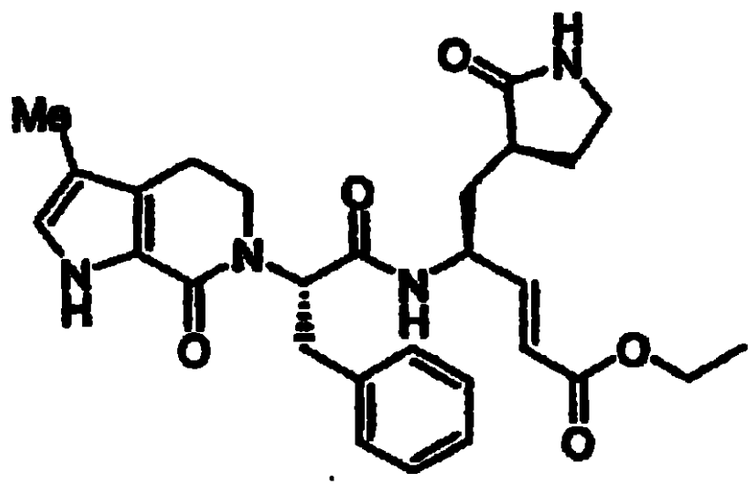
El compuesto del título fue preparado de D-propargilalanina por un proceso análogo a aquel descrito en el Ejemplo 22 para la conversión de D-(4-fluorofenilalanina) a producto R2 utilizando intermediarios F y trans-(3'S,4S)-4-tert-butiloxicarbonilamino-2-metil-5-(2'-oxopirrolidin-3'-il)pent-2-éster de etilo de ácido enóico (preparado de K1 en una manera similar a aquella descrita para la preparación X4 en el Ejemplo 27) y una desprotección alternada del intermediario correspondiente a V1 (LiI en piridina) donde fuere

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apropiado: IR (cm^{-1}) 3307, 1690, 1649; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, *J*= 7.1), 1.36-1.47 (m. 1H), 1.65-1.80 (m, 1H), 1.95-2.00 (m, 4H), 2.14-2.40 (m, 3H), 2.50 (s, 3H), 2.87-3.03 (m, 2H), 3.23-3.38 (m, 2H), 4.18 (q, 2H, *J*= 7.1), 4.56-4.68 (m, 1H), 5.63-5.72 (m, 1H), 6.34 (t, 1H, *J*= 7.3), 6.47 (s, 1H), 6.52-6.58 (m, 1H), 6.81 (s, 1H), 7.46 (dd, 1H, *J*= 7.3,1.6), 8.42 (dd, 1H, J= 7.3,1.6), 8.65 (d, 1H, *J*= 6.4), 9.54 (s, 1H).

EJEMPLO 43

Preparación del Compuesto 46:4S-[2S-(3-Metil-7-oxo-1,4,5,7-tetrahidropyrrolo[2,3-c]piridin-6-il)3-fenil-propioniIamino]-5-(2-oxo-pirrolidin-3-il)pent-2(trans)-éster de etilo de ácido enóico



3-(2-Hidroxi-etil)-5-iodo-4-metil-1H-pirrol-2-éster de tert-butilo de ácido carboxílico (0.34 mmol, 114 mg) en DMSO (2 mL) fue tratado con o-ácido iodoxibenzoico (IBX, 0.51 mmol, 148 mg), entonces mantenida a temperatura ambeinte durante 3h. La mezcla fue diluida con acetato de etilo (50 mL), lavada con salmuera (10 mL), entonces concentrada bajo presión reducida para proporcionar 84 mg (75%) de 5-iodo-4-metil-3-(2-oxo-etil)-1H-pirrol-2-éster de tert-butilo de ácido carboxílico. ^1H NMR ($CDCl_3$) d 9.63 (1H, s), 8.91 (1H, br s), 4.09 (2H, s), 2.62 (3H, s), 1.52 (9H, s).

5-Iodo-4-metil-3-(2-oxo-etil)-1H-pirrol-2- éster de tert-butilo de ácido carboxílico (0.25 mmol, 84 mg) en MeOH (2 mL) fue tratado con éster de metilo de fenilalanina (0.25 mmol, 45 mg), entonces

tratado con cianoborohidruro de sodio (0.25 mmol, 16 mg). La mezcla fue mantenida a temperatura ambiente durante 3h, entonces concentrada bajo presión reducida. Purificación del residuo por cromatografía de gel de sílica da 80 mg (46%) de 5-iodo-3-[2S-(1-metoxicarbonil-2-fenil-etilamino)-etil]-4-metil-1H-pirrol-2-éster de terf-butilo de ácido carboxílico. ^{1}H NMR ($CDCl_3$) d 8.81 (1H. br s), 7.30-7.13 (5H, m), 3.61 (3H, s), 3.55 (1H, t, *J* = 6.8), 2.94 (2H, d, *J*= 6.3), 2.90-2.78 (2H, m), 2.76-2.70 (1H, m), 2.62-2.56 (1H, m), 1.94 (3H, s), 1.51 (9H, s).

5-Iodo-3-[2S-(1-metoxicarbonil-2-fenil-etilamino)-etil]-4-metil-1H-pirrol-2-éster de terf-butilo de ácido carboxílico (0.37 mmol, 0.18 g) en dioxano (2 mL) at 0 °C fue tratada con HCl (0.37 mmol, 1 mL de 4M en dioxano). La mezcla fue mantenida a 0 °C durante 15 minutos, entonces concentrada bajo presión reducida. El residuo fue diluido con DMF (3 mL), entonces tratado con HOBT (0.37 mmol, 50 mg), DCC (0.37 mmol, 77.0 mg), and K_2CO_3 (0.74 mmol, 0.10 g). La mezcla fue agitada a temperatura ambiente durante 30 minutos, entonces diluida con acetato de etilo (50 mL), lavada con salmuera (10 mL), entonces concentrada bajo presión reducida. El residuo fue purificado por cromatografía de gel de sílica para proporcionar 21 mg (13%) de 2S-(3-metil-7-oxo-1,4,6,7-tetrahidro-pirrolo[2,3-c]piridin-6-il)-3-éster de metilo de ácido fenilpropiónico. Fue notificado que este material tuvo de-iodinatado inadvertidamente. ^{1}H NMR ($CDCl_3$) d 9.28 (1H, br s), 7.31-7.18 (5H, m), 6.64 (1H, s), 5.33 (1H, dd, J = 10.4,5.6), 3.79-3.74 (1H, m), 3.75 (3H, s), 3.57-3.42 (4H, m), 3.14 (1H, dd, J = 14.5,10.4), 2.59-2.49 (2H, m), 2.00 (3H, s). MS (FAB) 311 (MH^+).

2S-(3-metil-7-oxo-1,4,6,7-tetrahidro-pirrolo[2,3-c]piridin-6-il)-3-fenil éster de metilo de ácido propiónico (0.07 mmol, 21 mg) en 1:1 dioxano-agua (3 mL) fue tratado con hidróxido de litio (0.2 mmol, 5 mg), entonces calentado a reflujo durante 30 minutos. La solución fue acidificada con ácido cítrico acuoso saturado (3 mL), entonces extractado con acetato de etilo (15 mL), lavada con

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salmuera (5 mL), y concentrada bajo presión reducida para proporcionar 15 mg (75%) de 2S-(3-metil-7-oxo-1,4,5,7-tetrahidro-pirrolo[2,3-c]piridin-6-il)-3-fenil de ácido propiónico. Este material (15 mg, 0.05 mmol) fue unido a 4S-amino-5-(2-oxo-pirrolidin-3S-il)-pent-2(trans)-éster de etilo de ácido enóico (11 mg, 0.05 mmol) en DMF (1 mL) por tratamiento con amina de diisopropiletilo (0.02 mL, 0.01 mmol) y HATU (19 mg, 0.05 mmol) a temperatura ambiente durante 2 h. La solución resultante fue lavada con salmuera (10 mL), y extractada con EtOAc (30 mL). Los orgánicos fueron concentrados bajo presión reducida y el residuo purificado por cromatografía de fase preparativa reversible (CH_3CN-H_2O) para proporcionar 10-mg (40 %) de 4S-[2S-(3-metil-7-oxo-1,4,5,7-tetrahidro-pirrolo[2,3-c]piridin-6-il)-3-fenil-propioniiamino]-5-(2-oxo-pirrolidin-3-il)pent-2(trans)-éster de etilo de ácido enoico. ^{1}H NMR ($CDCl_3$) d 10.21 (1H, br s), 7.54 (1H, d, *J* = 7.7), 7.26-7.11 (4H, m), 6.80 (1H, d, *J* = 15.6), 6.62 (1H, br s), 6.23 (1H, br s), 5.82 (1H, dd, *J* = 15.5,5.4), 5.28 (1H, t, *J* = 8.0), 4.68-4.50 (1H, m), 4.19 (2H, q, *J*= 7.1), 3.67-2.96 (6H, m), 2.56-2.51 (3H, m), 2.21-2.09 (2H, m), 1.96 (3H, s), 1.75-1.64 (1H, m), 1.53-1.43 (3H, m), 1.29 (3H. t, *J* = 7.1). HRMS (FAB) 639.1577 (MCs^+, calcd. 639.1584).

Los resultados de las pruebas dirigidas usando ejemplarmente compuestos de la invención están descritos abajo.

EVALUACIÓN BIOLOGICA Y BIOQUIMICA

Inhibición de proteasa de Rinovirus 3C:

Las soluciones depositadas (50 mM, en DMSO) de varios compuestos fueron preparadas; las diluciones fueron en el mismo solvente. Las proteasas de rinovirus recombinantes de 3C proteases (ver Birch y otros, "Purificación de rinovirus humano recombinante de proteasas 14 3C expresada en Esquerichia coli," *Protein Expr. Pur.* (1995), vol. 6(5), 609-618) de serotipos 14,16, y 2 fueron preparadas por los procedimientos cromatográficos normales siguientes: (1) intercambio de lón usando flujo rápido de sefarosa Q de farmacia; (2) usando cromatografía de afinidad Affi-

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Gel Blue de Biorad.; y (3) calibrando el uso de Sefadex G-100 de farmacia. Cada muestra de ensayo contenía 2% DMSO, 50 mM de tris pH 7,6, 1 mM EDTA, un compuesto de prueba en la concentración indicada, aproximadamente 1 μM de sustrato, y 50-100 nM de proteasa. Los valores k_{obs}/I fueron obtenidos de reacciones iniciadas por adición de enzima distinta de sustrato. La actividad RVP fue medida en el ensayo de transferencia de energía de resonancia fluorecencia. El sustrato fue (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Fe-Gln-Gly-Pro-Val-Gly)-EDANS. En el peptida sin partir, la fluoerencia EDANS fue extinguida por la mitad próxima DABCYL. Cuando el peptida fue partido, la extinción fue revelada, y la actividad fue medida en un incremento en la señal fluorecencia. Los datos fueron analizados usando programas de ajuste no lineal normales (Enzfit), y están mostrados en la tabla de abajo. Los datos tabulados en la columna designada $k_{obs}/[I]$ fueron medidos de curvas de progreso en experimentos de inicio de enzima.

Ensayo de Célula Antirinoviral H1-HeLa

En este ensayo de protección de célula, la habilidad de los compuesto para la proteger de células con infección HRV fue media por el método de reducción de tinte XTT, el cual está descrito en Weislow y otros, J. Natl. Cancer Ints. (1989), vol. 81, 577-586. Las células H1-HeLa fueron infectadas con HRV-14 a una multiplicidad de infección (m.o.i.) de 0.13 (partículas de virus/células) o copia infectada con el medio solamente. Las células infectadas o copias infectadas fueron resuspendidas en células 8 x 10^5 por mL, e incubadas con concentraciones apropiadas de los compuestos a ser probados. Dos días más tarde, XTT/PMS fueron agregados a las placas de prueba y la cantidad de formazan producido fue cuantificada espectrofotométricamente a 450/650 nm. El valor EC_{50} fue calculado como la concentración de compuesto que incrementó el porcentaje de la producción formazan en compuesto tratado, células de virus infectadas a 50% de aquel producido por compuesto libre, células de copia infectadas. El 50% de dosis citotócica (CC_{50}) fue calculado como la concentración de

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compuesto que decreció el porcentaje de formazan producido en el compuesto tratado, células de copias infectadas a 50% de aquel producido por el compuesto libre, de células de copia infectada. El índice terapéutico (TI) fue calculado dividiendo el valor CC_{50} por el valor EC_{50}.

Todo lo referente a rinovirus humano (HRV) para uso en este ensayo fueron comprados de American Type Culture Collection (ATCC), excepto para serotipo-14 HRV (producido de la infección de clon cDNA construida por el Dr. Robert Rueckert, Instituto para Virología Molecular, Universidad de Wisconsin, Madison, Wisconsin). Los depósitos de HRV fueron propagados y ensayos virales fueron llevados a cabo en células H1-HeLa (ATCC). Las células crecieron en medio esencial mínimo con 10% de suero bobino fetal, disponibles de Life Technologies (Gaithersburg, MD). Los resultados de prueba para el ensayo HRV están mostrados en la tabla abajo.

Ensayo de Cultivo de Célula Anticoxsackieviral

Los tipos coxsackievirus A-21 (CAV-21) y B3 (CVB3) fueron comprados American Type Culture Collection (ATCC, Rockville, MD). Los depósitos de virus fueron propagados y ensayos antivirales fueron llevados a cabo en células H1-HeLa (ATCC). Las células crecieron en medio mínimo esencial con 10% de suero bobino fetal (Life Technologies, Gaithersburg, MD). La habilidad de los compuestos de esta invención para proteger células contra ya sea infección de CAV-21 o CVB3 fue medida por el método de reducción de tinte XTT. Este método está descrito en Weislow y otros, J. Natl. Cancer Ints. (1989), vol. 81, 577-586. Las células H1-HeLa fueron infectadas con CAV-21 o CVB3 en una multiplicidad de infección (m.o.i.) de 0.025 o 0.075, respectivamente, o copia infectada con el medio solamente. Las células H1-HeLa fueron plateadas a 4×10^4 células por fuente en una placa de 96-fuente e incubadas con concentraciones apropiadas del compuesto de

prueba. Un día (CVB3) o dos días (CAV-21) más tarde, XTT/PMS fueron agregados a las placas de prueba y la cantidad de formazan producido fue cuantificada espectrofotométricamente a 450/650 nm. El EC_{50} fue calculado como la concentración de compuesto que incrementó la producción formazan en compuesto tratado, células de virus infectadas a 50% de aquella producido por el compuesto libre, células no infectadas. El 50% de dosis citotóxica (CC_{50}) fue calculado como la concentración de compuesto que decreció la producción de formazan en el compuesto tratado, las células no infectadas a 50% de aquella producida en el compuesto libre, células no infectada. El índice terapéutico (TI) fue calculado dividiendo el CC_{50} por el EC_{50}.

Ensayos de Cultivo de Célula Anti-Enteroviral y Anti-Ecoviral

El tipo Ecovirus 11 (ECHO 11) fue comprado de ATCC (Rockville, MD). Los depósitos de virus fueron propagados y ensayos antivirales fueron llevados a cabo en células MRC-5 (ATCC). Las células crecieron en medio mínimo esencial con 10% de suero bobino fetal (Life Technologies, Gaithersburg, MD). La habilidad de los compuestos de esta invención para proteger células contra infección ECHO 11 fue medida por el método de reducción de tinte XTT (Weislow y otros, J. Natl. Cancer Ints. (1989), vol. 81, 577-586). Las células MRC-5 fueron infectadas con ECHO 11 en un m.o.i. de 0.003 o 0.004, respectivamente, o copia infectada con medio solamente. Las células o no infectadas fueron agregadas a 1×10^4 células por fuente e incubadas con concentraciones apropiadas del compuesto. Cuatro días más tarde, XTT/PMS fueron agregados a las placas de prueba, y la cantidad de formazan producido fue cuantificado espectrofotométricamente a 450/650 nm. El EC_{50} fue calculado como la concentración de compuesto que incrementó la producción de formazan en compuesto tratado, células de virus infectadas a 50% de aquella producida por el compuesto libre, células no infectadas. El 50% de dosis citotóxica (CC_{50}) fue calculado como la concentración de compuesto

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que decreció la producción de formazan en el compuesto tratado, las células no infectadas a 50% de aquella producida en el compuesto libre, células no infectada. El índice terapéutico (TI) fue calculado dividiendo el CC_{50} por el EC_{50}. La actividad de los compuestos contra el tipo enterovirus 70 (EV70) puede ser medida por el mismo ensayo tal como se describió arriba en esta sección. El tipo de enterovirus 70 (EV70) puede ser obtenido de American Type Culture Collection ATCC (Rockville, MD).

Los resultados obtenidos para los compuestos de la invención pueden ser comparados con los resultados obtenidos de la misma manera para los compuestos de control WIN 51711, WIN 52084, y WIN 54954 (obtenidos de Sterling-Winthrop Pharmaceuticals), Pirodavir (obtenida de Janssen Pharmaceuticals), y Pleconaril (preparado de acuerdo al método descrito en Diana y otros, J. Med. Chem. (1995), vol. 38, 1355). Los datos antivirales obtenidos para los compuestos de prueba están mostrados en la tabla abajo. La designación "ND" indica que el valor no fue determinado para el compuesto, y la designación "NA" no es medio aplicable.

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TABLA

Compu.#	Estereotipo de Virus	$K_{obs}/[I]$ ($M^{-1}s^{-1}$)	EC_{50}(μM)	CC_{50} (μM)	II
1+2 (1:1)	HRV-14[a]	36,900	0.179	50.1	280
	HRV-1A	ND	0.825	74.1	90
	HRV-10	ND	0.145	60.3	416
1	HRV-14	114,000	0.033	50.1	1518
	CAV-21[c]	ND	1.48	>10	>7
	ECHO-11[d]	ND	0.16	>10	>63
	CVB3[e]	ND	0.539	>10	>19
	ENT-70[f]	ND	0.012	>10	>833
3	HRV-14	2,900	1.27	>10	>8
4	HRV-14	574	ND	ND	ND
5	HRV-14	329,000	0.016	>10	>625
	CAV-21	ND	1.39	>10	>7
	ECHO-11	ND	0.054	>10	>185
	CVB3	ND	0.577	>10	>17
	ENT-70	ND	0.018	>10	>556
6	HRV-14	37,400	0.034	>10	>294
	CAV-21	ND	4.68	>10	>2
	ECHO-11	ND	0.346	>10	>29
	CVB3	ND	2.50	>10	>4
	ENT-70	ND	0.061	>10	>164
7	HRV-14	81,000	0.014	>10	>714
8	HRV-14	7,660	0.888	>10	>11
9	HRV-14	5,040	0.518	>10	>19
10	HRV-14	113,600	0.104	>10	>96
	HRV-1A	ND	1.182	>10	>9
	HRV-10	ND	1.406	>10	>7
11	HRV-14	193,000	<0.0032	>10	>3125
12	HRV-14	25,800	0.075	>10	>133
13+14 (1:1)	HRV-14	31,000	ND	ND	ND
15	HRV-14	6,500	0.178	>10	>56
16	HRV-14	74,000	0.325	>10	>31
17	HRV-14	348	>10	>10	ND
18	HRV-14	116,000	0.125	>10	>80
19	HRV-14	380,000	0.003	>1	>333
20	HRV-14	600,000	0.015	>10	>667
21	HRV-14	6,340	0.469	>10	>21
22	HRV-14	18,500	1.0	>10	>10
23	HRV-14	385,000	0.064	>10	>156

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24	HRV-14	8,800	ND	ND	ND
25	HRV-14	1,250,000	0.002	>10	>5000
	HRV-1A	ND	0.015	>10	>667
	HRV-10	ND	0.004	>10	>2500
	HRV-2	ND	0.004	>10	>2500
	HRV-16	ND	0.005	>10	>2000
	HRV-3	ND	0.004	>10	>2500
	HRV-25	ND	0.022	>10	>454
	HRV-9	ND	0.01	>10	>1000
	HRV-39	ND	0.009	>10	>1111
	HRV-87	ND	0.008	>10	>1250
26	HRV-14	170,000	0.055	>10	>182
	HRV-1A	ND	0.014	>10	>714
	HRV-10	ND	0.027	>10	>370
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.050	>10	>200
	HRV-3	ND	0.029	>10	>344
	HRV-25	ND	0.102	>10	>98
	HRV-9	ND	0.045	>10	>222
	HRV-39	ND	0.047	>10	>212
	HRV-87	ND	0.021	>10	>476
	CAV-21	ND	0.121	>10	>82
	ECHO-11	ND	0.036	>10	>277
	CVB3	ND	0.016	>10	>625
	CVB2[e]	ND	0.055	>10	>182
	CVB5[d]	ND	0.018	>10	>556
	ECHO-6[f]	ND	0.017	>10	>588
	ECHO-9[f]	ND	0.015	>10	>666
27+28 (1:1)	HRV-14	3,750	1.78	>10	>7
29	HRV-14	148,000	0.079	>10	>126
	HRV-1A	ND	0.046	>10	>217
	HRV-10	ND	0.046	>10	>217
30	HRV-14	133,500	0.024	>10	>416
31	HRV-14	223,400	0.022	>10	>454
	HRV-1A	ND	0.036	>10	>277
	HRV-10	ND	0.048	>10	>208
	HRV-2	ND	0.013	>10	>769

	HRV-16	ND	0.038	>10	>263
	HRV-3	ND	0.021	>10	>476
	HRV-25	ND	0.087	>10	>114
	HRV-9	ND	0.044	>10	>227
	HRV-39	ND	0.043	>10	>232
	HRV-87	ND	0.021	>10	>476
	CAV-21	ND	0.161	>10	>62
	ECHO-11	ND	0.013	>10	>769
	CVB3	ND	0.024	>10	>416
	CVB2	ND	0.057	>10	>175
	CVB5	ND	0.047	>10	>212
	ECHO-6	ND	0.021	>10	>476
	ECHO-9	ND	0.012	>10	>833
32	HRV-14	127,500	0.126	>10	>79
	HRV-1A	ND	0.179	>10	>55
	HRV-10	ND	0.156	>10	>64
	HRV-2	ND	0.105	>10	>95
	HRV-16	ND	0.184	>10	>54
	HRV-3	ND	0.059	>10	>169
	HRV-25	ND	0.547	>10	>18
	HRV-9	ND	0.500	>10	>20
	HRV-39	ND	0.410	>10	>24
	HRV-87	ND	0.033	>10	>303
33	HRV-14	1,800,000	0.001	>10	>10000
	HRV-2	ND	0.003	>10	>3333
	HRV-16	ND	0.006	>10	>1666
	HRV-3	ND	0.003	>10	>3333
	HRV-25	ND	0.028	>10	>357
	HRV-9	ND	0.015	>10	>666
	HRV-39	ND	0.004	>10	>2500
	HRV-87	ND	0.005	>10	>2000
	CAV-21	ND	0.004	>10	>2500
	ECHO-11	ND	0.016	>10	>625
	CVB3	ND	0.003	>10	>3333
	CVB2	ND	0.015	>10	>666
	CVB5	ND	0.025	>10	>400
	ECHO-6	ND	0.015	>10	>666
	ECHO-9	ND	0.003	>10	>3333
34	HRV-14	45,100	0.122	>10	>81
	HRV-2	ND	0.154	>10	>64
	HRV-16	ND	0.543	>10	>18
	HRV-3	ND	0.061	>10	>163
	HRV-25	ND	0.923	>10	>10
	HRV-9	ND	0.593	>10	>16
	HRV-39	ND	0.441	>10	>22
	HRV-87	ND	0.033	>10	>303
35	HRV-14	220	>10	>10	NA
36	HRV-14	4,540	9.0	>100	>11

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37	HRV-14	177,000	0.162	>10	>62
	HRV-1A	ND	0.108	>10	>93
	HRV-10	ND	0.041	>10	>244
	HRV-2	ND	0.037	>10	>270
	HRV-16	ND	0.072	>10	>138
	HRV-3	ND	0.043	>10	>232
	HRV-25	ND	0.162	>10	>61
	HRV-9	ND	0.121	>10	>82
	HRV-39	ND	0.016	>10	>625
	HRV-87	ND	0.058	>10	>172
38	HRV-14	0.08[1]	16.8	>100	>6
39	HRV-14	200,000	0.040	>10	>250
	HRV-1A	ND	0.042	>10	>238
	HRV-10	ND	0.088	>10	>113
	HRV-2	ND	0.016	>10	>625
	HRV-16	ND	0.057	>10	>175
	HRV-3	ND	0.039	>10	>256
	HRV-25	ND	0.107	>10	>93
	HRV-9	ND	0.048	>10	>208
	HRV-39	ND	0.048	>10	>208
	HRV-87	ND	0.017	>10	>588
40	HRV-14	186,000	0.027	>10	>370
	HRV-2	ND	0.052	>10	>192
	HRV-16	ND	0.177	>10	>56
	HRV-3	ND	0.056	>10	>178
	HRV-25	ND	0.490	>10	>20
	HRV-9	ND	0.219	>10	>46
	HRV-39	ND	0.163	>10	>61
	HRV-87	ND	0.083	>10	>120
41	HRV-14	60,500	0.062	>10	>161
	HRV-2	ND	0.155	>10	>64
	HRV-16	ND	0.416	>10	>24
	HRV-3	ND	0.054	>10	>185
	HRV-25	ND	0.829	>10	>12
	HRV-9	ND	0.562	>10	>17
	HRV-39	ND	0.445	>10	>22
	HRV-87	ND	0.060	>10	>166
	CAV-21	ND	0.593	>10	>17
	ECHO-11	ND	0.186	>10	>54
	CVB3	ND	0.117	>10	>85
	CVB2	ND	0.213	>10	>47
	CVB5	ND	0.199	>10	>50
	ECHO-6	ND	0.147	>10	>68
	ECHO-9	ND	0.106	>10	>94
42	HRV-1A	38,200	0.168	>10	>59
	HRV-2	ND	0.161	>10	>62
	HRV-16	ND	0.402	>10	>24
	HRV-3	ND	0.152	>10	>65

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	HRV-25	ND	0.611	>10	>16
	HRV-9	ND	0.521	>10	>19
	HRV-39	ND	0.158	>10	>63
	HRV-87	ND	ND	>10	ND
43	HRV-14	382	>10	>10	NA
44	HRV-14	12,500	ND	ND	ND
45	HRV-14	673	ND	ND	ND
WIN 51711	HRV-14	ND	0.78	>60	>77
WIN 52084	HRV-14	ND	0.07	>10	>143
WIN 54954	HRV-14	ND	2.13	>63	>30
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
Pirodavir	HRV-14	ND	0.03	>10	>300
	CAV-21	ND	>100	>100	NA
	CVB3	ND	>100	>100	NA
	EV-11	ND	3.7	>10	>3
	ENT-70	ND	0.06	>10	>167
Pleconaril	HRV-14	ND	0.01	>10	>1000
	CAV-21	ND	0.09	>10	>107
	CVB3	ND	>10	>10	NA
	ECHO-11	ND	0.16	>10	>62

[a]HRV = rinovirus humano o serotipo designado.

[b]3C actividad de inhibición de proteasa.

[c]CAV-21 = coxsackievirus A21.

[d]ECHO-11 = ecovirus 11.

[e]CVB3 = coxsackievirus B3.

[f]ENT-70 = enterovirus 70.

[g]CVB2 = coxsackievirus B2

[h]CVB5 = coxsackievirus B5

[i]ECHO-6 = echovirus 6

[j]ECHO-6 = echovirus 9

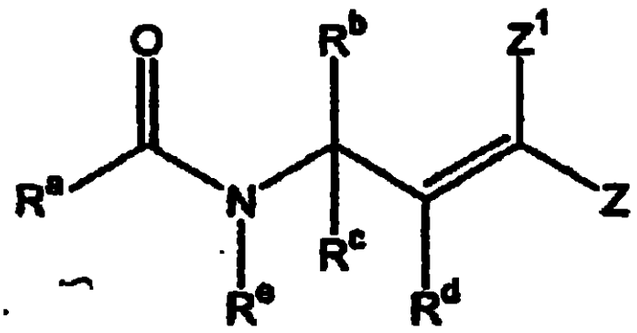
Valor [g]K_i, μM.

Aunque la invención ha sido descrita en términos de modalidades preferidas y ejemplos específicos, aquellos versados en el arte reconocerán que varios cambios y modificaciones pueden ser hechos sin apartarse del espíritu y alcance de la invención. Además, la invención debería entenderse como estando limitada por la descripción detallada anterior, pero como estando definida por las reivindicaciones adjuntas y sus equivalentes.

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REIVINDICAMOS:

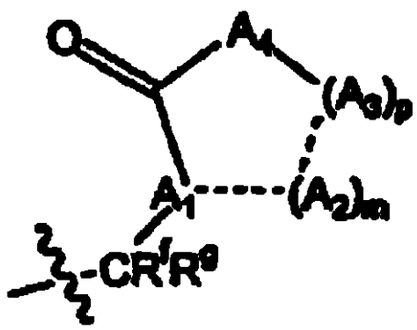
1. Un compuesto que tiene la fórmula:



en la cual:

R^a es heterocicloalquilalquilo o heterocicloalquilo sustituido o no sustituido;

R^b es un sustituyente que tiene la fórmula



en la cual:

R^f y R^g son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^h)(R^i)$, $N(R^j)$, S, S(O), $S(O)_2$, o O; donde cada R^h, R^i y R^j es independientemente H o alquilo inferior;

cada A_3 presente esta independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^k)$, $C(R^h)(R^i)$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^k)(R^l)$,

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$C(R^h)(R^i)(R^j)$, y $O(R^i)$, donde cada R^h, R^i y R^j es independientemente H o alquilo inferior, cada R^k es H, alquilo, arilo, o acilo, y cada R^l es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada línea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2está ausente (es decir, m=0); y

R^c es H, halógeno o un grupo de alquilo inferior sustituido o no sustituido;

R^d es H, halógeno, hidróxilo, un alquilo sustituido o no sustituido, grupo alcoxi o alquiltio;

R^e es H o un grupo alquilo sustituido o no sustituido; y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^n$, $-CO_2R^n$, -CN, $-C(O)NR^nR^o$, $-C(ONR^nOR^o$, $-C(S)R^n$, $-C(S)NR^nR^o$, $-NO_2$, $-SOR^o$, $-SO_2R^n$, $-SO_2NR^nR^o$, $-SO_2(NR^n)(OR^o)$, $-SONR^n$, $-SO_3R^n$, $-PO(OR^n)_2$, $-PO(OR^n)(OR^o)$, $-PO(NR^nR^o)(OR^p)$, $-PO(NR^nR^o)(NR^pR^q)$, $-C(O)NR^nNR^oR^p$, $-C(S)NR^nNR^oR^p$, en el cual R^n, R^o, R^p y R^q son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^n, R^o, R^p y R^q, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

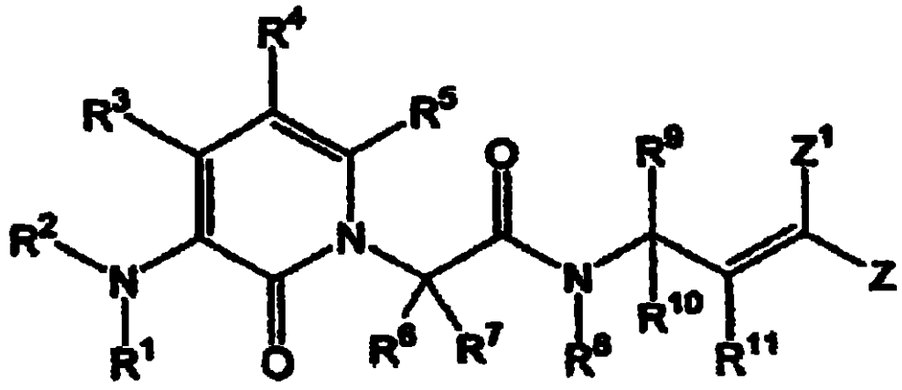
o Z y Z^l, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^l están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo.

o una prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvente farmacéuticamente aceptable de estos.

2. El compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvente farmacéuticamente aceptable de acuero con la reivindicación 1, en la cual R^8 es heterocicloalquilalquilo sustituido o no sustituido.

3. El compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvente farmacéuticamente aceptable de acuero con la reivindicación 1, en la cual la mitad de alquilo del grupo heterocicloalquilalquilo sustituido o no sustituido es una mitad de alquilo saturado sustituido o no sustituido.

4. Un compuesto que tiene la fórmula:



(I)

en la cual:

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuado;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, o un grupo alcoxicarbonilo, en los cuales cada una de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo en los grupos de arriba puede ser

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sustituida o no sustituida, o un grupo adecuado de protección de nitrógeno;

R^3 es H o un sustituyente adecuable; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o grupo heteroarilo, el cual puede ser opcionalmente sustituido;

R^4 es H o un sustituyente adecuable;

la línea punteada representa una unión opcional

R^5 es H o un sustituyente adecuable;

R^6 es H o un grupo alquilo sustituido o no sustituido; o

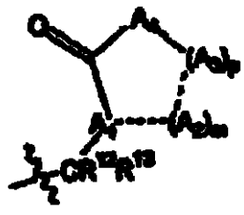
R^5 junto con R^6 forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido;

R^7 y R^{10} son independientemente H, halógeno o un grupo de alquilo más bajo sustituido o no sustituido;

R^8 es H o un grupo alquilo inferior sustituido o no sustituido;

R^{11} es H, halógeno, hidróxilo, un grupo alquiltio o alcox, de alquilo sustituido o no sustituido;

R^9 es un sustituyente que tiene la fórmula:



En la cual,

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cada A_3 presente este independientemente $C(R^{14})(R^{15})$, $N(R^{15})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, y $O(R^{18})$, donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, cada R^{17} es H, alquilo, arilo, o acilo, y cada R^{18} es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$, $(A_3)_p$, A_4, y C=O, donde cada linea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2está ausente (es decir, m=0); y

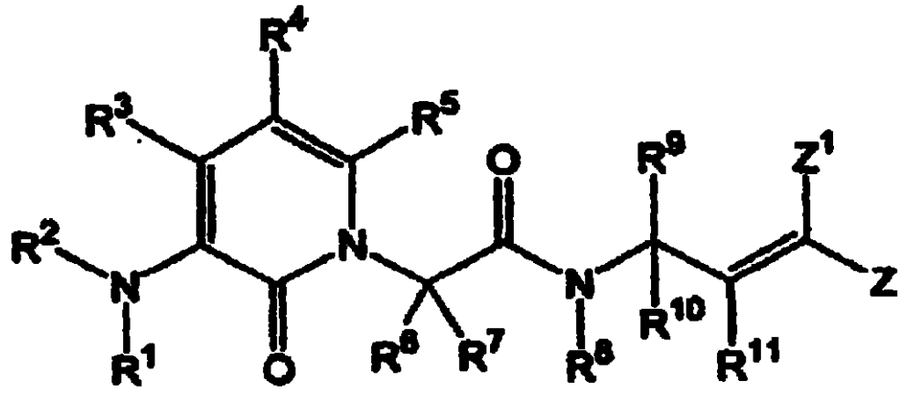
Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

o Z y Z^1, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^1 están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo,

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o una prodroga, sal farmacéuticamente aceptable metabolito farmacéuticamente activo o soluble farmacéuticamente aceptable de ésta.

5. Un compuesto que tiene la fórmula:



(I)

en la cual:

R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuado;

R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, o un grupo alcoxicarbonilo, en los cuales cada una de las mitades de alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo en los grupos de arriba puede ser sustituida o no sustituida, o un grupo adecuado de protección de nitrógeno;

R^3 es H o un sustituyente adecuable; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable; o

R^2 junto con R^3 forman un grupo heterocicloalquilo o grupo heteroarilo, el cual puede ser opcionalmente sustituido;

R^4 es H o un sustituyente adecuable;

la línea punteada representa una unión opcional

R^5 es H o un sustituyente adecuable;

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R^6 es H o un grupo alquilo sustituido o no sustituido; o

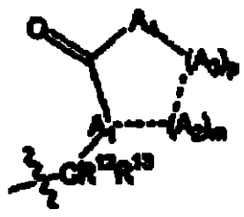
R^5 junto con R^6 forman un grupo heterocicloalquilo, el cual puede ser opcionalmente sustituido;

R^7 y R^{10} son independientemente H, halógeno o un grupo de alquilo más bajo sustituido o no sustituido;

R^8 es H o un grupo alquilo inferior sustituido o no sustituido;

R^{11} es H, halógeno, hidróxilo, un grupo alquiltio o alcox, de alquilo sustituido o no sustituido;

R^9 es un sustituyente que tiene la fórmula:



En la cual,

R^{12} y R^{13} son independientemente H o alquilo inferior;

m es 0 o 1;

p es un entero de desde 0 hasta 5;

A_1 es CH o N;

A_2 es $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cada A_3 presente esta independientemente $C(R^{14})(R^{15})$, $N(R^{16})$, S, S(O), $S(O)_2$, o O; donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior;

cuando p es 1, 2, 3, 4, o 5, A_4 es $N(R^{17})$, $C(R^{14})(R^{15})$, o O; y cuando p es 0 (por ejemplo, A_3 no está presente), A_4 es $N(R^{17})(R^{18})$, $C(R^{14})(R^{15})(R^{16})$, y $O(R^{18})$, donde cada R^{14}, R^{15} y R^{16} es independientemente H o alquilo inferior, cada R^{17} es H, alquilo, arilo, o acilo, y cada R^{18} es H, alquilo, o arilo;

provisto que no más de dos heteroátomos ocurren consecutivamente en el anillo arriba descrito formado por A_1, $(A_2)_m$,

$(A_3)_p$, A_4, y C=O, donde cada linea punteada en el anillo describe una unión simple cuando A_2 está presente (es decir, m=1) y un átomo de hidrógeno cuando A_2está ausente (es decir, m=0); y

Z y Z^1 son independientemente H, F, un grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo heterocicloalquilo, grupo arilo o grupo heteroarilo, $-C(O)R^{19}$, $-CO_2R^{19}$, -CN, $-C(O)NR^{19}R^{20}$, $-C(ONR^{19}OR^{20}$, $-C(S)R^{19}$, $-C(S)NR^{19}R^{20}$, $-NO_2$, $-SOR^{20}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{20}$, $-SO_2(NR^{19})(OR^{20})$, $-SONR^{19}$, $-SO_3R^{19}$, $-PO(OR^{19})_2$, $-PO(OR^{19})(OR^{20})$, $-PO(NR^{19}R^{20})(OR^{21})$, $-PO(NR^{19}R^{20})(NR^{21}R^{22})$, $-C(O)NR^{19}NR^{20}R^{21}$, $-C(S)NR^{19}NR^{20}R^{21}$, en el cual R^{19}, R^{20}, R^{21} y R^{22} son independientemente H, grupo alquilo sustituido o no sustituido, grupo cicloalquilo, grupo arilo, grupo heterocicliloalquilo, un grupo acilo o un grupo tioacilo, en el cual cualesquiera dos de los R^{19}, R^{20}, R^{21} y R^{22}, tomados juntos con los átomo los cuales ellos están unidos, forman un grupo heterocíclico, el cual puede ser opcionalmente sustituido.

o Z y Z^1, junto con el átomo los cuales están unidos, forman un grupo cicloalquilo o heterocicloalquilo, donde Z y Z^1 están definidos arriba excepto por la mitades que no forman el grupo cicloalquilo o heterocicloalquilo,

o una prodroga, sal farmacéuticamente aceptable metabolito farmacéuticamente activo o soluble farmacéuticamente aceptable de ésta.

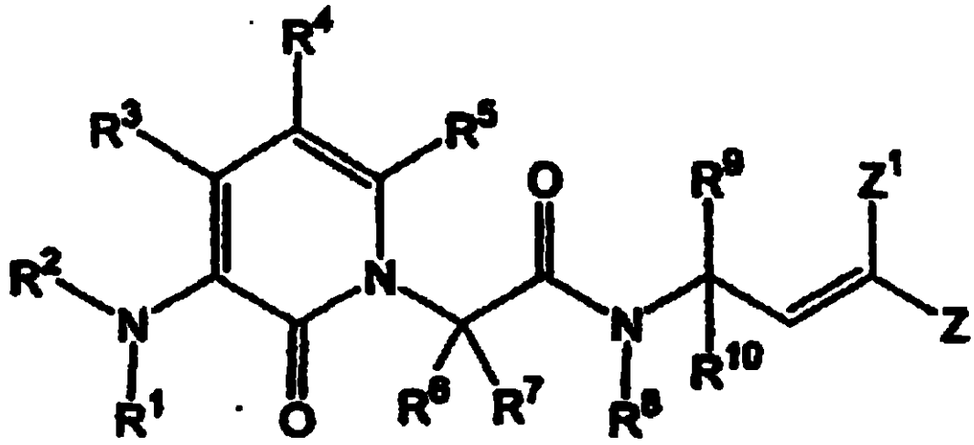
6. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4, en el cual R^1, R^2, R^3, y R^{10} son cada uno H.

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7. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 en el cual R^4, R^5 y R^8 son sustituyentes adecuables, dichos sustituyentes adecuables son independientemente seleccionados de H, alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, nitro, amino, ciano, halógeno, hidróxilo, alcoxi, ariloxi, cicloalcoxi, heterocicloalcoxi, heteroariloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, arilloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquiloxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquiloxicarbonilo, carbóxilo, carbamoilo, formilo, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilamino carbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilo, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, ariltio, y heteroariltio, en el cual cualesquiera de los alquilo, arilo, cicloalquilo, heterocicloalquilo, mitades de heteroarilo presentes en los sustituyentes de arriba son opcionalmente sustituidos.

8. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:

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en la cual

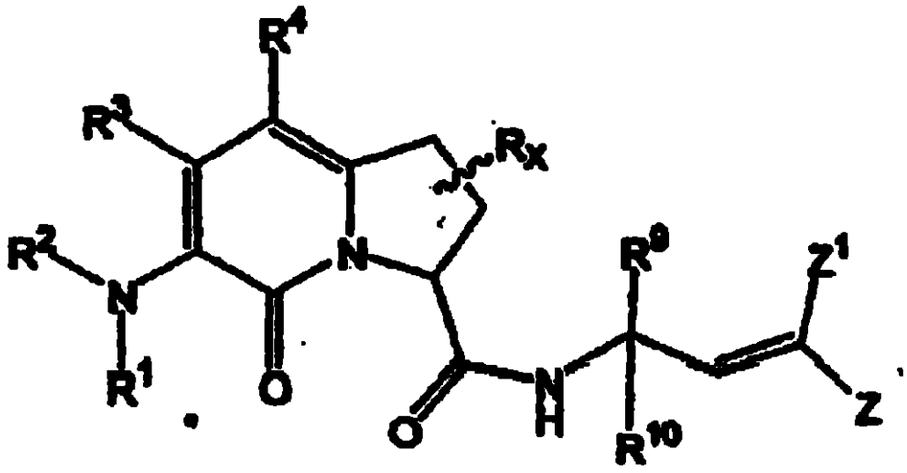
R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de la mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidos o no sustituidos;

R^8 es un grupo sustituido o no sustituido;

y R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, Z y Z^1, son como sean definido en la reivindicación 4.

9. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:

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en la cual:

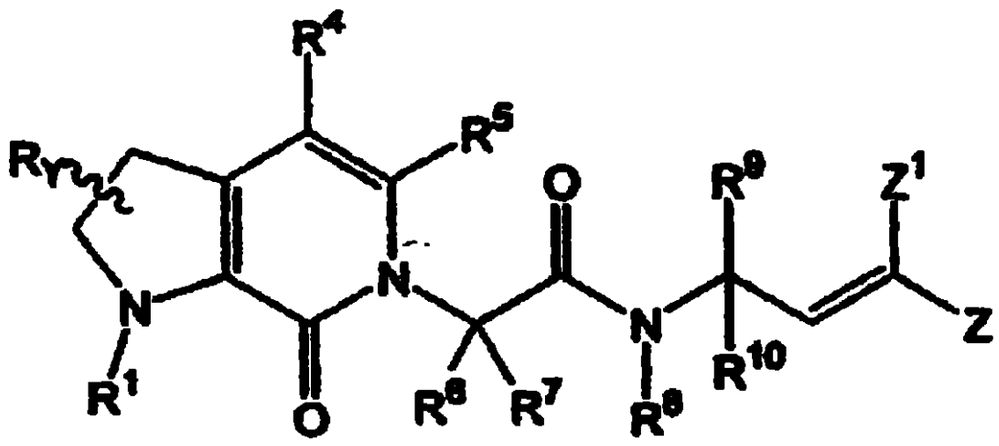
R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo arilioxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de las mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidas o no sustituidas;

R_x representa uno o más suetituyentes adecuables;

y R^1, R^3, R^4, R^9, R^{10}, Z y Z^1, son como sean definido en la reivindicación 4.

10. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:

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en la cual:

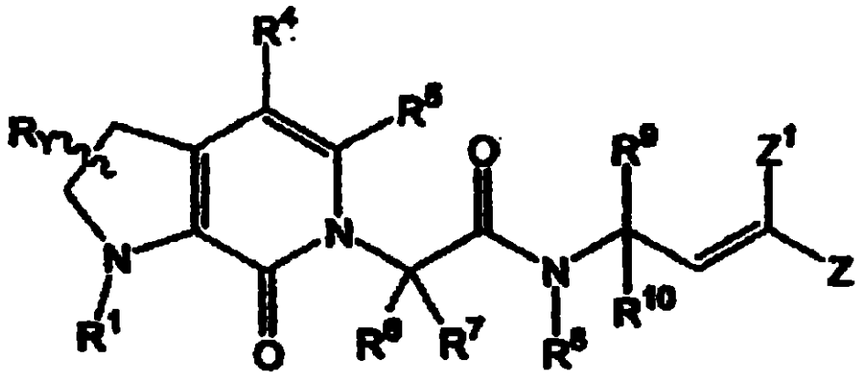
R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R^6 es un grupo alquilo sustituido o no sustituido;

R_y representa uno o más sustituyentes adecuables;

y R^1, R^4, R^5, R^9, Z y Z^1 son como se han definido en la reivindicación 4.

11. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:



en la cual:

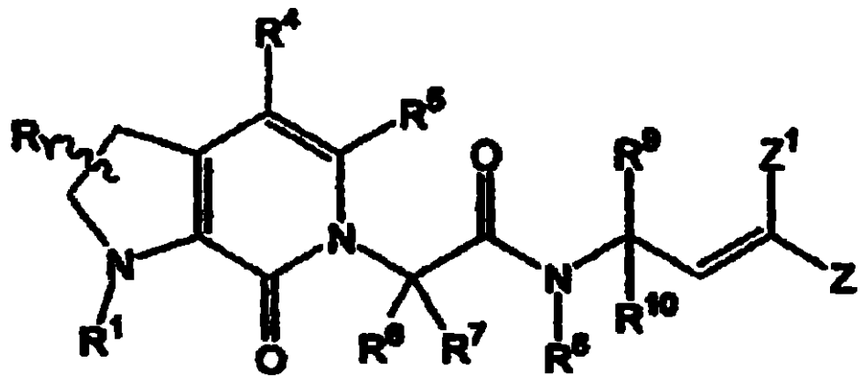
R^7, R^8 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R_y representa H o uno o más sustituyentes adecuables;

R^4 y R^5 son independientemente H o uno o más sustituyentes adecuables descritos arriba; y

R^1, R^6, R^9, Z y Z^1, y las variables contenidas aquí en la presente, son como se han definido en la reivindicación 4.

12. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:



en la cual:

R^7, R^9 y R^{10} son independientemente H o un grupo alquilo inferior sustituido o no sustituido;

R_y representa H o uno o más sustituyentes adecuables;

R^4 y R^5 son independientemente H o uno o más sustituyentes adecuables descritos arriba; y

R^1, R^6, R^9, Z y Z^1, y las variables contenidas aquí en la presente, son como se han definido en la reivindicación 4.

13. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo a cualesquiera una de las reivindicaciones 4, 5, 8 o 9, en la cual R^2 está seleccionado de un grupo alquiloxicarbonilo sustituido o no sustituido, alquilcarbonilo, cicloalquiloxicarbonilo, arilcarbonilo, grupo heterocicloalquilcarbonilo o heteroarilcarbonilo.

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14. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 13, en la cual R^2 es un grupo heteroarilcarbonilo, en el cual la mitad de heteroarilo es un heterocicio de 5-miembros que tiene desde uno hasta tres heteroátomos seleccionados de O, N, y S.

15. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 14, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es un heterocicio de 5-miembros que tiene por lo menos un heteroátomo de nitrógeno y por lo menos un heteroátomo de oxigeno.

16. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 15, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es 1,2-oxazolilo sustituido o no sustituido, 1,3-oxazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, o 1,2,5-oxadiazolilo.

17. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 16, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es seleccionada de 1,2,4-oxadiazolilo de monometilo sustituido y no sustituido.

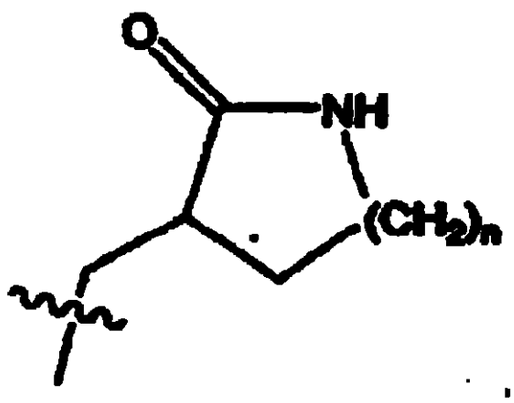
18. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 16, en la cual R^2 es heteroarilcarbonilo, donde la mitad heteroarilo es seleccionada de 3-isoxazolilo y 5-isoxazolilo, cada una sustituida o no sustituida con uno o dos sustituyentes seleccionados de los grupos metilo y halógenos.

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19. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo a cualesquera una de las reivindicaciones 4, 5, 8, 10, 11 o 12, en la cual R^8 es H o alquilo inferior sustituido o no sustituido, arilalquilo, heteroarilalquilo, grupo cicloalquilo, una mitad de hidrocarburo saturado de cadena recta o una mitad de hidrocarburo no saturado.

20. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 19, en la cual R^8 es H, etilo, 2-propin-1-ilo, metiloxiciohexilo, o bencilo sustiuido o no sustituido, en la cual la mitad de fenilo del bencilo sustituido comprende uno o más sustituyentes independientemente seleccionados de alquilo inferior, alcoxi inferior y halógeno.

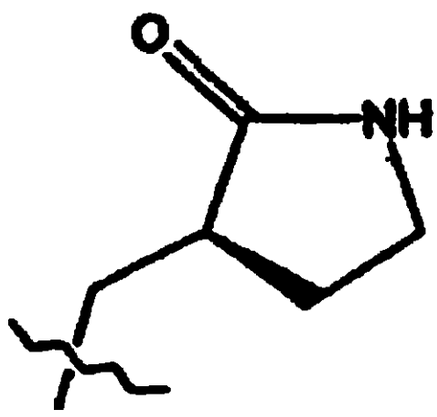
21. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo a cualesquiera una de las reivindicaciones 4, 5, 8, 9, 10, 11 o 12, en la cual R^8 es seleccionado de -$CH_2CH_2C(O)NH_2$; -$CH_2CH_2C(O)NH$-alquilo; -$CH_2NHC(O)CH_3$; y



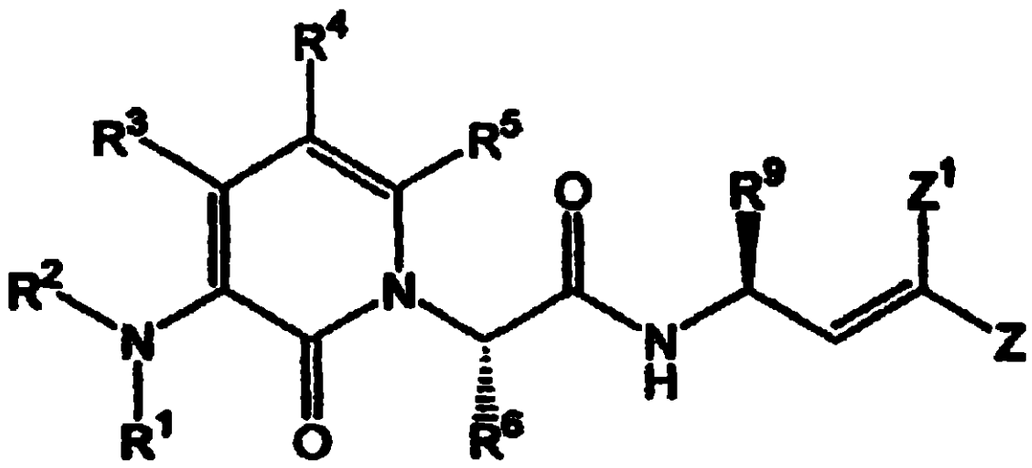
, donde n es 1 o 2.

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22. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 21, en la cual R^9 es



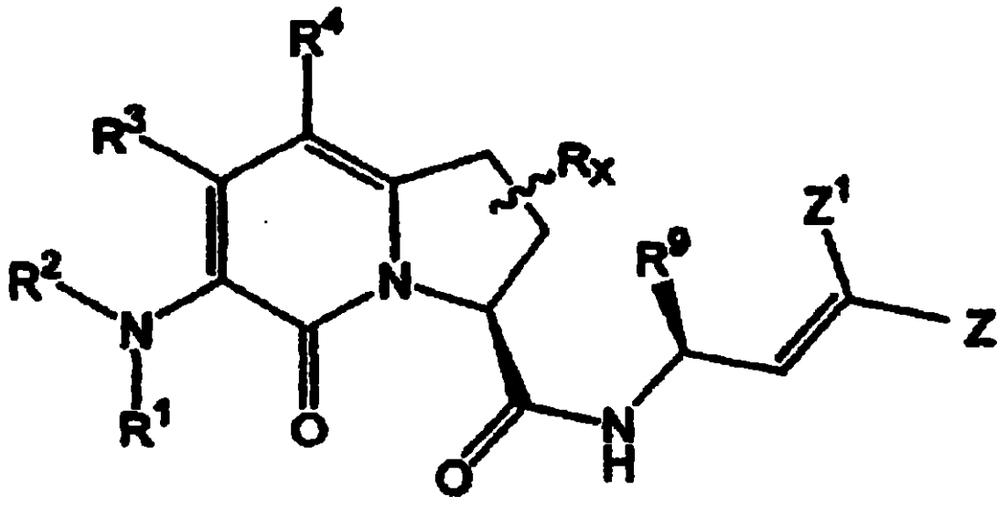
23. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 4 que tiene la fórmula:



en la cual R^1, R^2, R^3, R^4, R^5, R^6, R^9, Z y Z^1 son se definió en la reivindicación 8.

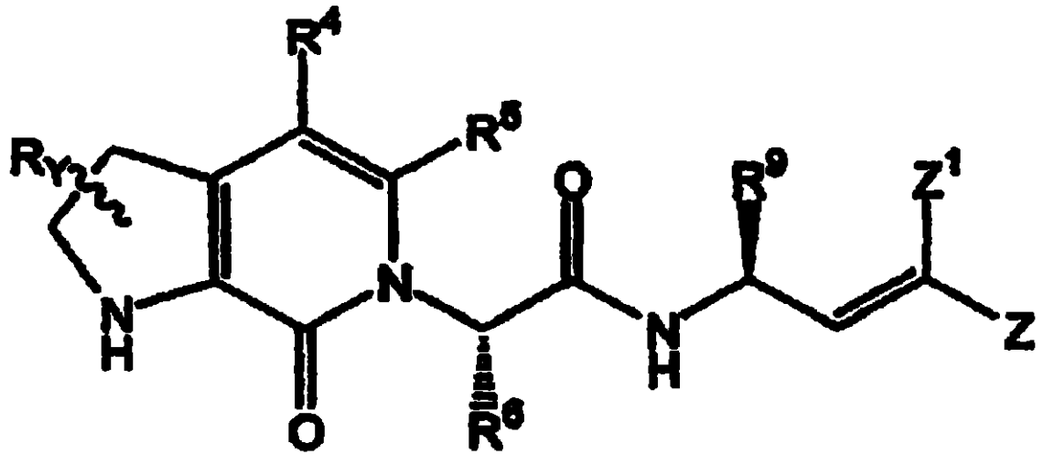
24. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 9, que tiene la fórmula:

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en la cual R^1, R^2, R^3, R^4, R^9, R_x, Z y Z^1 son como se definió en la reivindicación 9.

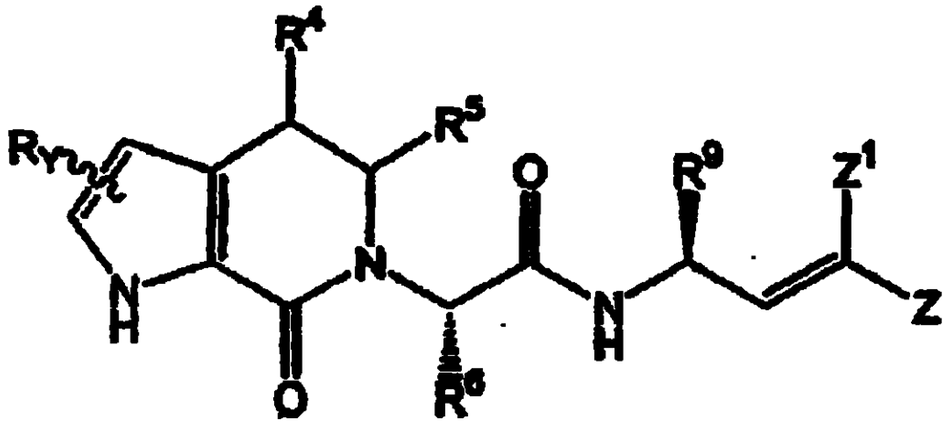
25. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 10 que tiene la fórmula:



en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son como se definieron en la reivindicación 10.

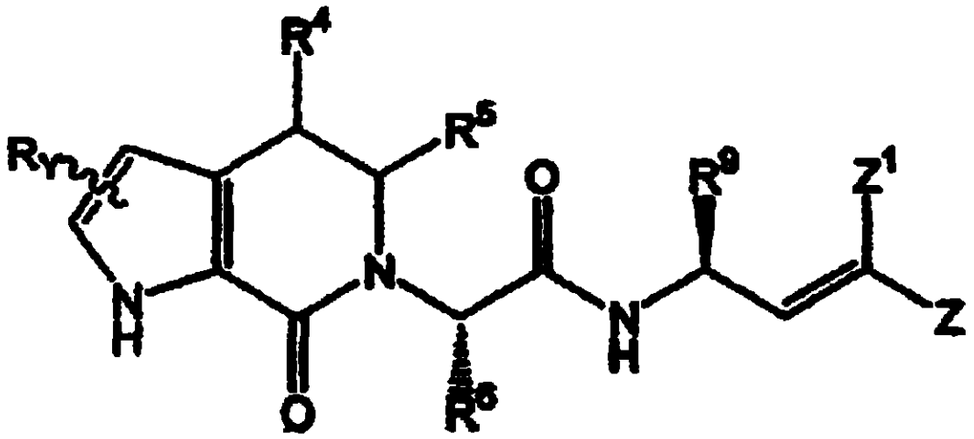
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26. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 11 que tiene la fórmula:



en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son como se definieron en la reivindicación 11.

27. Un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmcéuticamente aceptable de acuerdo con la reivindicación 12 que tiene la fórmula:



en el cual R^4, R^5, R^6, R^9, R_y, Z y Z^1 son como se definieron en la reivindicación 12.

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28. Un compuesto de acuerdo con las reivindicaciones 4 o 5 que tiene actividad antipicornaviral correspondiente con un EC_{50} de menos de o igual a 100 μM en un ensayo de cultivo de célula H1-HeLa.

29 Una composición farmacéutica comprende:

una cantidad terapéuticamente efectiva de por lo menos un agente antipicornaviral seleccionado de compuestos, prodrogas, sales farmacéuticamente aceptables, metabolitos farmacéuticamente activos, y solubles farmacéuticamente aceptables definidos en las reivindicaciones 4 o 5; y

un portador farmacéuticamente aceptable, diluyente, vehículo, o excipiente.

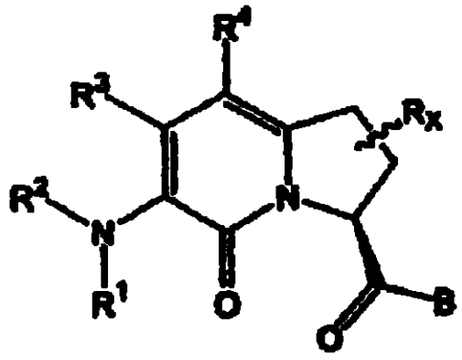
30. Un método de tratar una condición de enfermedad de mamífero mediada por actividad de proteasa picornaviral, comprende administrar a un mamífero en necesidad de ésta una cantidad terapéuticamente efectiva de por lo menos un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmacéuticamente aceptable definido en las reivindicaciones 4 o 5.

31. Un método de inhibir la actividad de una proteasa picornaviral 3C, comprende contactar la proteasa picornaviral 3C con una cantidad efectiva de por lo menos un compuesto, prodroga, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o soluble farmacéuticamente aceptable definido en las reivindicaciones 4 o 5.

32. Un método tal como está definido en la reivindicación 31, en el cual la proteasa picornaviral 3C es una proteasa rinoviral.

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33. Un compuesto que tiene la fórmula:



en la cual:

R^3 y R^4 son independientemente H o sustituyentes adecuables.;

R_x representa H o uno o más sustituyentes adecuables.;

B es H, $-OR^{24}$, donde R^{24} es un grupo protector adecuable para una mitad de carbóxilo; y

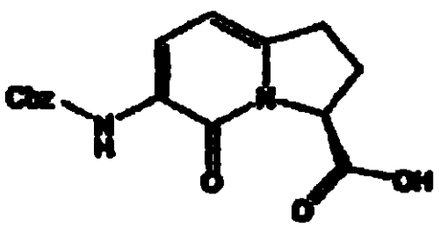
R^1 es H, un grupo alquilo inferior sustituido o no sustituido o un grupo de protección de nitrógeno adecuable;

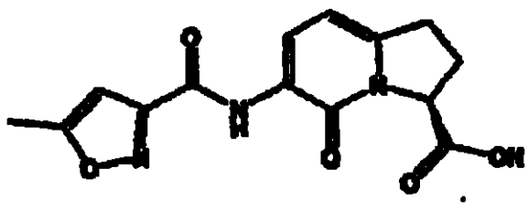
R^2 es un grupo alquilcarbonilo, un grupo arilcarbonilo, un grupo cicloalquilcarbonilo, un grupo heterocicloalquilcarbonilo, un grupo heteroarilcarbonilo, un grupo ariloxicarbonilo o un grupo alquiloxicarbonilo, en los cuales cada una de las mitades de los alquilo, arilo, cicloalquilo, heterocicloalquilo y heteroarilo de los grupos de arriba es sustituidas o no sustituidas, o un grupo de protección de nitrógeno sustituido o no sustituido; o

R^1 junto con R^2 forman un grupo de protección de nitrógeno adecuable;

o una sal farmacéuticamente aceptable de ésta.

34. Un compuesto de acuerdo con la reivindicación 33 que tiene la fórmula:

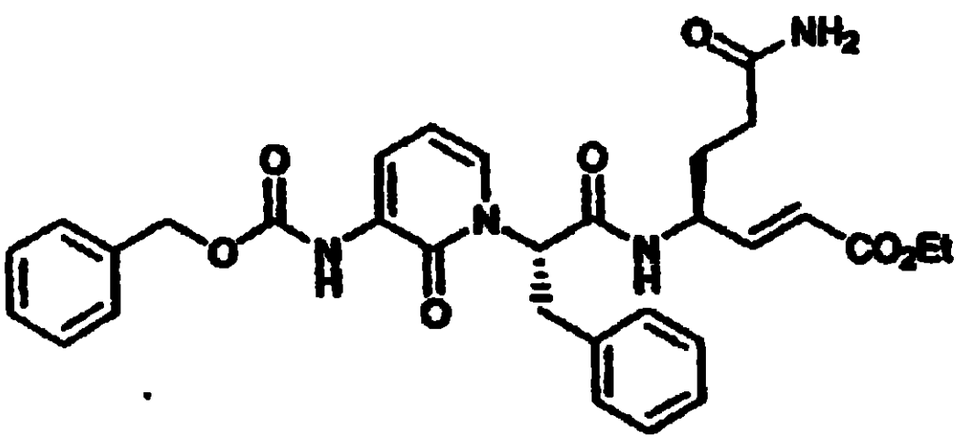




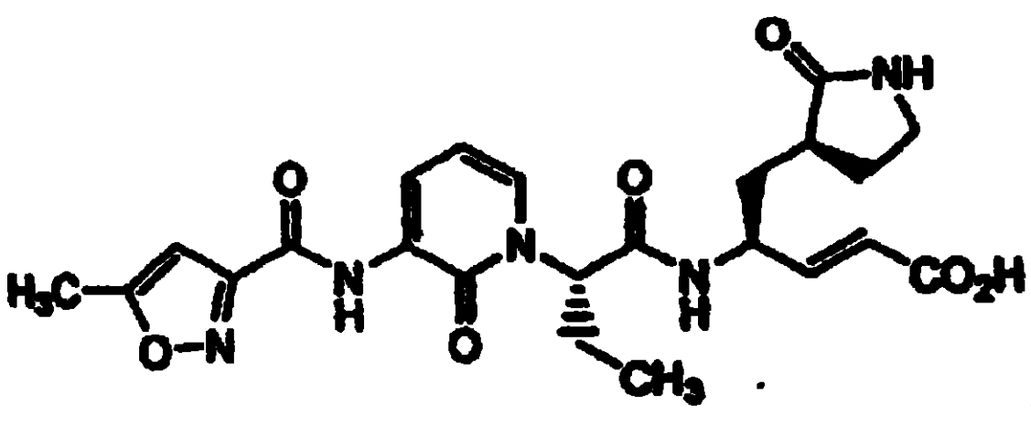
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o una sal farmacéuticamente aceptable de ésta.

35. Un compuesto seleccionado de:

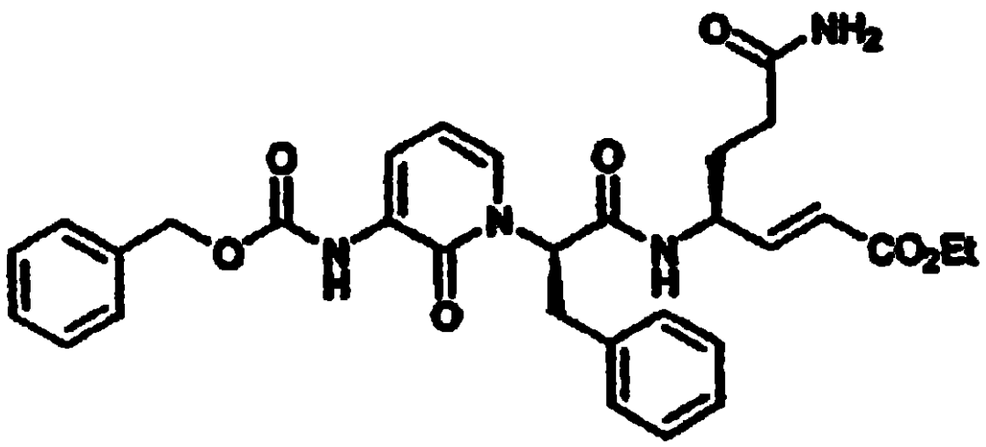


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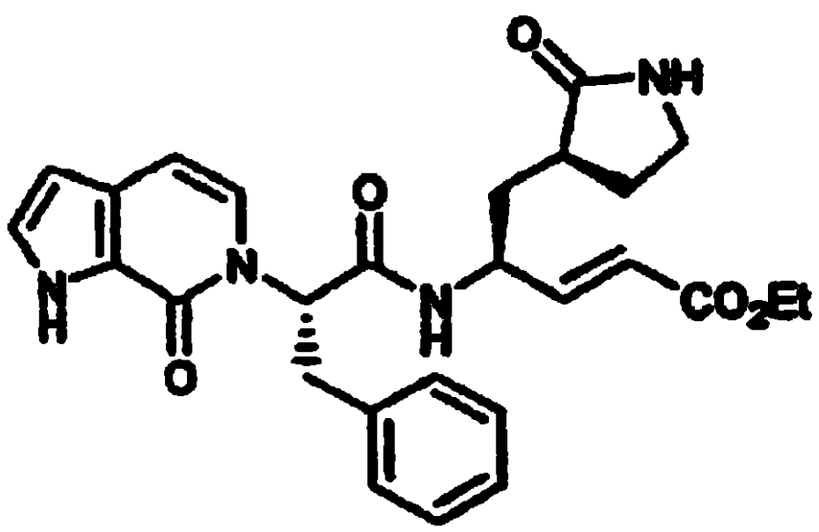


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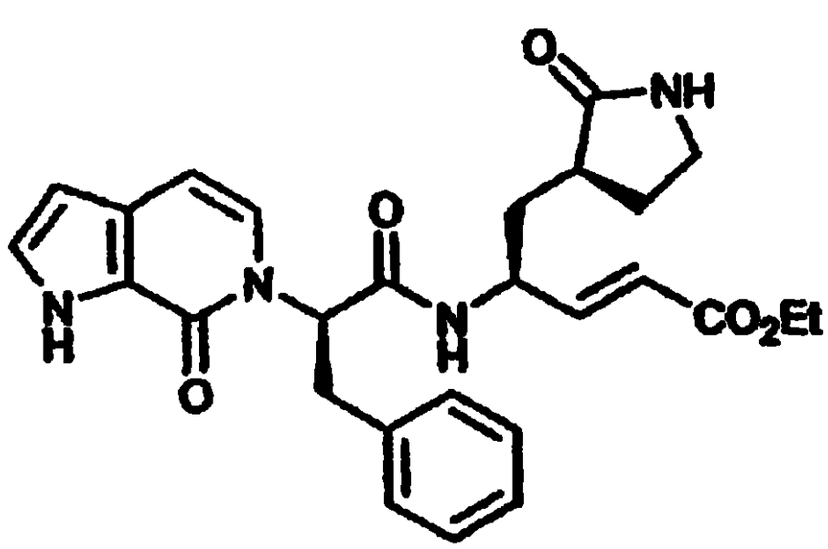
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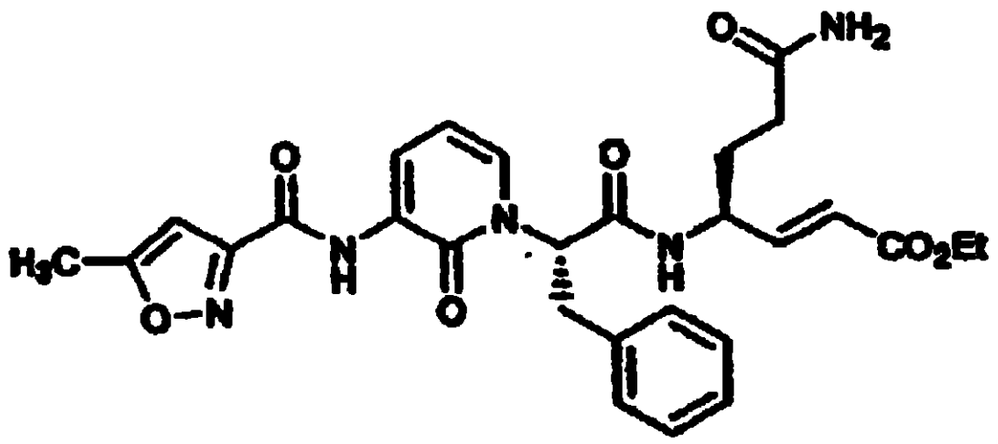
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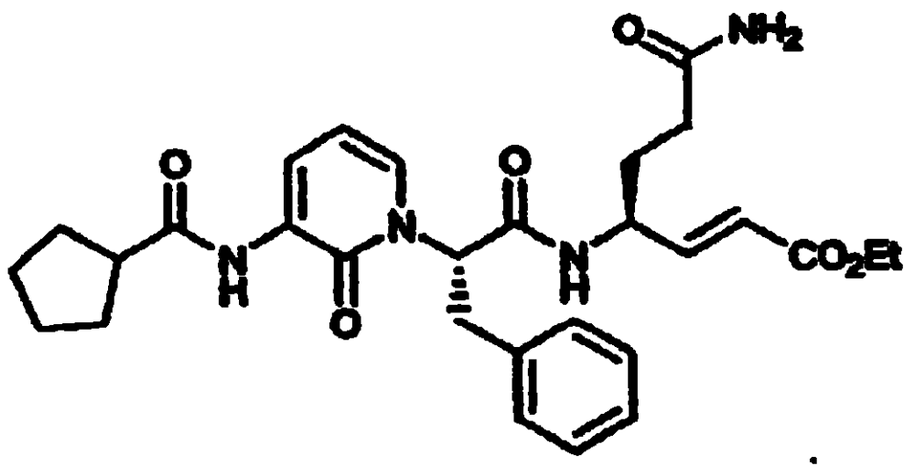


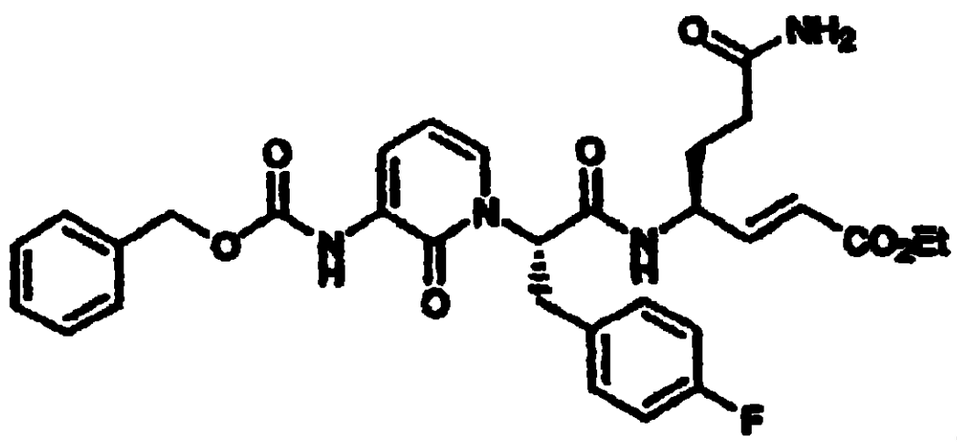
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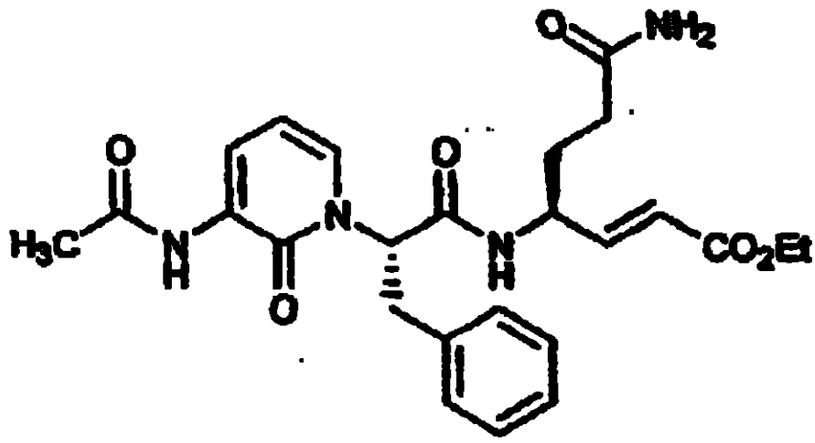
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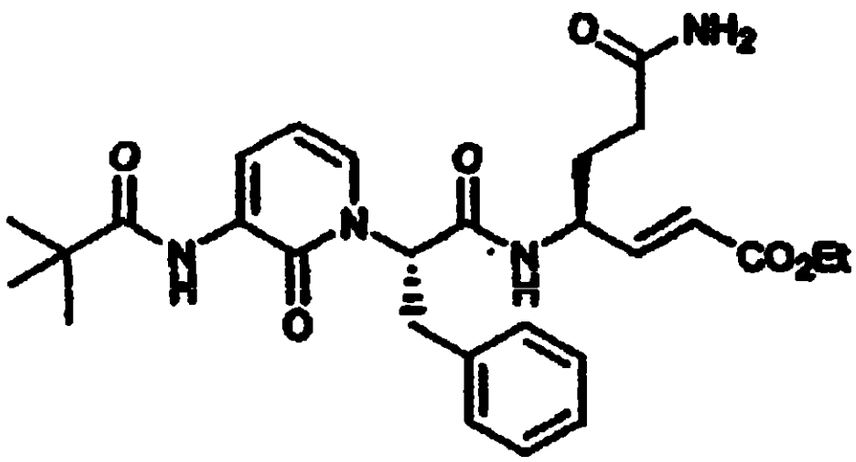


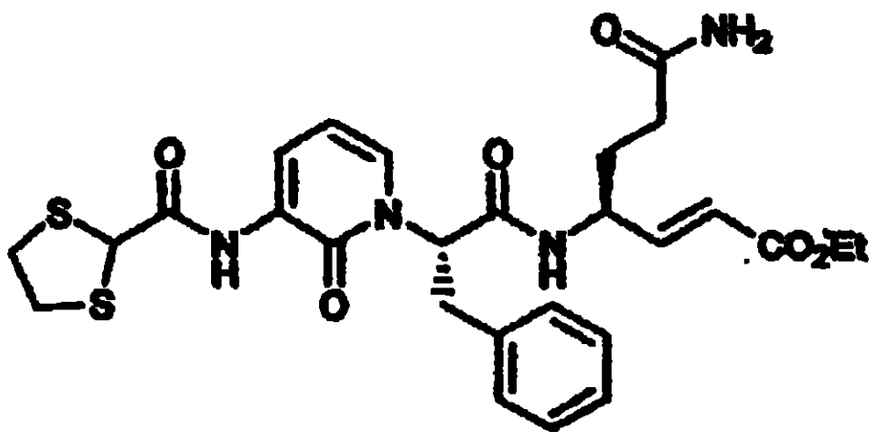




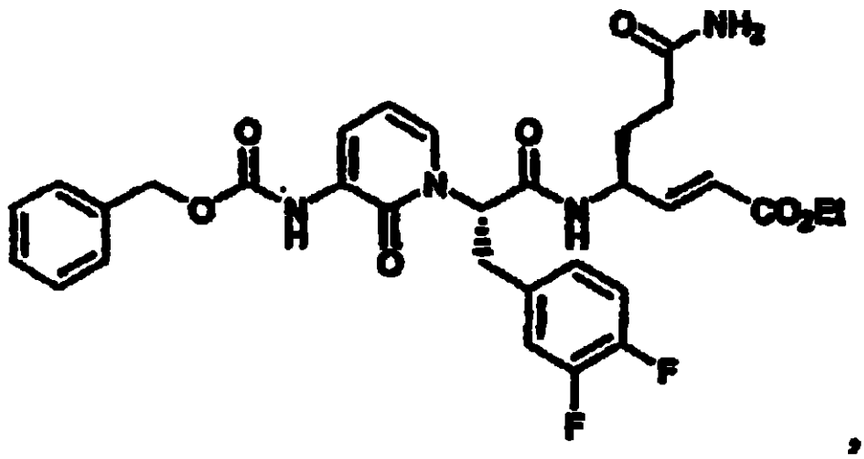
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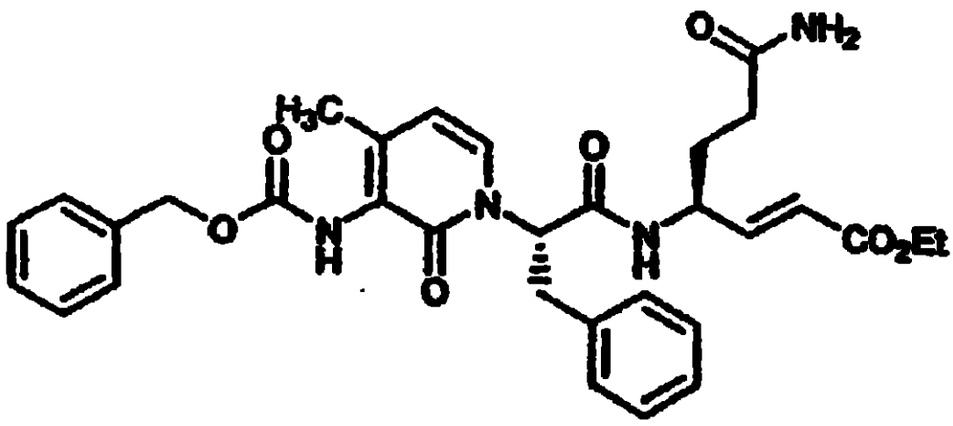


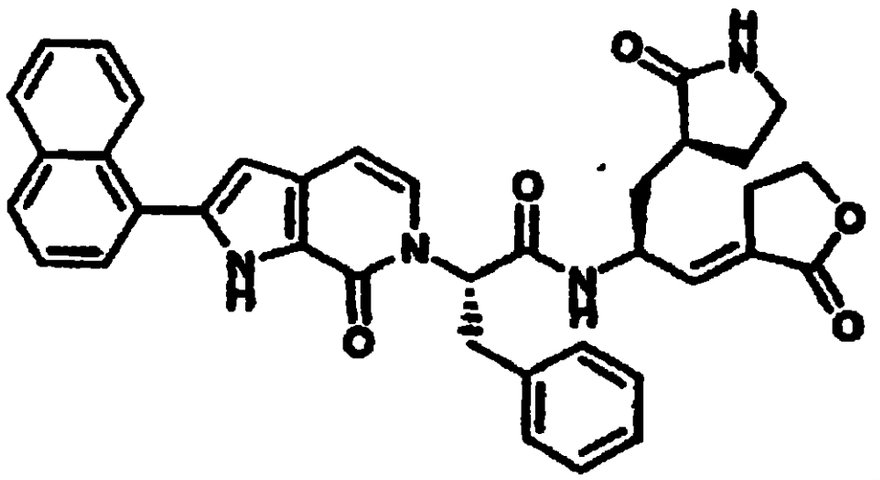




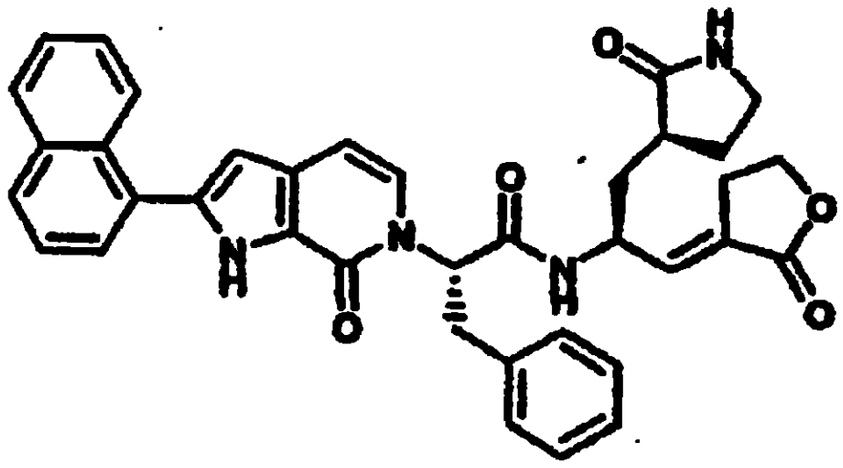
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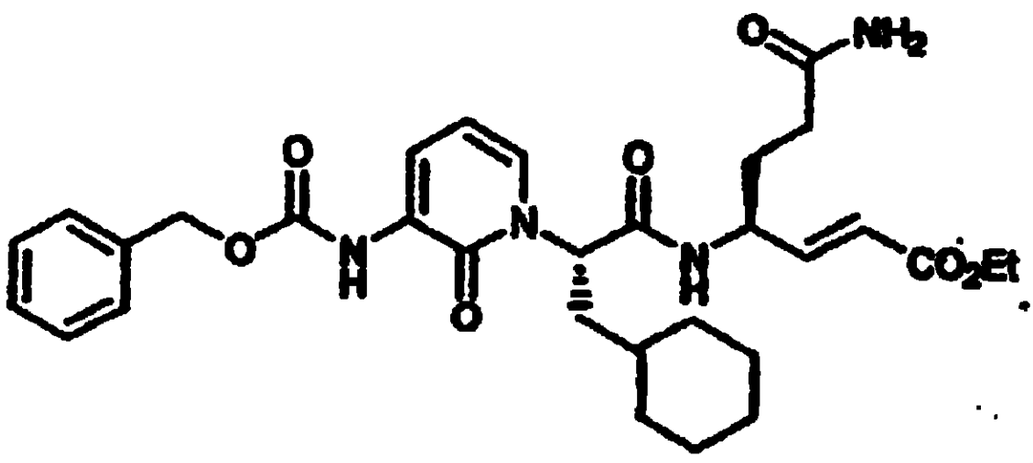


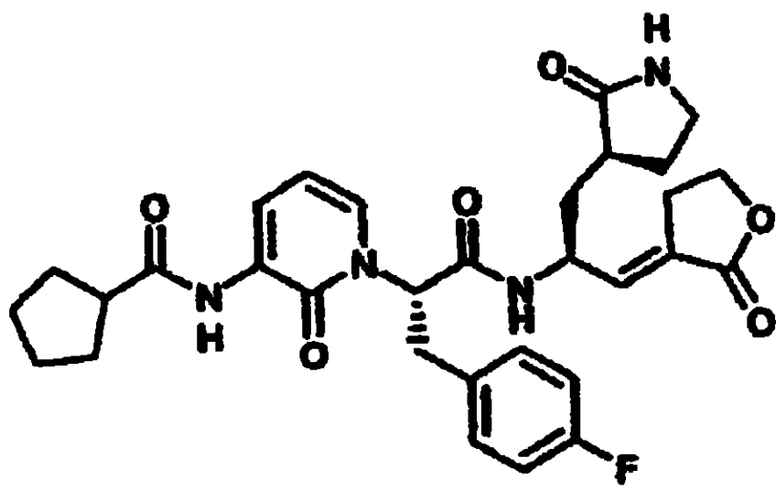




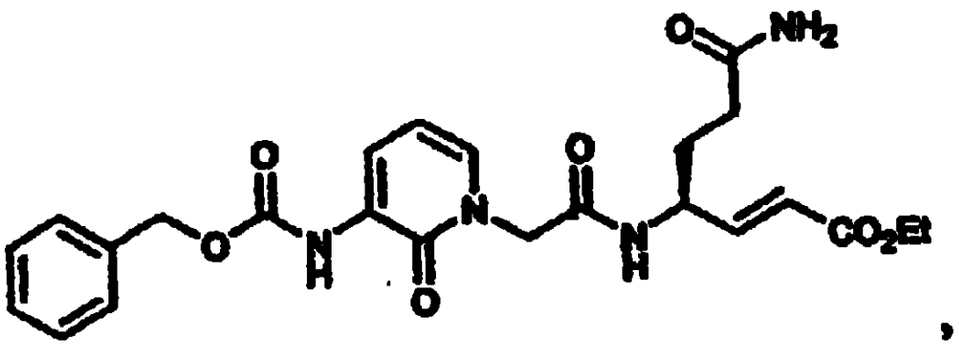
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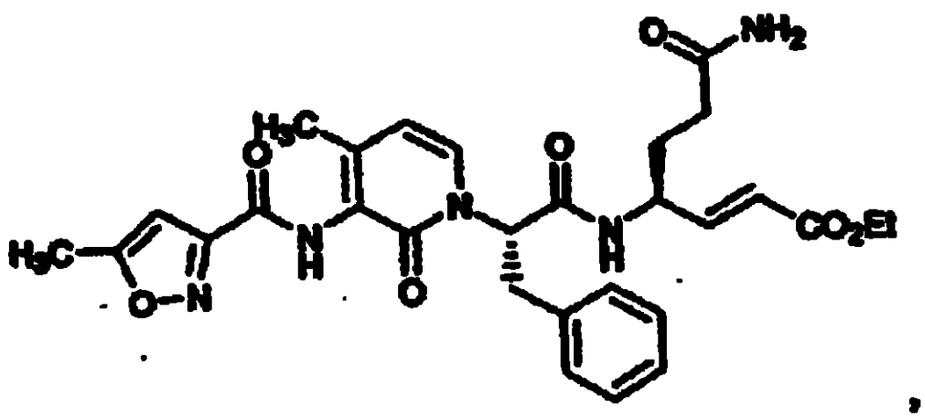


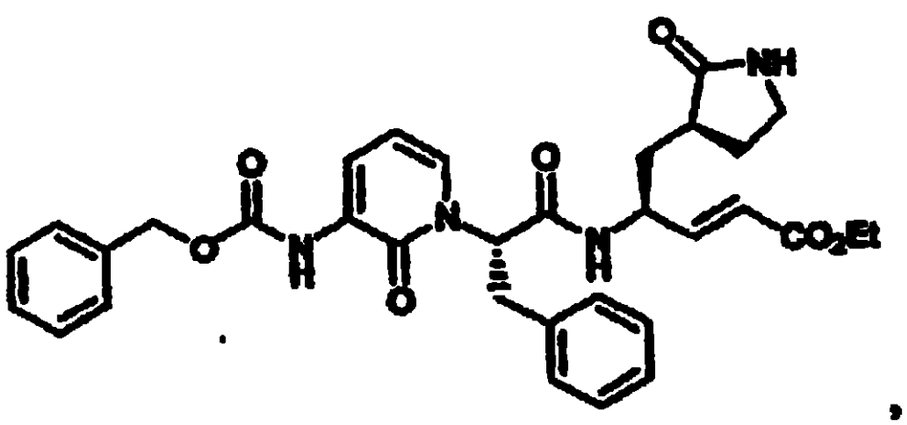


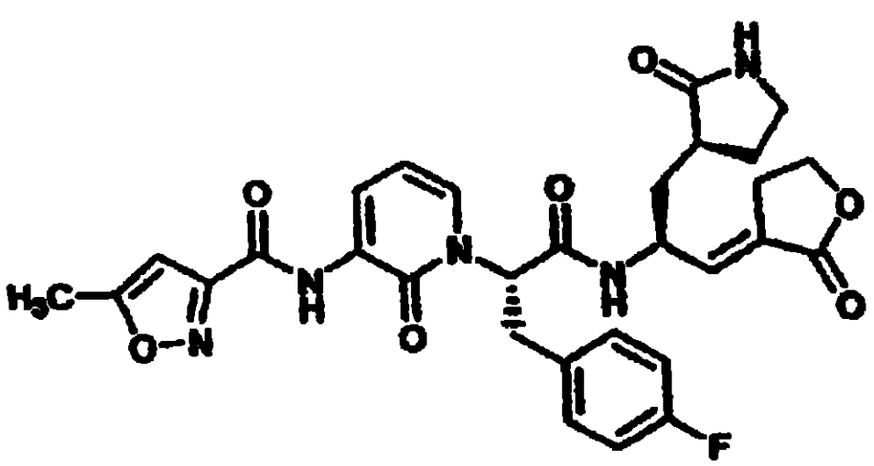


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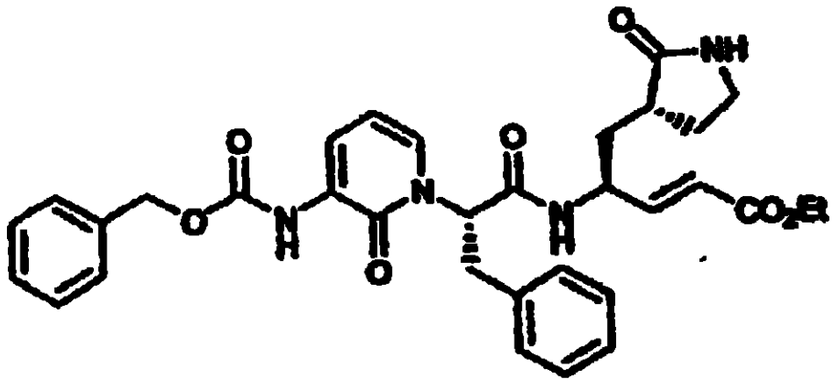


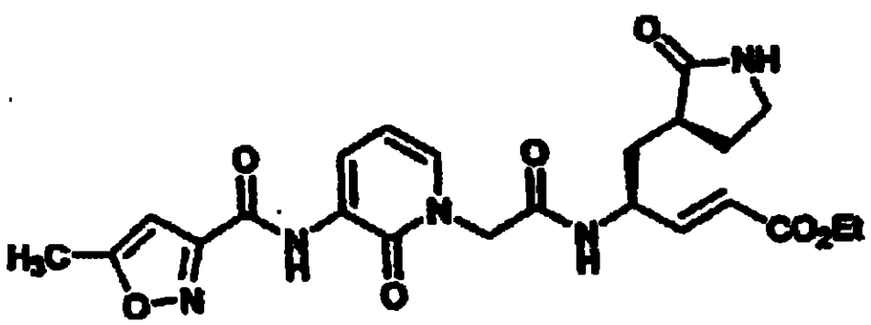


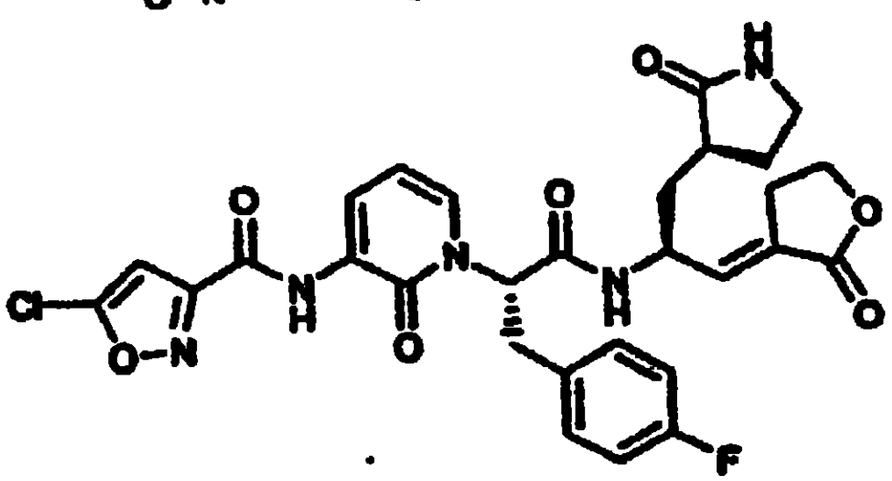


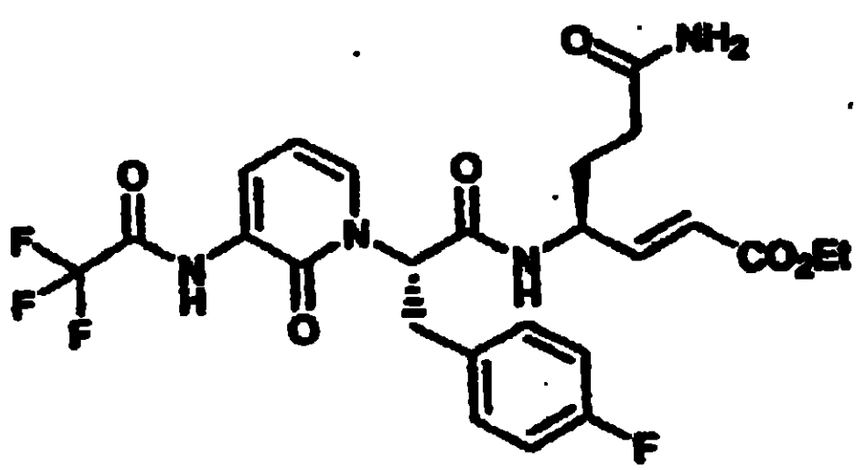


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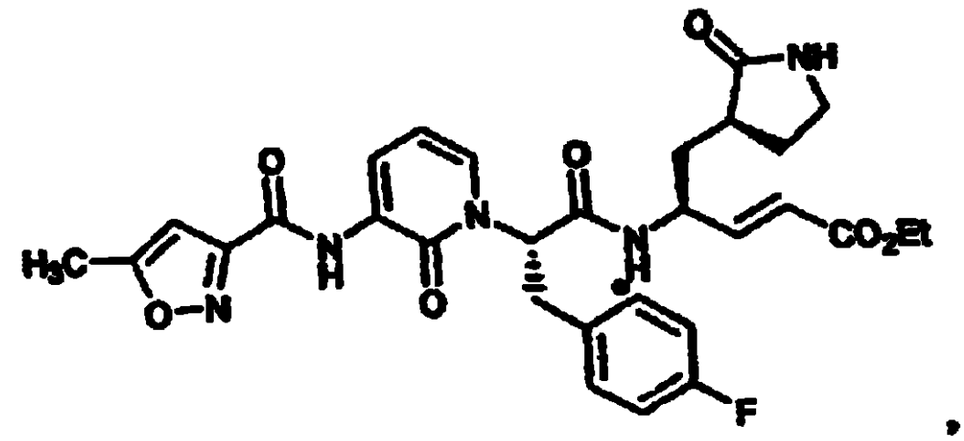


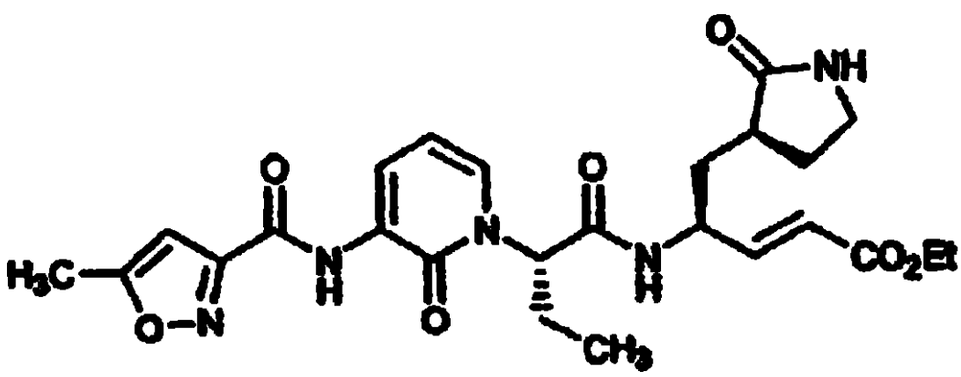


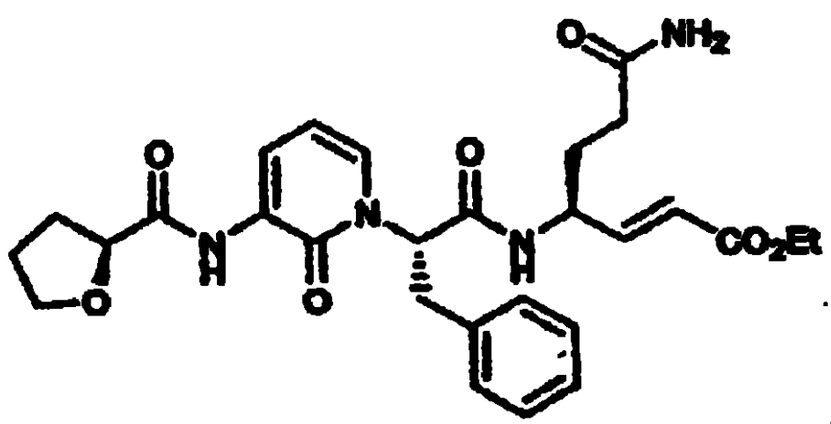


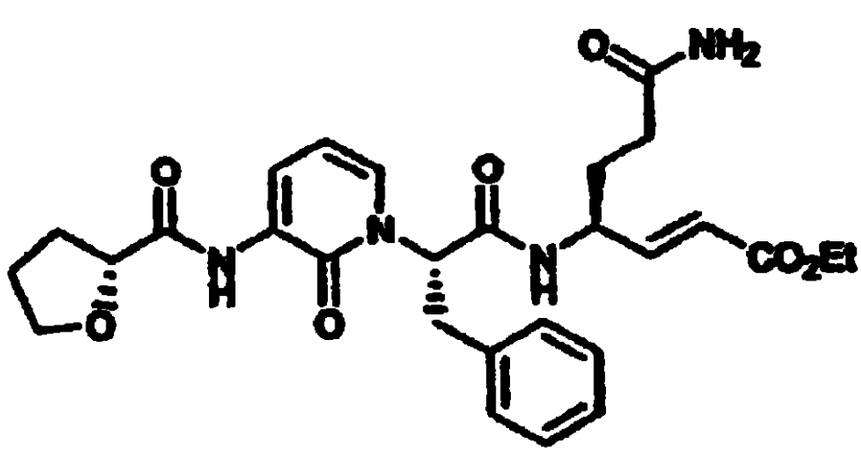
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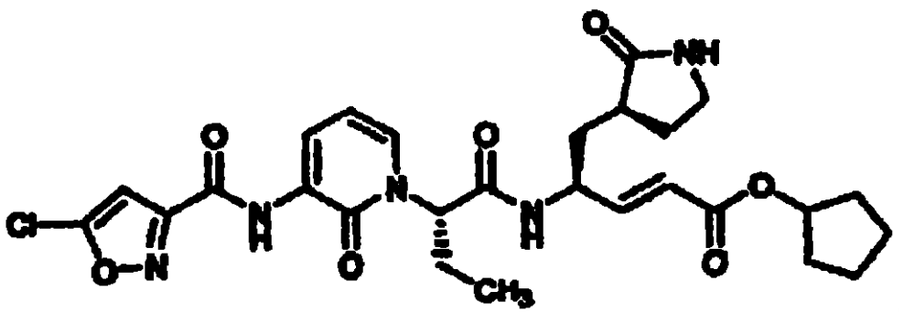


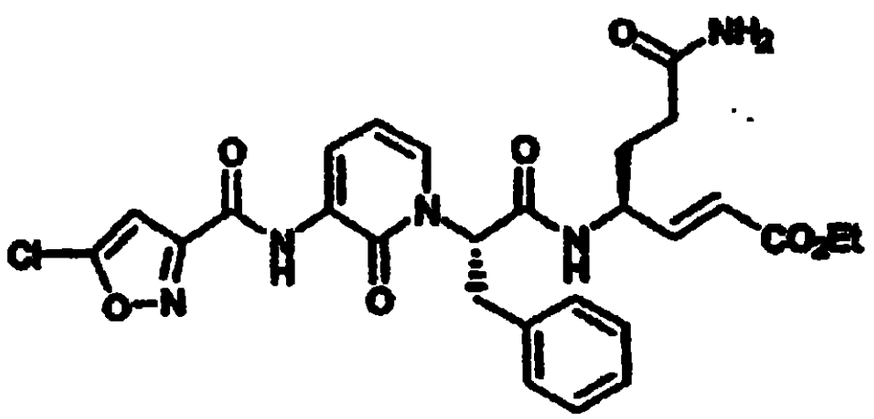


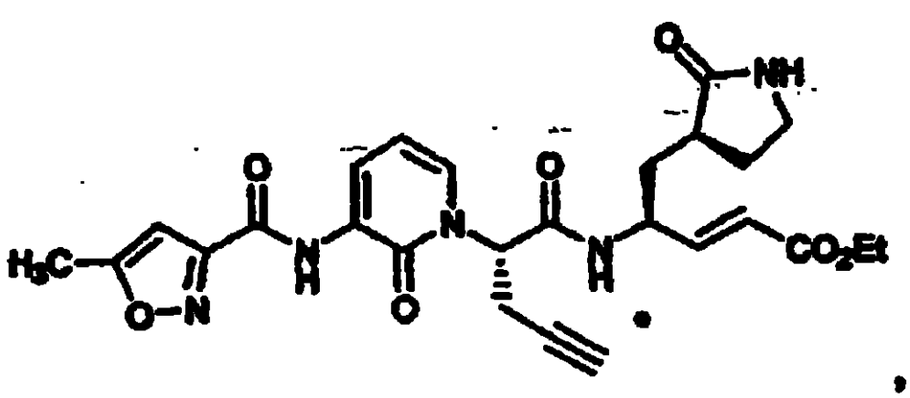


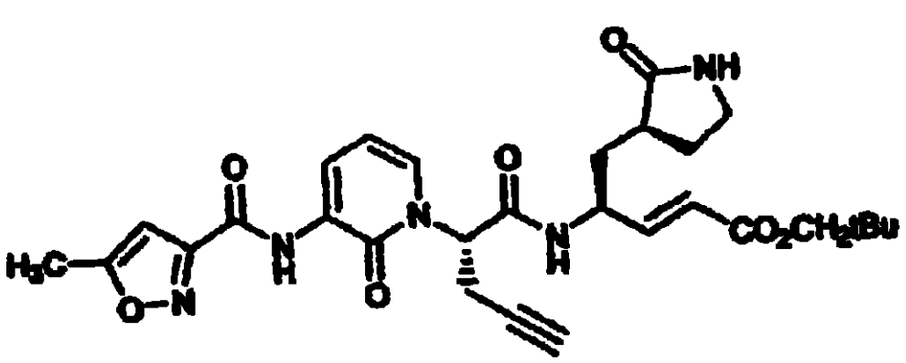


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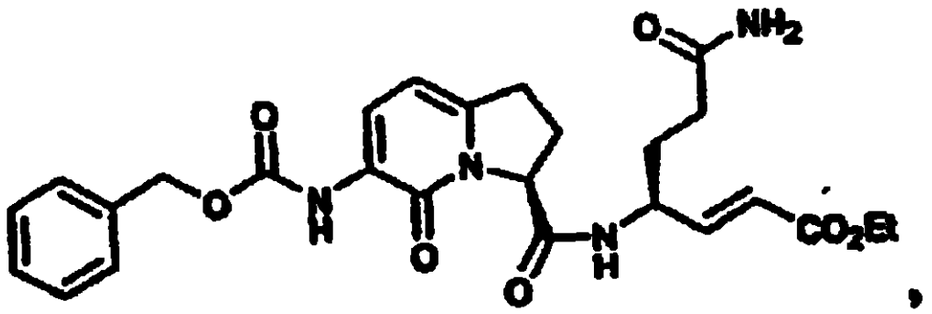


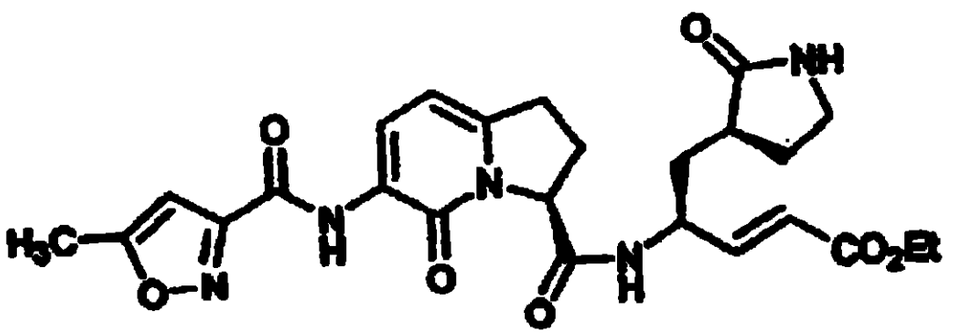


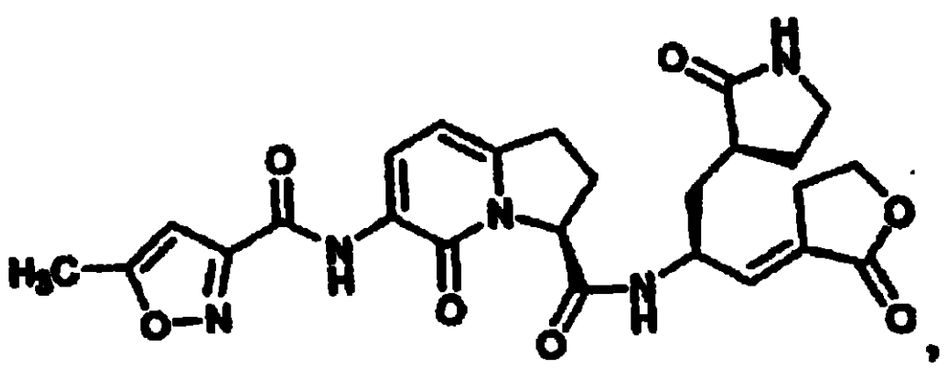


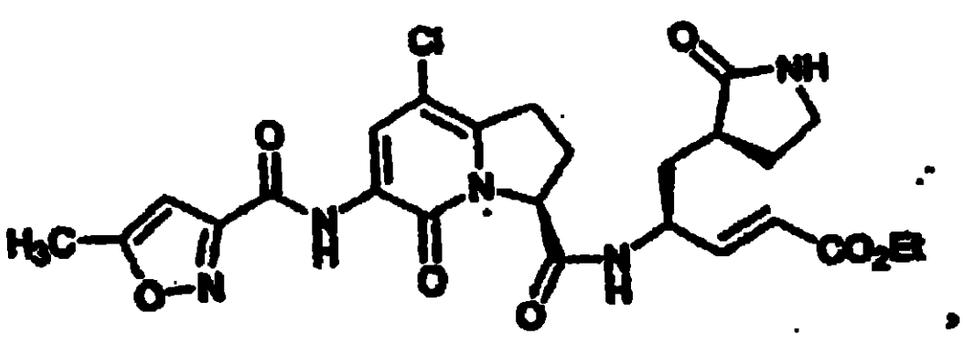


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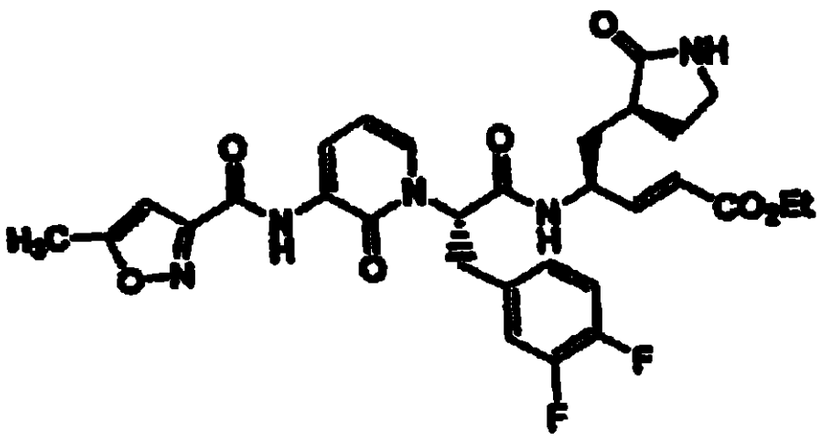


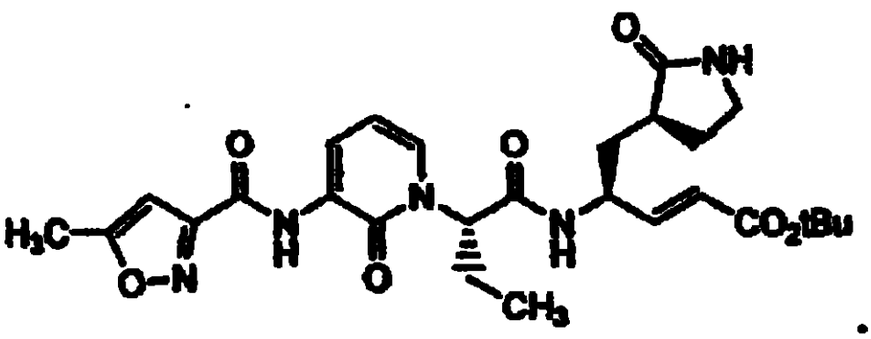






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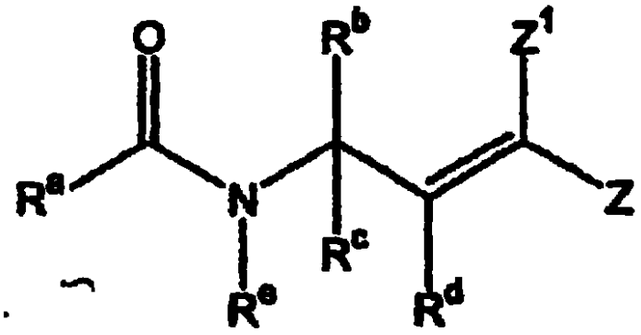


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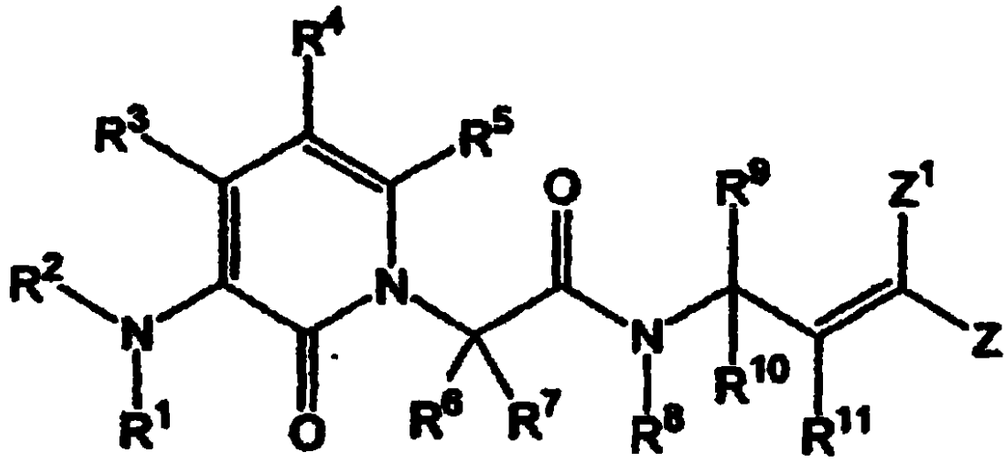
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RESUMEN DE LA REVELACI N

Un compuesto que tiene la fórmula:



donde las variables de la fórmula son como se definieron aquí en la presente, son revelados que ventajosamente inhiben o bloquean la actividad biológica de la proteasa picornaviral 3C. También revelados son compuestos de la fórmula:



donde las variables de la fórmula son como se han definido aquí en la presente que ventajosamente inhiben o bloquean la actividad biológica de la proteasa picornaviral 3C. Esos compuestos, así como también las composiciones farmacéuticas que contienen esos compuestos, son útiles para el tratamiento de pacientes o huéspedes infectados con uno o más picornaviruses, tales como RVP. Los intermediarios y métodos sintéticos para preparar tales compuestos están también descritos.

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ES TRADUCCIÓN FIEL Y COMPLCETA DE LOS DOCUMENT S ADJUNT S.