

HEPATITIS C VIRUS INHIBITORS

FIELD OF THE INVENTION

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The present invention is generally directed to antiviral compounds, and more specifically directed to compounds which inhibit the functioning of the NS3 protease encoded by Hepatitis C virus (HCV), compositions comprising such compounds and methods for inhibiting the functioning of the NS3 protease.

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BACKGROUND OF THE INVENTION

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* (2001), 345, 41-52).

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. (Poynard, T. et al. *Lancet* (1998), 352, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* (2000), 343, 1666-1672). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive

stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

5 Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

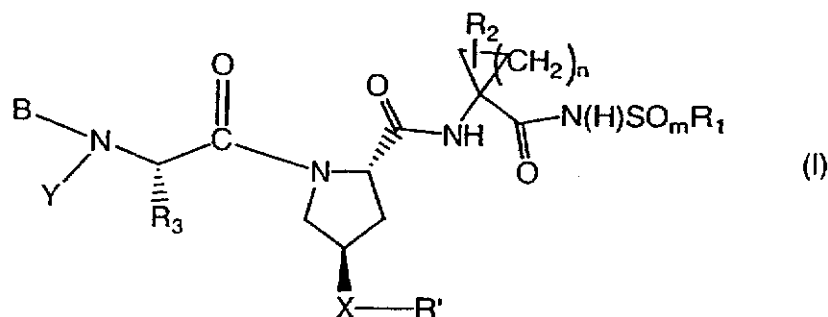
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 The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non- structural (NS) 15 proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one, as yet poorly characterized, cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (henceforth referred to as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both 20 in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A- NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, 25 enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

 Among the compounds that have demonstrated efficacy in inhibiting HCV 30 replication, as selective HCV serine protease inhibitors, are the peptide compounds disclosed in U.S. Patent No. 6,323,180.

SUMMARY OF THE INVENTION

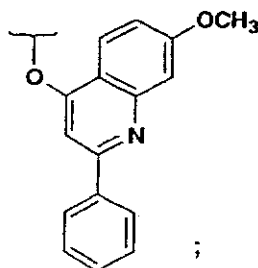
The present invention provides a compound of formula I, including
 5 pharmaceutically acceptable salts, solvates or prodrugs thereof,



wherein:

- 10 (a) R_1 is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl;
- (b) m is 1 or 2;
- (c) n is 1 or 2;
- (d) R_2 is H C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl, each optionally substituted with halogen;
- 15 (e) R_3 is C_{1-8} alkyl optionally substituted with halo, cyano, amino, C_{1-6} dialkylamino, C_{6-10} aryl, C_{7-14} alkylaryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, wherein the cycloalkyl or alkylcycloalkyl are optionally substituted with hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} alkoxy; or R_3 together with the carbon atom to which it is attached forms a C_{3-7} cycloalkyl group optionally substituted with C_{2-6} alkenyl;
- 20 (f) Y is H, phenyl substituted with nitro, pyridyl substituted with nitro, or C_{1-6} alkyl optionally substituted with cyano, OH or C_{3-7} cycloalkyl; provided that if R_4 or R_5 is H then Y is H;
- 25 (g) B is H, C_{1-6} alkyl, $R_4-(C=O)-$, $R_4O(C=O)-$, $R_4-N(R_5)-C(=O)-$, $R_4-N(R_5)-C(=S)-$, R_4SO_2- , or $R_4-N(R_5)-SO_2-$;

- (h) R_4 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, $-OC(O)C_{1-6}$ alkyl, C_{1-6} alkoxy, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl, each optionally substituted with hydroxy, carboxyl, $(C_{1-6}$ alkoxy)carbonyl, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl, halogen, nitro, hydroxy, amido, (lower alkyl) amido, or amino optionally substituted with C_{1-6} alkyl; (iv) Het; (v) bicyclo(1.1.1)pentane; or (vi) $-C(O)OC_{1-6}$ alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;
- (i) R_5 is H; C_{1-6} alkyl optionally substituted with 1-3 halogens; or C_{1-6} alkoxy provided R_4 is C_{1-10} alkyl;
- (j) X is O, S, SO, SO_2 , OCH_2 , CH_2O or NH;
- (k) R' is Het; or C_{6-10} aryl or C_{7-14} alkylaryl, optionally substituted with R^a ; and
- (l) R^a is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, halo- C_{1-6} alkyl, CF_3 , mono- or di- halo- C_{1-6} alkoxy, cyano, halo, thioalkyl, hydroxy, alkanoyl, NO_2 , SH, , amino, C_{1-6} alkylamino, di (C_{1-6}) alkylamino, di (C_{1-6}) alkylamide, carboxyl, (C_{1-6}) carboxyester, C_{1-6} alkylsulfone, C_{1-6} alkylsulfonamide, di (C_{1-6}) alkyl(alkoxy)amine, C_{6-10} aryl, C_{7-14} alkylaryl, or a 5-7 membered monocyclic heterocycle;
- with the proviso that X- R' is not



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or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The present invention also provides compositions comprising the compounds or pharmaceutically acceptable salts, solvates or prodrugs thereof and a pharmaceutically acceptable carrier. In particular, the present invention provides pharmaceutical compositions useful for inhibiting HCV NS3 comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier.

The present invention further provides methods for treating patients infected with HCV, comprising administering to the patient a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof. Additionally, the present invention provides methods of inhibiting HCV NS3 protease by administering to a patient an effective amount of a compound of the present invention.

By virtue of the present invention, it is now possible to provide improved drugs comprising the compounds of the invention which can be effective in the treatment of patients infected with HCV. Specifically, the present invention provides peptide compounds that can inhibit the functioning of the NS3 protease, e.g., in combination with the NS4A protease.

DETAILED DESCRIPTION OF THE INVENTION

Stereochemical definitions and conventions used herein generally follow McGraw-Hill Dictionary of Chemical Terms, S. P. Parker, Ed., McGraw-Hill Book Company, New York (1984) and Stereochemistry of Organic Compounds, Eliel, E. and Wilen, S., John Wiley & Sons, Inc., New York (1994). Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or

l meaning that the compound is levorotatory and (+) or d, meaning the compound, is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer of a mirror image pair may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture.

The nomenclature used to describe organic radicals, e.g., hydrocarbons and substituted hydrocarbons, generally follows standard nomenclature known in the art, unless otherwise specifically defined. Combinations of groups, e.g., alkylalkoxyamine, include all possible stable configurations, unless otherwise specifically stated. Certain radicals and combinations are defined below for purposes of illustration.

The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical composition, but differ with regard to the arrangement of the atoms or groups in space.

The term "diastereomer" refers to a stereoisomer which is not an enantiomer, e.g., a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

The term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

5 The term "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from a compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or
10 acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445. The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

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The term "therapeutically effective amount" means the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a
20 combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

The term "compounds of the invention", and equivalent expressions, are
25 meant to embrace compounds of Formula I, and pharmaceutically acceptable salts, and solvates, e.g. hydrates. Similarly, reference to intermediates, is meant to embrace their salts, and solvates, where the context so permits. References to the compound of the invention also include the preferred compounds of Formula II and III.

30 The term "derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or

an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, and the like.

The term "prodrug" as used herein means derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active in vivo. A prodrug of a compound may be formed in a conventional manner with a functional group of the compounds such as with an amino, hydroxy or carboxy group when present. The prodrug derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutical carrier, i.e., adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and

dispensing agents, depending on the nature of the mode of administration and dosage forms. Ingredients listed in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA (1999) for example, may be used.

5 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable risk/benefit ratio.

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 The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and (iii) relieving the disease,
15 disorder or condition, i.e., causing regression of the disease, disorder and/or condition. The term "substituted" as used herein includes substitution at from one to the maximum number of possible binding sites on the core, e.p., organic radical, to which the substituent is bonded, e.g., mono-, di-, tri- or tetra- substituted, unless otherwise specifically stated.

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 The term "halo" as used herein means a halogen substituent selected from bromo, chloro, fluoro or iodo. The term "haloalkyl" means an alkyl group that is substituted with one or more halo substituents.

25 The term "alkyl" as used herein means acyclic, straight or branched chain alkyl substituents and includes, for example, methyl, ethyl, propyl, butyl, tert-butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl. Thus, C₁₋₆ alkyl refers to an alkyl group having from one to six carbon atoms. The term "lower alkyl" means an alkyl group having from one to six, preferably from one to four
30 carbon atoms. The term "alkylester" means an alkyl group additionally containing an ester group. Generally, a stated carbon number range, e.g., C₂₋₆ alkylester, includes all of the carbon atoms in the radical.

The term "alkenyl" as used herein means an alkyl radical containing at least one double bond, e.g., ethenyl (vinyl) and alkyl.

5 The term "alkoxy" as used herein means an alkyl group with the indicated number of carbon atoms attached to an oxygen atom. Alkoxy includes, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is referred to in the art as tert-butoxy. The term "alkoxycarbonyl" means an alkoxy group additionally containing a carbonyl group.

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 The term "cycloalkyl" as used herein means a cycloalkyl substituent containing the indicated number of carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and spiro cyclic groups such as spirocyclopropyl as spirocyclobutyl. The term "cycloalkoxy" as used herein
15 means a cycloalkyl group linked to an oxygen atom, such as, for example, cyclobutyloxy or cyclopropyloxy. The term "alkylcycloalkyl" means a cycloalkyl group linked to an alkyl group. The stated carbon number range includes the total number of carbons in the radical, unless otherwise specifically stated. This a C₄₋₁₀ alkylcycloalkyl may contain from 1-7 carbon atoms in the alkyl group and from 3-9
20 carbon atoms in the ring, e.g., cyclopropylmethyl or cyclohexylethyl.

 The term "aryl" as used herein means an aromatic moiety containing the indicated number of carbon atoms, such as, but not limited to phenyl, indanyl or naphthyl. For example, C₆₋₁₀ aryl refers to an aromatic moiety having from six to ten
25 carbon atoms which may be in the form of a monocyclic or bicyclic structure. The term "haloaryl" as used herein refers to an aryl mono, di or tri substituted with one or more halogen atoms. The terms "alkylaryl", "arylalkyl" and "arylalkyl" mean an aryl group substituted with one or more alkyl groups. Thus, a C₇₋₁₄ alkylaryl group may have from 1-8 carbon atoms in the alkyl group for a monocyclic aromatic and from 1-
30 4 carbon atoms in the alkyl group for a fused aromatic. The aryl radicals include those substituted with typical substituents known to those skilled in the art, e.g., halogen, hydroxy, carboxy, carbonyl, nitro, sulfo, amino, cyano, dialkylamino

haloalkyl, CF_3 , haloalkoxy, thioalkyl, alkanoyl, SH, alkylamino, alkylamide, dialkylamide, carboxyester, alkylsulfone, alkylsulfonamide and alkyl(alkoxy)amine. Examples of alkylaryl groups include benzyl, butylphenyl and 1-naphthylmethyl. The terms "alkylaryloxy" and "alkylarylester" mean alkylaryl groups containing an
5 oxygen atom and ester group, respectively.

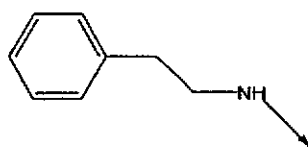
The term "carboxyalkyl" as used herein means a carboxyl group (COOH) linked through an alkyl group as defined above and includes, for example, butyric acid.

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The term "alkanoyl" as used herein means straight or branched 1-oxoalkyl radicals containing the indicated number of carbon atoms and includes, for example, formyl, acetyl, 1-oxopropyl (propionyl), 2-methyl-1-oxopropyl, 1-oxohexyl and the like.

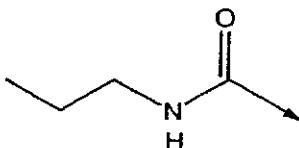
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The term "amino aralkyl" as used herein means an amino group substituted with an aralkyl group, such as the following amino aralkyl



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The term "alkylamide" as used herein means an amide mono-substituted with an alkyl, such as



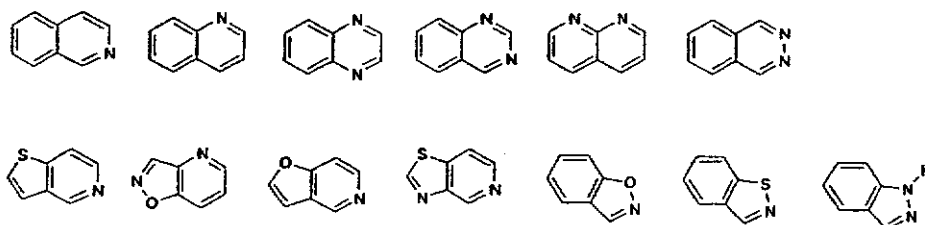
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The term "carboxyalkyl" as used herein means a carboxyl group (COOH) linked through a alkyl group as defined above and includes, for example, butyric acid.

The term "heterocycle", also referred to as "Het", as used herein means 7-12 membered bicyclic heterocycles and 5-7 membered monocyclic heterocycles.

Preferred bicyclic heterocycles are 7-12 membered fused bicyclic ring systems (both rings share an adjacent pair of atoms) containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur, wherein both rings of the heterocycle are fully unsaturated. The nitrogen and sulfur heteroatoms atoms may be optionally oxidized. The bicyclic heterocycle may contain the heteroatoms in one or both rings. The bicyclic heterocycle may also contain substituents on any of the ring carbon atoms, e.g., one to three substituents. Examples of suitable substituents include C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, C₃₋₇ cycloalkoxy, halo-C₁₋₆ alkyl, CF₃, mono-or di- halo-C₁₋₆ alkoxy, cyano, halo, thioalkyl, hydroxy, alkanoyl, NO₂, SH, , amino, C₁₋₆ alkylamino, di (C₁₋₆) alkylamino, di (C₁₋₆) alkylamide, carboxyl, (C₁₋₆) carboxyester, C₁₋₆ alkylsulfone, C₁₋₆ alkylsulfonamide, C₁₋₆ alkylsulfoxide, di (C₁₋₆) alkyl(alkoxy)amine, C₆₋₁₀ aryl, C₇₋₁₄ alkylaryl, and a 5-7 membered monocyclic heterocycle. When two substituents are attached to vicinal carbon atoms of the bicyclic heterocycle, they can join to form a ring, e.g., a five, six or seven membered ring system containing up to two heteroatoms selecting from oxygen and nitrogen. The bicyclic heterocycle may be attached to its pendant group, e.g. X in Formula I, at any atom in the ring and preferably carbon.

Examples of bicyclic heterocycles include, but are not limited to, the following ring systems:

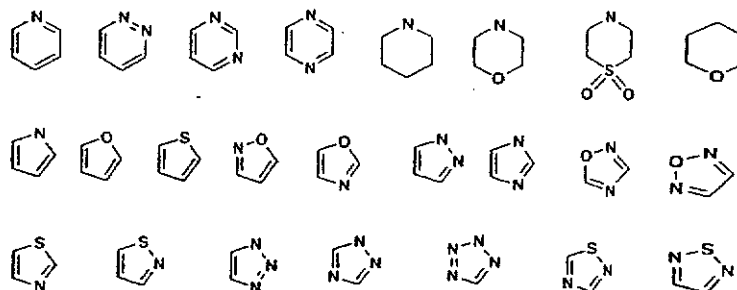


Preferred monocyclic heterocycles are 5-7membered saturated, partially saturated or fully unsaturated ring system (this latter subset herein referred to as

unsaturated heteroaromatic) containing in the ring from one to four heteroatoms selected from nitrogen, oxygen and sulfur, wherein the sulfur and nitrogen heteroatoms may be optionally oxidized. The monocyclic heterocycle may also contain substituents on any of the ring atoms, e.g., one to three substituents.

- 5 Examples of suitable substituents include C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, C₃₋₇ cycloalkoxy, halo-C₁₋₆ alkyl, CF₃, mono-or di- halo-C₁₋₆ alkoxy, cyano, halo, thioalkyl, hydroxy, alkanoyl, NO₂, SH, , amino, C₁₋₆ alkylamino, di (C₁₋₆) alkylamino, di (C₁₋₆) alkylamide, carboxyl, (C₁₋₆) carboxyester, C₁₋₆ alkylsulfone, C₁₋₆ alkylsulfoxide, C₁₋₆ alkylsulfonamide, di (C₁₋₆) alkyl(alkoxy)amine, C₆₋₁₀ aryl,
- 10 C₇₋₁₄ alkylaryl and 5-7 membered monocyclic heterocycle. The monocyclic heterocycle may be attached to its pendant group, e.g. X in Formula I, at any atom in the ring

Examples of monocyclic heterocycles include, but are not limited to, the following:



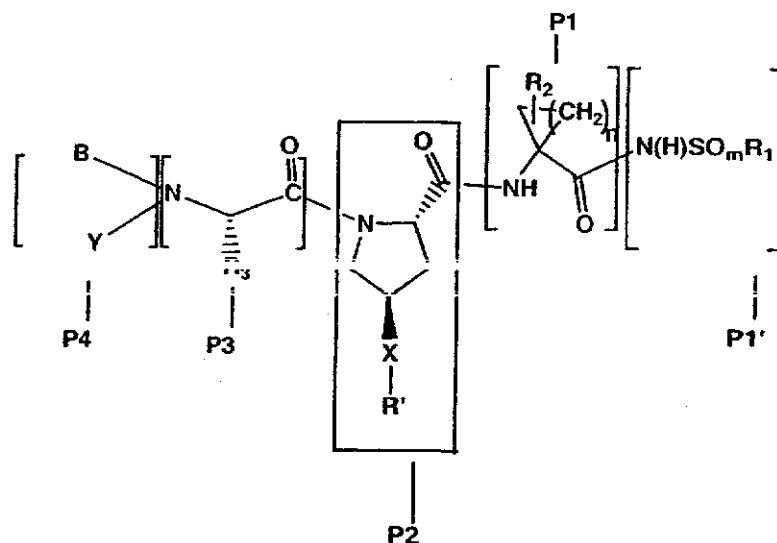
- Those skilled in the art will recognize that the heterocycles used in the compounds of the present invention should be stable. Generally, stable compounds are those which can be synthesized, isolated and formulated using techniques known the those skilled in the art without degradation of the compound.
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- Where used in naming compounds of the present invention, the designations "P1", P1, P2, P3 and P4", as used herein, map the relative positions of the amino acid residues of a protease inhibitor binding relative to the binding of the natural peptide cleavage substrate. Cleavage occurs in the natural substrate between P1 and P1'
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where the nonprime positions designate amino acids starting from the C-terminus end of the peptide natural cleavage site extending towards the N-terminus; whereas, the prime positions emanate from the N-terminus end of the cleavage site designation and extend towards the C-terminus. For example, P1' refers to the first position away from the right hand end of the C-terminus of the cleavage site (ie. N-terminus first position); whereas P1 starts the numbering from the left hand side of the C-terminus cleavage site, P2: second position from the C-terminus, etc.)(see Berger A. & Schechter I., Transactions of the Royal Society London series (1970), B257, 249-264].

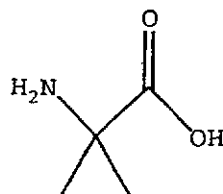
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Thus in the compounds of formula I, the "P1' to P4" portions of the molecule are indicated below:

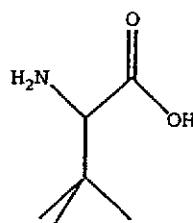


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As used herein the term "1-aminocyclopropyl-carboxylic acid" (Acca) refers to a compound of formula:



As used herein the term "*tert*-butylglycine" refers to a compound of the formula:

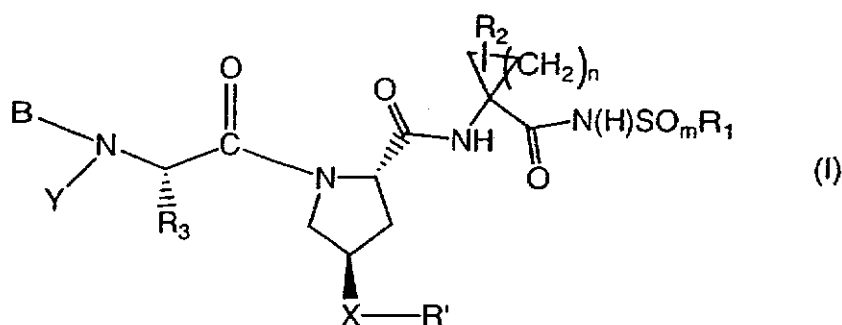


- 5 The term "residue" with reference to an amino acid or amino acid derivative means a radical derived from the corresponding α -amino acid by eliminating the hydroxyl of the carboxy group and one hydrogen of the α -amino acid group. For instance, the terms Gln, Ala, Gly, Ile, Arg, Asp, Phe, Ser, Leu, Cys, Asn, Sar and Tyr represent the "residues" of *L*-glutamine, *L*-alanine, glycine, *L*-isoleucine, *L*-arginine, 10 *L*-aspartic acid, *L*-phenylalanine, *L*-serine, *L*-leucine, *L*-cysteine, *L*-asparagine, sarcosine and *L*-tyrosine, respectively.

- The term "side chain" with reference to an amino acid or amino acid residue means a group attached to the α -carbon atom of the α -amino acid. For example, the 15 R-group side chain for glycine is hydrogen, for alanine it is methyl, for valine it is isopropyl. For the specific R-groups or side chains of the α -amino acids reference is made to A.L. Lehninger's text on Biochemistry (see chapter 4).

The compounds of the present invention have the structure of Formula I:

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wherein:

- (a) R_1 is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl;
- (b) m is 1 or 2;
- (c) n is 1 or 2;
- 5 (d) R_2 is H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl, each optionally substituted with halogen;
- (e) R_3 is C_{1-8} alkyl optionally substituted with halo, cyano, amino, C_{1-6} dialkylamino, C_{6-10} aryl, C_{7-14} alkylaryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl,

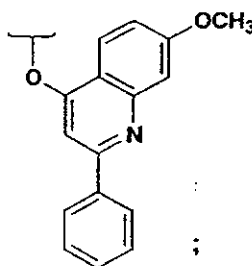
10 wherein the cycloalkyl or alkylcycloalkyl are optionally substituted with hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} alkoxy; or R_3 together with the carbon atom to which it is attached forms a C_{3-7} cycloalkyl group optionally substituted with C_{2-6} alkenyl;
- 15 (f) Y is H, phenyl substituted with nitro, pyridyl substituted with nitro, or C_{1-6} alkyl optionally substituted with cyano, OH or C_{3-7} cycloalkyl; provided that if R_4 or R_5 is H then Y is H;
- (g) B is H, C_{1-6} alkyl, $R_4-(C=O)-$, $R_4O(C=O)-$, $R_4-N(R_5)-C(=O)-$, $R_4-N(R_5)-C(=S)-$, R_4SO_2- , or $R_4-N(R_5)-SO_2-$;
- 20 (h) R_4 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, $-OC(O)C_{1-6}$ alkyl, C_{1-6} alkoxy, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido;

(ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl, each optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl,

25 amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl, halogen, nitro, hydroxy, amido, (lower alkyl) amido, or amino optionally substituted with C_{1-6} alkyl; (iv) Het; (v) bicyclo(1.1.1)pentane; or (vi) $-C(O)OC_{1-6}$ alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

30 (i) R_5 is H; C_{1-6} alkyl optionally substituted with 1-3 halogens; or C_{1-6} alkoxy provided R_4 is C_{1-10} alkyl;

- (j) X is O, S, SO, SO₂, OCH₂, CH₂O or NH;
- (k) R' is Het; or C₆₋₁₀ aryl or C₇₋₁₄ alkylaryl, optionally substituted with R^a; and
- (l) R^a is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, C₃₋₇ cycloalkoxy, halo-C₁₋₆ alkyl, CF₃, mono- or di- halo-C₁₋₆ alkoxy, cyano, halo, thioalkyl, hydroxy, alkanoyl, NO₂, SH, , amino, C₁₋₆ alkylamino, di (C₁₋₆) alkylamino, di (C₁₋₆) alkylamide, carboxyl, (C₁₋₆) carboxyester, C₁₋₆ alkylsulfone, C₁₋₆ alkylsulfonamide, di (C₁₋₆) alkyl(alkoxy)amine, C₆₋₁₀ aryl, C₇₋₁₄ alkylaryl, or a 5-7 membered monocyclic heterocycle;
- with the proviso that X- R' is not

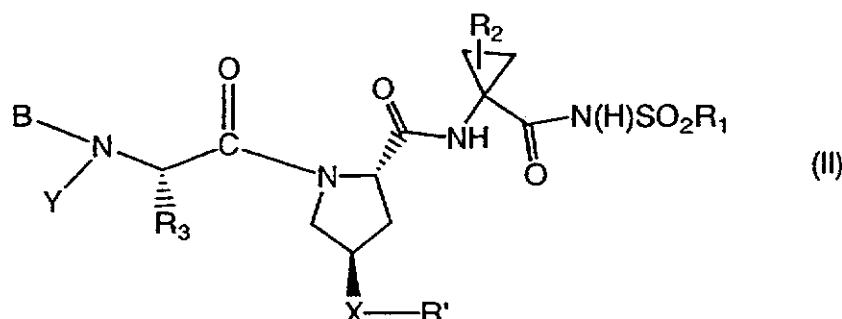


or a pharmaceutically acceptable salt, solvate or prodrug thereof.

- Preferably, R₂ is C₂₋₆ alkenyl; R₃ is C₁₋₈ alkyl optionally substituted with C₁₋₆ alkoxy, or C₃₋₇ cycloalkyl; Y is H; B is R₄-(C=O)-, R₄O(C=O)-, or R₄-N(R₅)-C(=O)-; R₄ is C₁₋₁₀ alkyl optionally substituted with 1-3 halogen or C₁₋₆ alkoxy; or C₃₋₇ cycloalkyl or C₄₋₁₀ alkylcycloalkyl; R₅ is H; X is O or NH; and R' is Het.

- The substituents from each grouping may be selected individually and combined in any combination which provides a stable compound in accordance with the present invention. Also, more than one substituent from each group may be substituted on the core group provided there are sufficient available binding sites. For example, each of the following R_a substituents, C₁₋₆ alkoxy, C₆ aryl and a 5-7 membered monocyclic heterocycle, may be substituted on a bicyclic heterocycle R'.

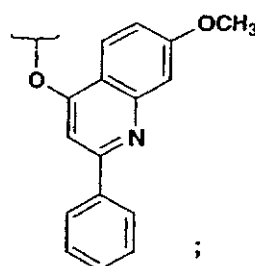
In a preferred aspect, the compounds of the present invention have the structure of Formula II:



wherein:

- 5 (a) R_1 is C_{3-7} cycloalkyl;
- (b) R_2 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl;
- (c) R_3 is C_{1-8} alkyl optionally substituted with C_6 aryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester, C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl;
- 10 (d) Y is H;
- (e) B is H, C_{1-6} alkyl, $R_4-(C=O)-$, $R_4O(C=O)-$, $R_4-N(R_5)-C(=O)-$, $R_4-N(R_5)-C(=S)-$, R_4SO_2- , or $R_4-N(R_5)-SO_2-$;
- (f) R_4 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, C_{1-6} alkoxy; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl; or (iii) C_{6-10} aryl or C_{7-16} arylalkyl; each optionally substituted with C_{1-6} alkyl or halogen;
- 15 (g) R_5 is H or C_{1-6} alkyl optionally substituted with 1-3 halogens;
- (h) X is O or NH;
- (i) R' is Het; or C_{6-10} aryl optionally substituted with R^a ; and
- 20 (j) R^a is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo, amino, C_6 aryl, or a 5-7 membered monocyclic heterocycle;

with the proviso that X_a-R' is not

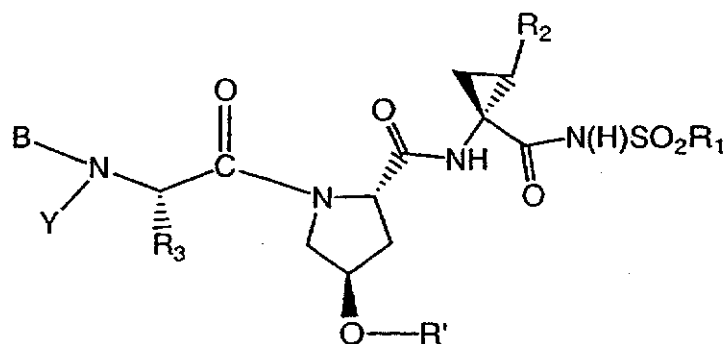


or a pharmaceutically acceptable salt, solvate or prodrug thereof.

- 5 In one preferred aspect of the invention, R' is a bicyclic heterocycle. Preferably, the bicyclic heterocycle contains 1 or 2 nitrogen atoms and optionally a sulfur atom or an oxygen atom in the ring. Preferably, the heterocycle is substituted with at least one of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₆ aryl, and a 5-7 membered monocyclic heterocycle. More preferably, R' is a bicyclic heterocycle containing 1
10 nitrogen atom and substituted with methoxy and at least one of a C₆ aryl and a 5-7 membered monocyclic heterocycle.

- In another preferred aspect of the invention, R' is a monocyclic heterocycle. Preferably, the heterocycle contains 1 or 2 nitrogen atoms and optionally a sulfur
15 atom or an oxygen atom in the ring. Preferably, the heterocycle is substituted with at least one of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₆₋₁₀ aryl, C₇₋₁₄ alkylaryl, or a 5-7 membered monocyclic heterocycle. More preferably, R' is a monocyclic heterocycle containing
20 1 or 2 nitrogen atoms and substituted with methoxy and at least one of a C₆ aryl and a 5-7 membered monocyclic heterocycle.

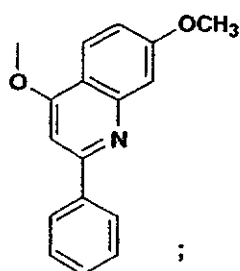
 In a more preferred aspect of the invention, the compounds have the structure of Formula III



(III)

wherein:

- (a) R_1 is C_{3-7} cycloalkyl;
- (b) R_2 is C_{2-6} alkenyl;
- (c) R_3 is C_{1-8} alkyl;
- (d) Y is H;
- (e) B is $R_4O(C=O)-$, or $R_4-N(R_5)-C(=O)-$;
- (f) R_4 is C_{1-10} alkyl;
- (g) R_5 is H;
- (h) R' is a bicyclic heterocycle optionally substituted with R^a ; and
- (i) R^a is C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_6 aryl, or a 5-7 membered monocyclic heterocycle; with the proviso that O- R' is not



15

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

Preferably, R_1 is cyclopropyl or cyclobutyl, R_2 is vinyl, R_3 is t-butyl, R_4 is t-butyl and R' is quinoline or isoquinoline optionally substituted with R^a . Preferably, R^a includes at least one of C_{1-6} alkoxy, C_6 aryl and a 5-7 membered monocyclic

20

heterocycle. In a preferred aspect of the invention, R₁ is cyclopropyl, R₂ is vinyl, R₃ is t-butyl, R₄ is t-butyl, and R' is isoquinoline substituted with C₁₋₆ alkoxy and at least one of C₆ aryl or a 5-7 membered monocyclic heterocycle.

5 The compounds of the present invention, by virtue of their basic moiety, can form salts by the addition of a pharmaceutically acceptable acid. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic acid, including but not limited to hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, or organic acid such as *p*-toluenesulfonic, methanesulfonic,
10 acetic, benzoic, citric, malonic, fumaric, maleic, oxalic, succinic, sulfamic, or tartaric. Thus, examples of such pharmaceutically acceptable salts include chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate.

15 Salts of an amine group may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

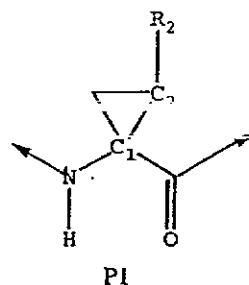
 Compounds of the present invention, which are substituted with an acidic
20 group, may exist as salts formed through base addition. Such base addition salts include those derived from inorganic bases which include, for example, alkali metal salts (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts and ammonium salts. In addition, suitable base addition salts include salts of physiologically acceptable organic bases such as
25 trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bishydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, ethylenediamine,
30 ornithine, choline, N,N'-benzylphenethylamine, chloroprocaine, diethanolamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane and tetramethylammonium hydroxide and basic amino acids such as lysine, arginine and

N-methylglutamine. These salts may be prepared by methods known to those skilled in the art.

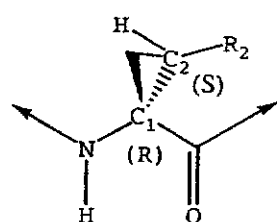
5 Certain compounds of the present invention, and their salts, may also exist in the form of solvates with water, for example hydrates, or with organic solvents such as methanol, ethanol or acetonitrile to form, respectively, a methanolate, ethanolate or acetonitrilate. The present invention includes each solvate and mixtures thereof.

10 In addition, compounds of the present invention, or a salt or solvate thereof, may exhibit polymorphism. The present invention also encompasses any such polymorphic form.

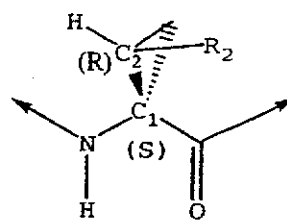
The compounds of the present invention also contain two or more chiral centers. For example, the compounds may include P1 cyclopropyl element of
15 formula



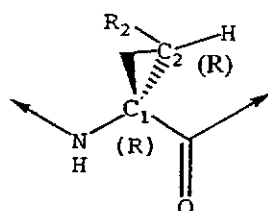
wherein C₁ and C₂ each represent an asymmetric carbon atom at positions 1 and 2 of the cyclopropyl ring. Notwithstanding other possible asymmetric centers at other
20 segments of the compounds, the presence of these two asymmetric centers means that the compounds can exist as racemic mixtures of diastereomers, such as the diastereomers wherein R₂ is configured either syn to the amide or syn to the carbonyl as shown below.



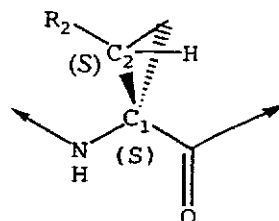
(1R, 2S)

 R_2 is syn to carbonyl

(1S, 2R)

 R_2 is syn to carbonyl

(1R, 2R)

 R_2 is syn to amide

(1S, 2S)

 R_2 is syn to amide

The present invention includes both enantiomers and mixtures of enantiomers such as racemic mixtures.

5

The enantiomers may be resolved by methods known to those skilled in the art, for example, by formation of diastereoisomeric salts which may be separated by crystallization, gas-liquid or liquid chromatography, selective reaction of one enantiomer with an enantiomer-specific reagent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by a separation technique, then an additional step is required to form the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

15

The compounds of the present invention may be in the form of a prodrug. Simple aliphatic or aromatic esters derived from, when present, acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it

is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or (alkoxycarbonyl)oxy)alkyl esters.

5 Certain compounds of the present invention may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of these compounds and mixtures thereof.

10

Certain compounds of the present invention may exist in zwitterionic form and the present invention includes each zwitterionic form of these compounds and mixtures thereof.

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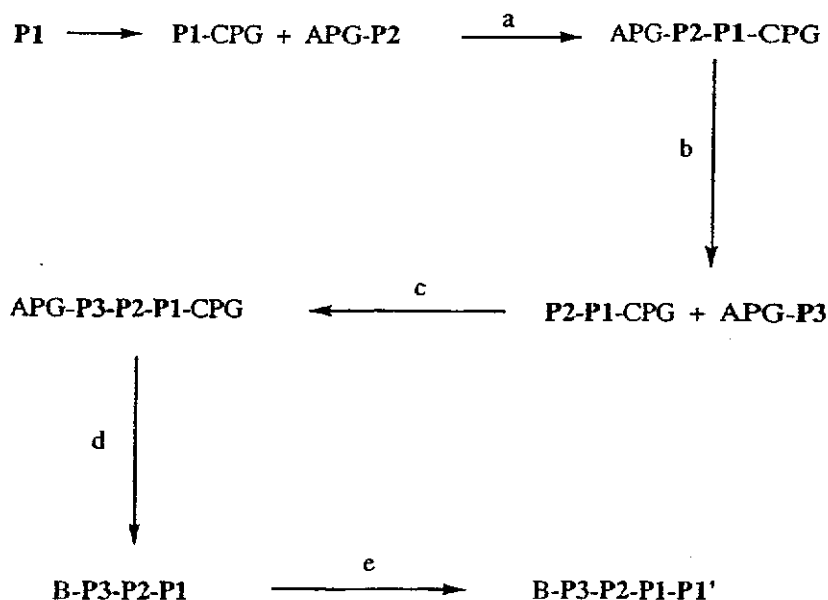
The starting materials useful to synthesize the compounds of the present invention are known to those skilled in the art and can be readily manufactured or are commercially available.

20 The compounds of the present invention can be manufactured by methods known to those skilled in the art, see e.p., US Patent No. 6,323,180 and US Patent Appl. 20020111313 A1. The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claimed invention. It will be recognized that it may be preferred or necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present invention. The details concerning the use of protecting groups in accordance with the present invention are known to those skilled in the art.

25

30 The compounds of the present invention may, for example, be synthesized according to a general process as illustrated in Scheme I (wherein CPG is a carboxyl protecting group and APG is an amino protecting group):

Scheme I



Briefly, the P1, P2, and P3 can be linked by well known peptide coupling techniques. The P1, P2, and P3 groups may be linked together in any order as long as the final compound corresponds to peptides of the invention. For example, P3 can be linked to P2-P1; or P1 linked to P3-P2.

Generally, peptides are elongated by deprotecting the α -amino group of the N-terminal residue and coupling the unprotected carboxyl group of the next suitably N-protected amino acid through a peptide linkage using the methods described. This deprotection and coupling procedure is repeated until the desired sequence is obtained. This coupling can be performed with the constituent amino acids in stepwise fashion, as depicted in Scheme I.

Coupling between two amino acids, an amino acid and a peptide, or two peptide fragments can be carried out using standard coupling procedures such as the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide) method, active ester (*p*-nitrophenyl ester, *N*-hydroxysuccinic imido ester) method, Woodward reagent K-method,

carbonyldiimidazole method, phosphorus reagents or oxidation-reduction methods. Some of these methods (especially the carbodiimide method) can be enhanced by adding 1-hydroxybenzotriazole or 4-DMAP. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

5

More explicitly, the coupling step involves the dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of a coupling agent to form a linking amide bond. Descriptions of such coupling agents are found in general textbooks on peptide chemistry, for example, M.

- 10 Bodanszky, "Peptide Chemistry", 2nd rev ed., Springer-Verlag, Berlin, Germany, (1993). Examples of suitable coupling agents are N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-[(3-dimethylamino)propyl]carbodiimide. A practical and useful coupling agent is the commercially available
- 15 (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxybenzotriazole or 4-DMAP. Another practical and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate. Still another practical and useful coupling agent is commercially available
- 20 O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, acetonitrile or dimethylformamide. An excess of a tertiary amine, e.g. diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine or 4-DMAP is added to maintain the reaction mixture at a pH of about 8. The reaction temperature
- 25 usually ranges between 0 °C and 50 °C and the reaction time usually ranges between 15 min and 24 h.

The functional groups of the constituent amino acids generally must be protected during the coupling reactions to avoid formation of undesired bonds.

- 30 Protecting groups that can be used are listed, for example, in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The

Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α -amino group of each amino acid to be coupled to the growing peptide chain must be protected (APG). Any protecting group known in the art can be used. Examples of such groups include: 1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and *p*-toluenesulfonyl; 2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted benzyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate groups such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl groups such as triphenylmethyl and benzyl; 6)trialkylsilyl such as trimethylsilyl; and 7) thiol containing groups such as phenylthiocarbonyl and dithiasuccinoyl.

The preferred α -amino protecting group is either Boc or Fmoc. Many amino acid derivatives suitably protected for peptide synthesis are commercially available. The α -amino protecting group of the newly added amino acid residue is cleaved prior to the coupling of the next amino acid. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethylformamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0°C and room temperature (rt or RT) usually 20-22°C.

Any of the amino acids having side chain functionalities must be protected during the preparation of the peptide using any of the above-described groups. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups for these side chain functionalities depend upon the amino acid and presence of other protecting groups in the peptide. The selection of such protecting groups is

important in that the group must not be removed during the deprotection and coupling of the α -amino group.

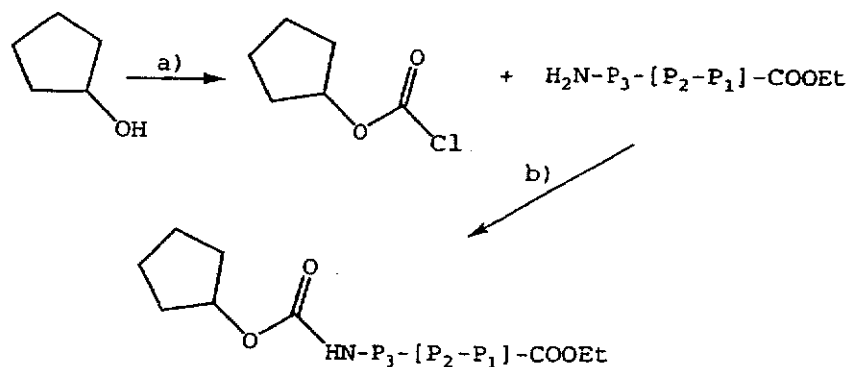
For example, when Boc is used as the α -amino protecting group, the following side chain protecting groups are suitable: *p*-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chain of amino acids such as Lys and Arg; acetamidomethyl, benzyl (Bn), or *tert*-butylsulfonyl moieties can be used to protect the sulfide containing side chain of cysteine; benzyl (Bn) ethers can be used to protect the hydroxy containing side chains of serine, threonine or hydroxyproline; and benzyl esters can be used to protect the carboxy containing side chains of aspartic acid and glutamic acid.

When Fmoc is chosen for the α -amine protection, usually *tert*-butyl based protecting groups are acceptable. For instance, Boc can be used for lysine and arginine, *tert*-butyl ether for serine, threonine and hydroxyproline, and *tert*-butyl ester for aspartic acid and glutamic acid. Triphenylmethyl (Trityl) moiety can be used to protect the sulfide containing side chain of cysteine.

Once the elongation of the peptide is completed all of the protecting groups are removed. When a liquid phase synthesis is used, the protecting groups are removed in whatever manner is dictated by the choice of protecting groups. These procedures are well known to those skilled in the art.

Further, the following guidance may be followed in the preparation of compounds of the present invention. For example, to form a compound where $R_4-C(O)-$, $R_4-S(O)_2-$, a protected P3 or the whole peptide or a peptide segment is coupled to an appropriate acyl chloride or sulfonyl chloride respectively, that is either commercially available or for which the synthesis is well known in the art. In preparing a compound where $R_4O-C(O)-$, a protected P3 or the whole peptide or a peptide segment is coupled to an appropriate chloroformate that is either commercially available or for which the synthesis is well known in the art. For Boc-derivatives $(Boc)_2O$ is used.

For example:



Cyclopentanol is treated with phosgene to furnish the corresponding
5 chloroformate.

The chloroformate is treated with the desired NH_2 -tripeptide in the presence of a base such as triethylamine to afford the cyclopentylcarbamate.

10 In preparing a compound where $\text{R}_4\text{-N(R}_5\text{)-C(O)-}$, or $\text{R}_4\text{-NH-C(S)-}$, a protected P3 or the whole peptide or a peptide segment is treated with phosgene followed by amine as described in SynLett. Feb 1995; (2); 142-144 or is reacted with the commercially available isocyanate and a suitable base such as triethylamine.

15 In preparing a compound where $\text{R}_4\text{-N(R}_5\text{)-S(O}_2\text{)}$, a protected P3 or the whole peptide or a peptide segment is treated with either a freshly prepared or commercially available sulfamyl chloride followed by amine as described in patent Ger. Offen.(1998), 84 pp. DE 19802350 or WO 98/32748.

20 The α -carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and t-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl
25 esters.

The resulting α -carboxylic acid (resulting from cleavage by mild acid, mild base treatment or mild reductive means) is coupled with a $R_1SO_2NH_2$ [prepared by treatment of R_1SO_2Cl in ammonia saturated tetrahydrofuran solution] in the presence of peptide coupling agent such as CDI or EDAC in the presence of a base such as
5 4-dimethylaminopyridine (4-DMAP) and/or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to incorporate the $P1'$ moiety, effectively assembling the tripeptide $P1'-P1-P2-P3-APG$. Typically, in this process, 1-5 equivalents of $P1'$ coupling agents are used.

10 Furthermore, if the $P3$ protecting group APG is removed and replaced with a B moiety by the methods described above, and the resulting α -carboxylic acid resulting from cleavage (resulting from cleavage by mild acid, mild base treatment or mild reductive means) is coupled with a $R_1SO_2NH_2$ [prepared by treatment of R_1SO_2Cl in ammonia saturated tetrahydrofuran solution or alternative methods
15 described herein] in the presence of peptide coupling agent such as CDI or EDAC in the presence of a base such as 4-dimethylaminopyridine (4-DMAP) and/or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to incorporate the $P1'$ moiety, the tripeptide $P1'-P1-P2-P3-B$ is prepared. Typically, in this process, 1-5 equivalents of $P1'$ coupling agents are used.

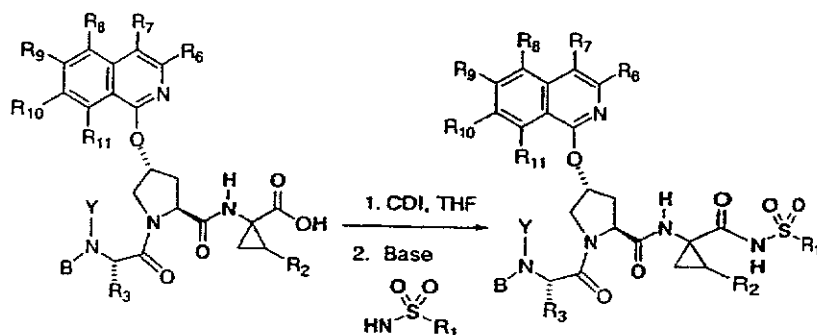
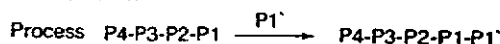
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Compounds of the present invention can be prepared by many methods including those described in the examples, below, and as described in U.S. Patent No. 6,323,180 and U.S. Patent Application No. 10/001,850 filed on November 20, 2001. The teachings of U.S. Patent No. 6,323,180 and U.S. Patent Application No.
25 10/001,850 are incorporated herein, in their entirety, by reference.

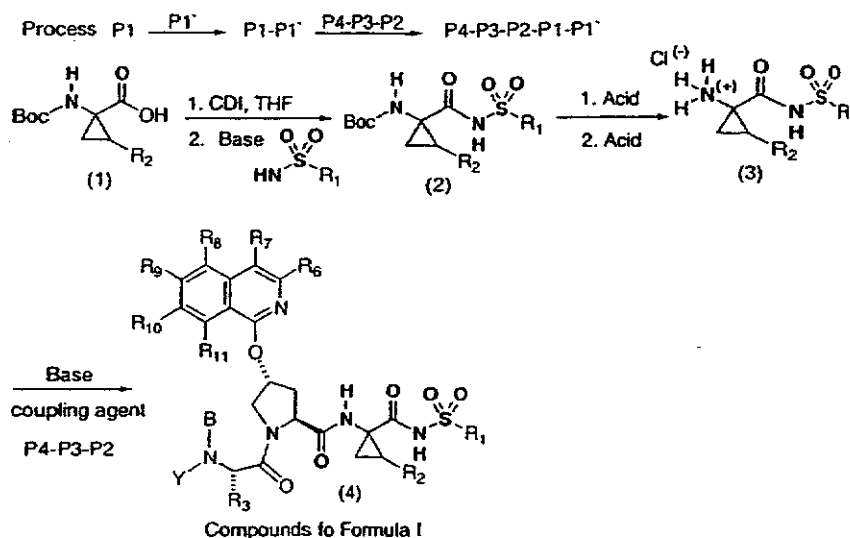
Scheme II further shows the general process wherein compounds of Formula I are constructed by the coupling of tripeptide carboxylic acid intermediate (1) with a $P1'$ sulfonamide. (It should be noted that the groups $R_6, R_7, R_8, R_9, R_{10}, R_{11}$ as shown
30 below represent substituents of the heterocyclic system.) Said coupling reaction requires treatment of carboxylic acid (1) with a coupling reagent such as carbonyl diimidazole in a solvent such as THF, which can be heated to reflux, followed by the

addition of the formed derivative of (1), to the P1' sulfonamide, in a solvent such as THF or methylene chloride in the presence of a base such as DBU.

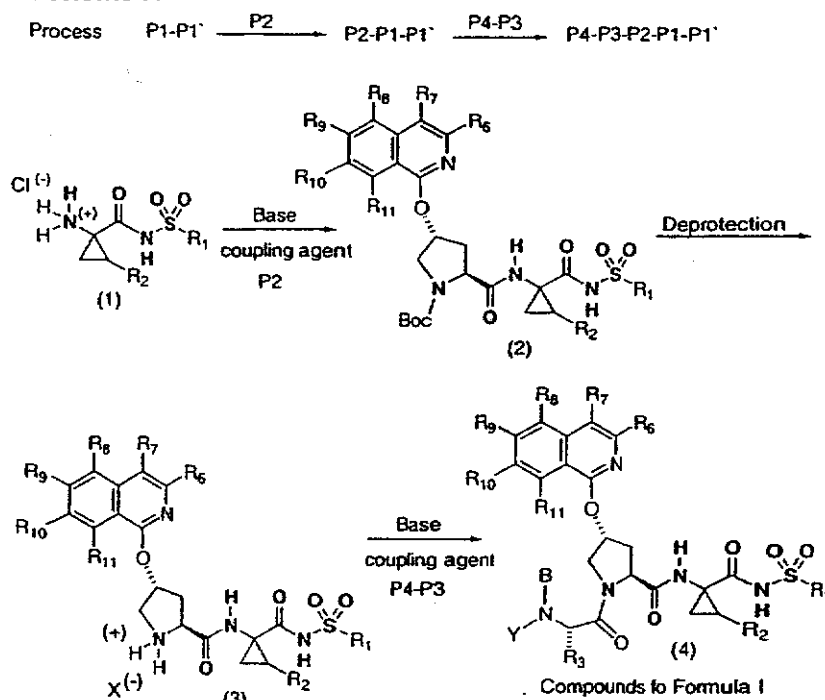
Scheme II



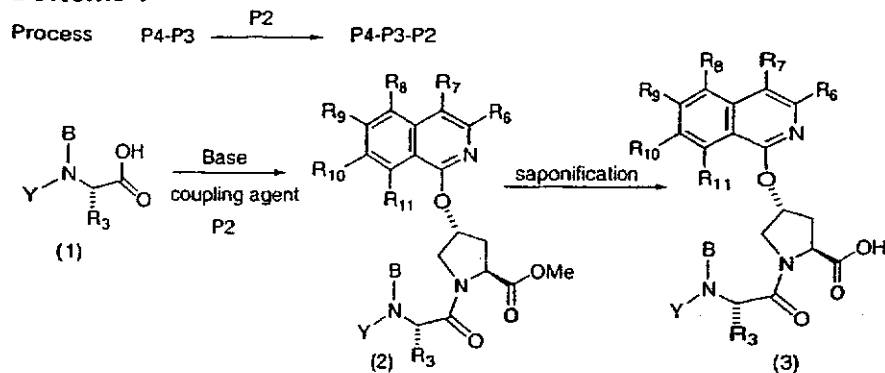
- An alternative process for the construction of compounds of Formula I is shown in Scheme III. Therein the P1' sulfonamide element is coupled to the P1 element using the process employed in Scheme 1. The resulting P1-P1' moiety can then be deprotected at it's amino terminus. In this general example a Boc protecting group is employed but one skilled in the art would recognize that a number of suitable amino protecting groups could be employed in this process. Said Boc protecting group can be removed using acid such as trifluoroacetic acid in a solvent such as dichloroethane to provide the deprotected amine as the TFA salt. Said TFA amine salt can be directly employed in the subsequent coupling reaction or as an alternative the TFA amine salt can be first converted to the HCl amine salt, and this HCl amine salt is used in said coupling reaction as shown in Scheme III. The coupling of said HCl amine salt (3) with the carboxyl terminus a P4-P3-P2 intermediate can be achieved using coupling reagents, such as HATU, in solvents such as dichloromethane to provide compounds of Formula I (4).

Scheme III

- An alternative process for the construction of compounds of Formula I is shown in Scheme IV. Herein the hydrochloride salt of the P1-P1' terminal amine (1) is coupled to the free carboxyl group of the P2 element using coupling agents such as
- 5 PyBOP, in the presence of a base such as diisopropyl amine, and in a solvent such as methylene chloride. The resulting P2-P1-P1' intermediate can be converted to compounds of Formula I in a two step process wherein the first step is deprotection of the P2 amine terminus using an acid such as TFA in a solvent such as methylene chloride. The resulting trifluoroacetic acid salt can be coupled with the carboxyl
- 10 terminus of the P4-P3 element using standard coupling agents such as PyBop in the presence of base such as diisopropyl amine, and using solvents such methylene chloride to provide compounds of Formula I (4).

Scheme IV

The P4-P3-P2 intermediate utilized in the above schemes can be constructed as previously described with a further description of this process shown in general Scheme V. Therein the free carboxyl terminus of the P4-P3 intermediate (1), can be coupled to the amino terminus of the P2 element to provide the P4-P3-P2 dipeptide (2). The carboxyl terminus of the P4-P3-P2 intermediate can be deprotected by saponification of the ester group to provide P4-P3-P2 as the free carboxylic acid (3). Intermediates like (3) can be converted to compounds of Formula I using the methods described herein.

Scheme V

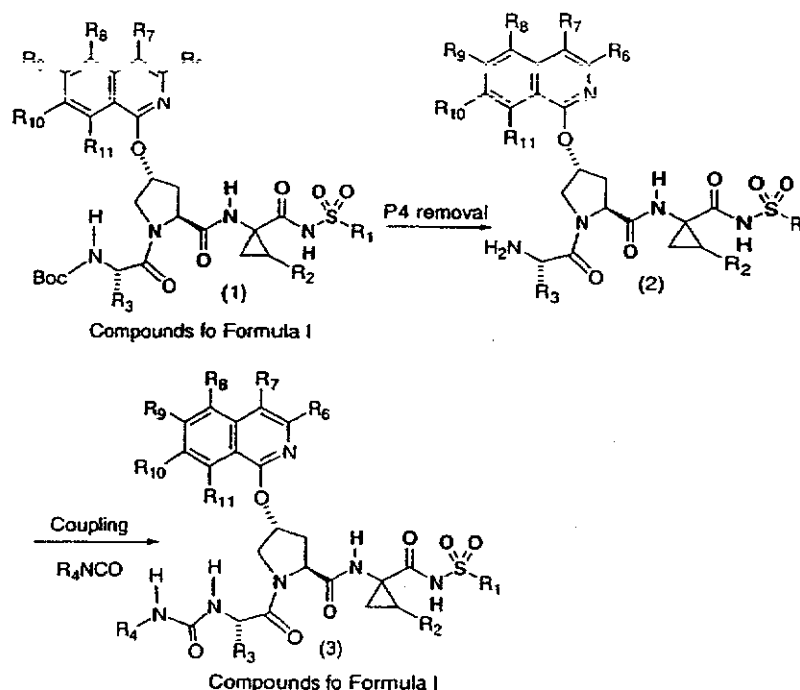
Compounds of Formula I can also be converted into other compounds of Formula I as described herein. An example of such a process is shown in Scheme VI wherein a compound of Formula I (1) which bears a Boc group at the P4 position is converted in a compound of Formula I (3) wherein said compound bears a urea group at the P4 position.

5 The conversion of (1) to (3) can be carried out in a two step process the first of which is the conversion of (1) to amine (2) by treatment of (1) with an acid such as TFA in a solvent such as methylene chloride. The resulting amine TFA salt can be treated with an isocyanate in the presence of one equivalent of base to provide a compound of Formula I (3) wherein the P3 moiety is capped with a urea. As

10 previously noted one skilled in the art will recognize that intermediate (2) can be used as starting materials for the preparation of compounds of Formula I wherein the P3 group is capped with an amide or a sulfonamide, or thiourea, or a sulfamide. The construction of said compounds of Formula I can be achieved using standard conditions for the formation of said P4 functionalities from amines.

Scheme VI

Process $P4-P3-P2-P1-P1' \longrightarrow P3-P2-P1-P1' \longrightarrow P4-P3-P2-P1-P1'$

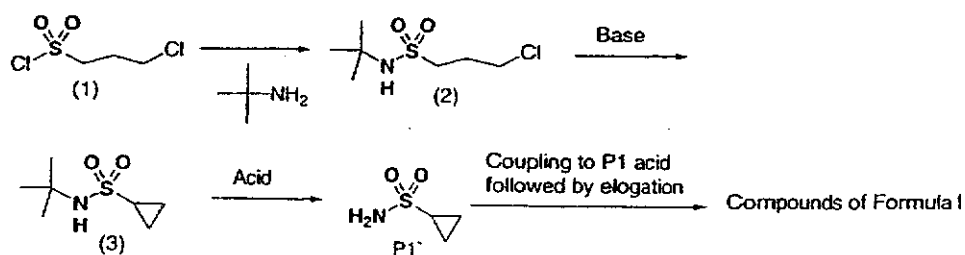


15

In the construction of compounds of Formula I, the P1' terminus is incorporated into the molecules using one of the general processes outlined above and described in more detail below. In some examples the P1' elements, that is the cycloalkyl- or

alkyl sulfonamides are commercially available or can be prepared from the corresponding alkyl- or cycloalkyl-sulfonyl chloride by treating said sulfonyl chloride with ammonia. Alternatively, these sulfonamides can be synthesized using the general process outline in Scheme VII. Therein commercially available 3-chloro-
 5 propylsulfonyl chloride (1) is converted to a suitable protected sulfonamide as for example by treatment with tert-butyl amine. The sulfonamide obtained (2) is then converted to the corresponding cycloalkylsulfonamide by treatment with two equivalents of a base such as butyl lithium in a solvent such as THF at low temperature. The resulting cycloalkylsulfonamide can be deprotected by treatment
 10 with an acid to provide the desired unprotected cycloalkylsulfoamide.

Scheme VII



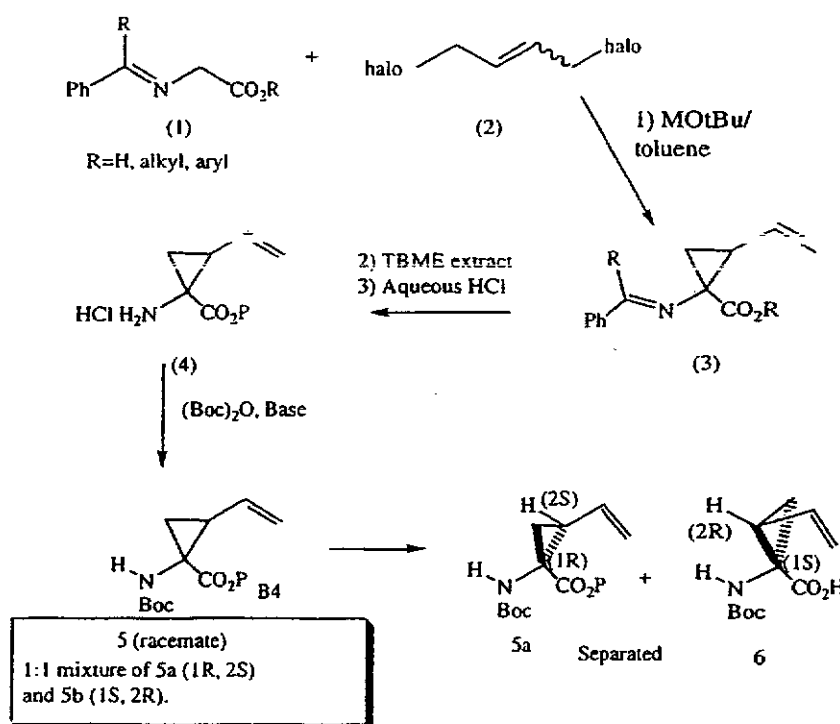
The P1 elements utilized in generating compounds of Formula I are in some cases commercially available, but are otherwise synthesized using the methods described
 15 herein and subsequently incorporated into compounds of Formula I using the methods described herein. The substituted P1 cyclopropylamino acids can be synthesized following the general process outline in Scheme VIII.

Treatment of commercially available or easily synthesized imine (1) with 1,4-
 20 dihalobutene (2) in presence of a base produces, provides the resulting imine (3). Acid hydrolysis of 3 then provides 4, which has an allyl substituent syn to the carboxyl group as a major product. The amine moiety of 4 can be protected using a Boc group to provide the fully protected amino acid 5. This intermediate is a racemate which can be resolved by an enzymatic process wherein the ester moiety of 5 is
 25 cleaved by a protease to provide the corresponding carboxylic acid. Without being bound to any particular theory, it is believed that this reaction is selective in that one of the enantiomers undergoes the reaction at a much greater rate than its mirror image

providing for a kinetic resolution of the intermediate racemate. In the examples cited herein, the more preferred stereoisomer for integration into compounds of Formula I is 5a which houses the (1R, 2S) stereochemistry. In the presence of the enzyme, this enantiomer does not undergo ester cleavage and thereby this enantiomer 5a is recovered from the reaction mixture. However, the less preferred enantiomer, 5b with houses the (1S, 2R) stereochemistry undergoes ester cleavage, i.e., hydrolysis, to provide the free acid 6. Upon completion of this reaction, the ester 5a can be separated from the acid product 6 by routine methods such as, for example, aqueous extraction methods or chromatography.

10

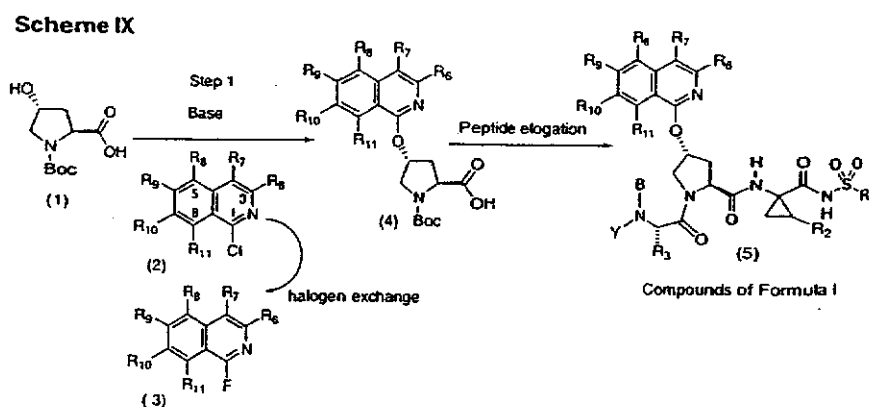
Scheme VIII



Procedures for making P2 intermediates and compounds of Formula I are shown in the Schemes below. It should be noted that in many cases reactions are depicted for only one position of an intermediate. However, it is to be understood that such reactions could be used to impart modifications to other positions within this

15

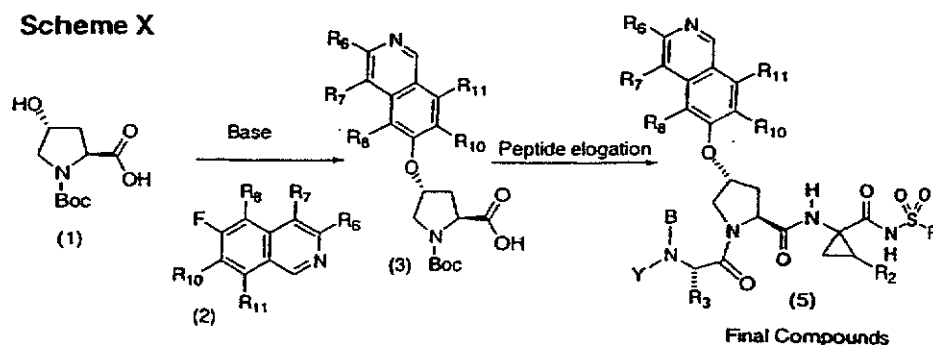
intermediate. Moreover, said intermediates, reaction conditions and methods given in the specific examples are broadly applicable to compounds with other substitution patterns. The general Schemes outlined below are followed with examples herein. Both general and specific examples are non-limiting, as for example the isoquinoline nucleus is shown as part of the general scheme, Scheme IX, however, this pathway represents a viable process for the construction of alternate heterocycle substituents as replacements for the isoquinoline element, such as quinolines, or pyridines.



Scheme IX shows the coupling of an N-protected C4-hydroxyproline moiety with a heterocycle to form intermediate (4) and the subsequent modification of said intermediate (4) to a compound of Formula I by the process of peptide elongation as described herein. It should be noted that in the first step, that is the coupling of the C4-hydroxy proline group with the heteroaryl element, a base is employed. One skilled in the art would recognized that this coupling can be done using bases such as potassium tert-butoxide, or sodium hydride, in solvent such as DMF or DMSO or THF. This coupling to the isoquinoline ring system occurs at the C1 position (numbering for isoquinoline ring system shown in intermediate 2 of Scheme IX) and is directed by the chloro group which is displaced in this process. It should be noted that the alternative leaving groups can be utilized at this position such as a fluoro as shown in the Scheme. Said fluoro intermediates (3) are available from the corresponding chloro compound using literature procedures described herein. It should also be noted that the position of the leaving group (chloro or fluoro) in a given ring system can vary as shown in Scheme X, wherein the leaving group (fluoro

in this example) is in the C6 position of the isoquinoline ring system of intermediate (2).

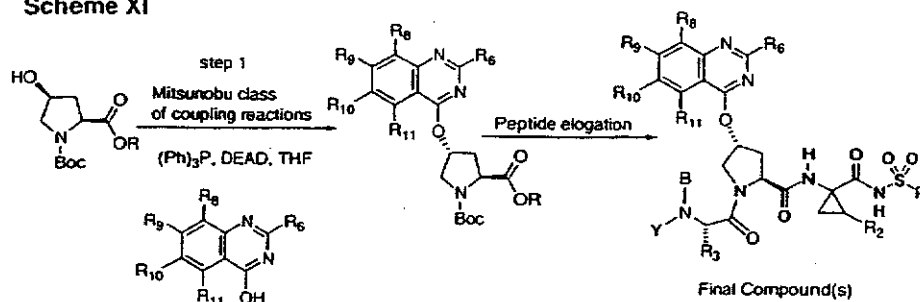
Scheme X



It should be further noted that the position of the ring heteroatom(s) in intermediates like (2) of Scheme IX and Scheme X is also variable, as defined by the term heterocycle described herein. In Scheme X intermediate (2) can be coupled to a C4-hydroxy proline derivative to provide the P2 element (3). This C6-substituted isoquinoline derivative can be converted to compounds of Formula I using the methods described herein.

- 10 An alternative to the method described above for the coupling of the C4-hydroxyproline to aromatics and heteroaromatics, is provided in the Mitsunobu reaction as depicted in

Scheme XI

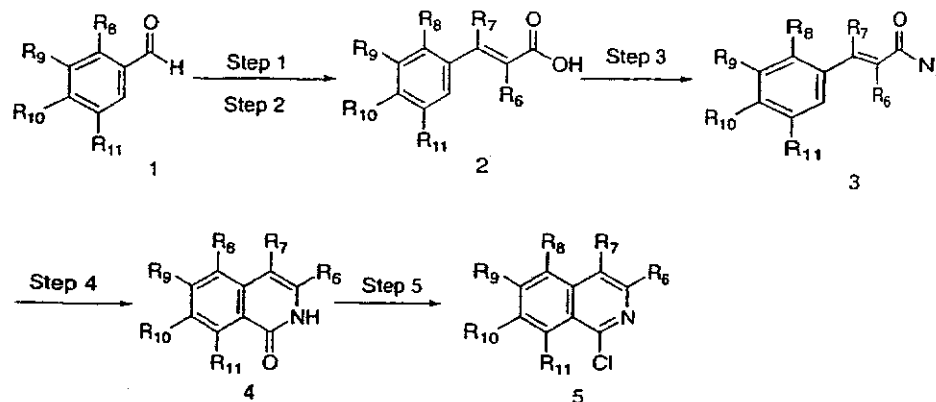


- 15 step 1 of Scheme XI. In this general reaction Scheme a C4-hydroxy proline derivative is coupled to a quinazoline ring system. This reaction makes use of reagents such as triphenylphosphine and DEAD (diethylazodicarboxylate) in aprotic solvents such as THF or dioxane and can be used for the formation of aryl and heteroaryl ethers. Note that in the course of this coupling reaction the stereochemistry of the C4 chiral center in the C4-hydroxyproline derivative is

inverted and thereby it is necessary to use the C4-hydroxyproline derivative housing the (S) stereochemistry at the C4 position as starting material. (as shown in Scheme XI). It should be noted that numerous modifications and improvements of the Mitsunobu reaction have been described in the literature, the teachings of which are incorporated herein.

In a subset of examples herein, isoquinolines are incorporated into the final compounds and specifically into the P2 region of said compounds. One skilled in the art would recognize that a number of general methods are available for the synthesis of isoquinolines. Moreover, said isoquinolines generated by these methods can be readily incorporated into final compounds of Formula I using the processes described herein. One general methodology for the synthesis of isoquinolines is shown in Scheme XII, wherein cinnamic acid derivatives, shown in general form as structure (2) are

Scheme XII



Reference: N. Briet et al, Tetrahedron, 2002, 5761

converted to 1-chloroisoquinolines in a four step process. Said chloroisoquinolines can be subsequently used in coupling reactions to C4-hydroxyproline derivatives as described herein. The conversion of cinnamic acids to chloroquinolines begins with the treatment of cinnamic acid with an alkylchloroformate in the presence of a base. The resulting anhydride is then treated with sodium azide which results in the formation of an acylazide (3) as shown in the Scheme. Alternate methods are available for the formation of acylazides from carboxylic acids as for example said carboxylic acid can be treated with diphenylphosphorylazide (DPPA) in an aprotic

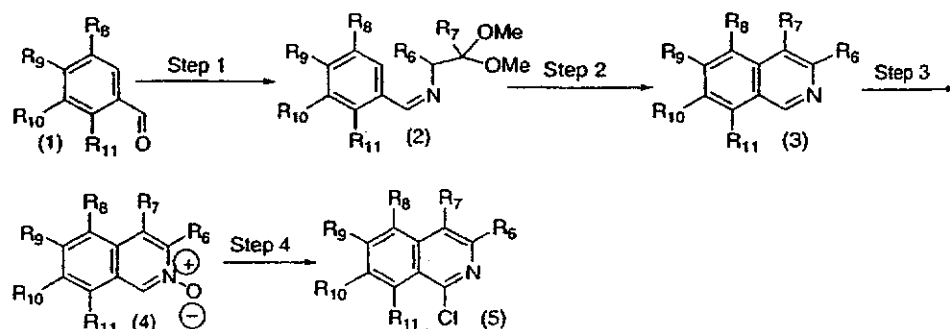
solvent such as methylene chloride in the presence of a base. In the next step of the reaction sequence the acylazide (3) is converted to the corresponding isoquinolone (4) as shown in the Scheme. In the event the acylazide is heated to a temperature of approximately 190 degrees celcius in a high boiling solvent such a diphenylmethane.

- 5 This reaction is general and provides moderate to good yields of substituted isoquinolone from the corresponding cinnamic acid derivatives. It should noted that said cinnamic acid derivatives are available commercially or can be obtained from the corresponding benzaldehyde (1) derivative by direct condensation with malonic acid or derivatives thereof and also by employing a Wittig reaction. The intermediate
- 10 isoquinolones (4) of Scheme XII can be converted to the corresponding 1-chloroisoquinoline by treatment with phosphorous oxychloride. This reaction is general and can be applied to any of the isoquinolones, quinolones or additional heterocycles as shown herein to covert a hydroxy substituent to the corresponding
- 15 chloro compound when said hydroxy is in conjugation with a nitrogen atom in said heterocyclic ring systems.

An alternative method for the synthesis of the isoquinoline ring system is the Pomeranz-Fritsh procedure. This general method is outlined in Scheme XIII. The process begins with the conversion of a benzaldehyde derivative (1) to a

20 functionalized imine (2). Said imine is then converted to the isoquinoline ring system by treatment with acid at elevated

Scheme XIII



Pomeranz-Fritsch synthesis

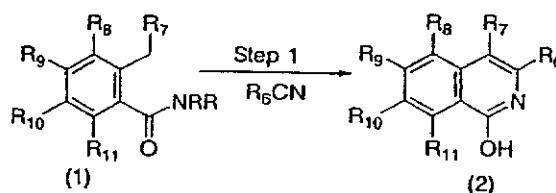
K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, *Heterocycles* 42(1) 1996, 415-422

temperature. This isoquinoline synthesis of Scheme XIII is general, and it should be noted that this process is particularly useful in procuring isoquinoline intermediates

that are substituted at the C8 position (note: in intermediate (3) of Scheme XIII the C8 position of the isoquinoline ring is substituted with substituent R_{11}). The intermediate isoquinolines (3) can be converted to the corresponding 1-chloroquinolines (5) in a two step process as shown. The first step in this sequence is the formation of the isoquinoline N-oxide(4) by treatment of isoquinoline (3) with meta-chloroperbenzoic acid in an aprotic solvent such as dichloromethane. Intermediate (4) can be converted to the corresponding 1-chloroquinoline by treatment with phosphorous oxychloride in refluxing chloroform. Note this two step process is general and can be employed to procure chloroisoquinolines and chloroquinolines from the corresponding isoquinolines and quinolines respectively.

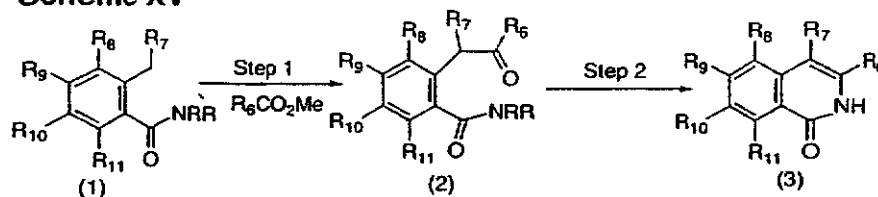
Another method for the synthesis of the isoquinoline ring system is shown in Scheme XIV. In this process an ortho-alkylbenzamide derivative (1) is treated with a strong

Scheme XIV

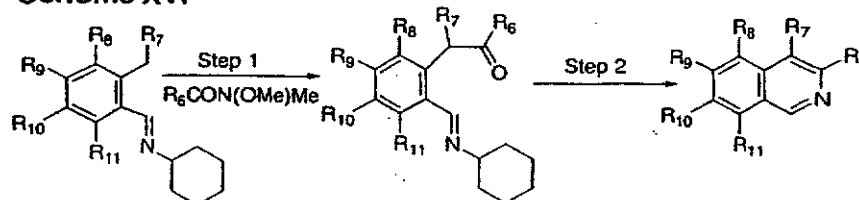


base such as tert-butyl lithium in a solvent such as THF at low temperature. To this reaction mixture is then added a nitrile derivative, which undergoes an addition reaction with the anion derived from deprotonation of (1), resulting in the formation of (2). This reaction is general and can be used for the formation of substituted isoquinolines. Intermediate (2) of Scheme XIV can be converted to the corresponding 1-chloroquinoline by the methods described herein.

An additional method for the synthesis of isoquinolines is shown in Scheme XV. The deprotonation of intermediate (1) using tert-butyl lithium is described above. In the present method however, said intermediate anion is trapped by an ester, resulting in the formation of intermediate (2) as shown below. In a subsequent reaction ketone (2) is condensed with ammonium acetate at elevated temperature providing for the formation of quinolone (3). This reaction is general and can be applied for the construction of substituted isoquinolones which can then be converted to the corresponding 1-chloroisoquinolines as described herein.

Scheme XV

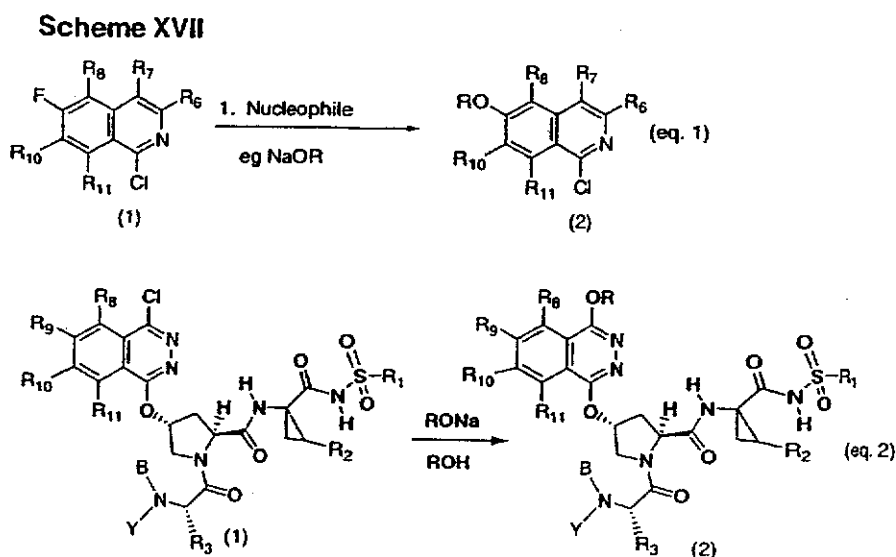
Yet an additional method for the construction of isoquinolines is found in Scheme XVI. In the first step of this process an ortho-alkylarylimine derivatives such as (1) is subjected to deprotonation conditions (sec-butyl lithium, THF) and the resulting anion is quenched by

Scheme XVI

L. Flippin, J. Muchowski, JOC, 1993, 2631-2632

the addition of an activated carboxylic acid derivative such as a Weinreb amide. The resulting keto imine (2) can be converted to the corresponding isoquinoline by condensation with ammonium acetate at elevated temperatures. This method is general and can be used for the synthesis of substituted isoquinolines. Said isoquinolines can be converted to the corresponding 1-chloroquinoline by the methods described herein.

The heterocycles described herein, and which are incorporated into the compounds of Formula I can be further functionalized. It is obvious to one skilled in the art that additional functionalization of said heterocycles can be done either before or after incorporation of these functionalities into compounds of Formula I. The following Schemes illustrate this point. For example Scheme XVII shows the conversion of a 1-chloro-

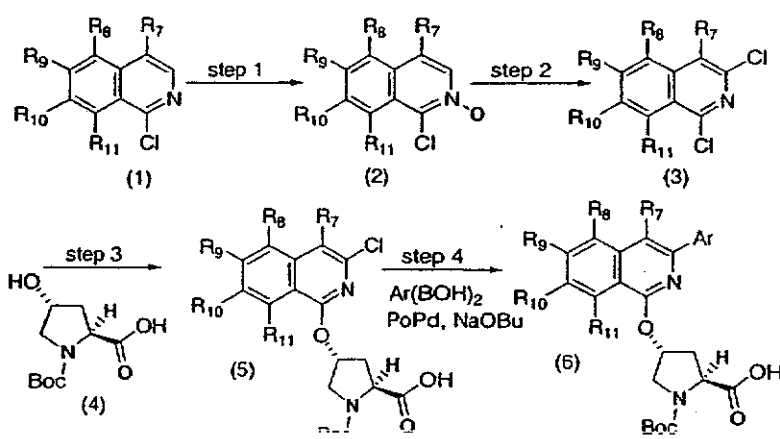


- 6-fluoro-isoquinoline to the corresponding 1-chloro-6-alkoxy-isoquinoline species, by treatment of (1) of (eq.1) with a sodium or potassium alkoxide species in the alcohol solvent from which the alkoxide is derived at room temperature. In some cases it may be necessary to heat the reaction to drive it to completion. Said chloroquinoline can be incorporated into a compound of Formula I using the art described herein. Modifications of a P2 heterocyclic element can also be done after it's incorporation into compounds of Formula I as shown in (eq.2) of Scheme VXII. Specifically compounds such as (1) in (eq. 2) which contain a leaving group in the phthalazine nucleus can be displaced by a nucleophile such as an alkoxide in solvents such as the corresponding alcohol from which the alkoxide is derived. These reaction scan be conducted at room temperature but in some cases it may be necessary to heat the reaction to drive it to completion.
- Scheme XVIII provides a general example for the modification of heterocycles as defined herein by employing palladium mediated coupling reactions. Said couplings can be employed to functionalize a heterocycle at each position of the ring system providing said ring is suitably activated or functionalized, as for example with a chloride as shown in the Scheme. This sequence begins with 1-chloroisoquinoline (1) which upon treatment with metachloroperbenzoic acid can be converted to the corresponding N-oxide (2). Said intermediate (2) can be converted to the corresponding 1,3-dichloroisoquinoline (3) by treatment with phosphorous

oxychloride in refluxing chloroform. Intermediate (3) can be coupled with N-Boc-4-hydroxyproline by the methods described herein to provide intermediate (5) as shown in the Scheme. Intermediate (5) can undergo a Suzuki coupling with an aryl boronic acid, in the presence of a palladium reagent and base, and in a solvent such as THF or toluene or DMF to provide the C3-arylisquinoline intermediate (6).

Heteroarylboronic acids can also be employed in this Pd mediated coupling process to provide C3-heteroarylisquinolines. Intermediate (6) can be converted into final compounds of Formula I by the methods described herein.

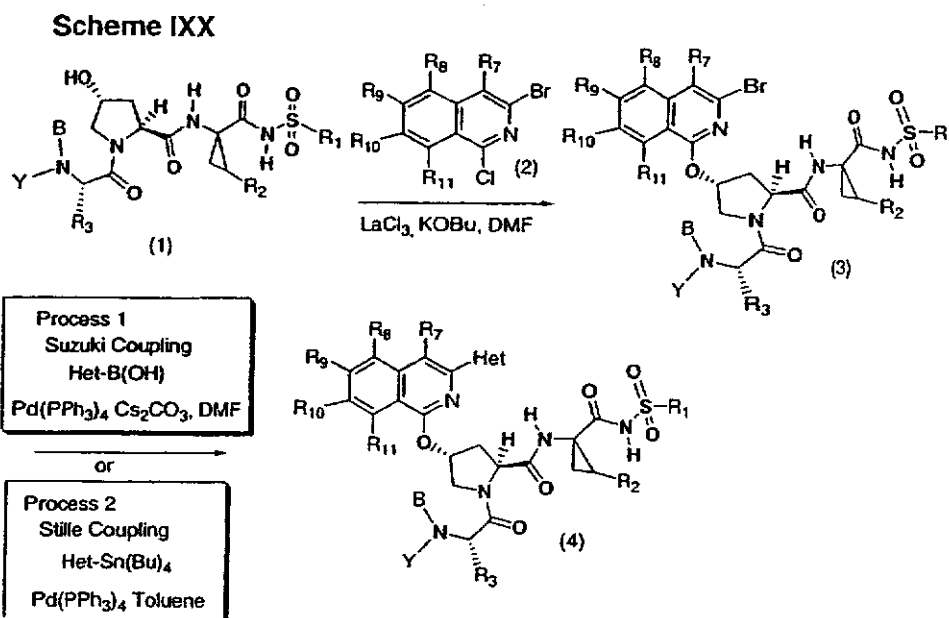
Scheme XVIII



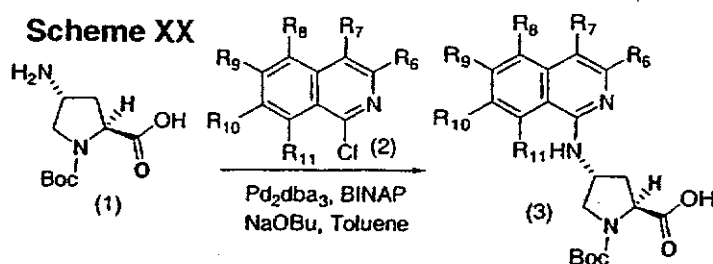
10.

Palladium mediated couplings of heteroaryl systems with aryl or heteroaryl elements can also be employed at a later synthetic stage in the construction of compounds of Formula I as shown in Scheme IXX. Therein tripeptide acylsulfonamide

intermediate (1) is coupled to a 1-chloro-3-bromoisoquinoline (2) using the previously described process of alkoxide displacement of an heteroarylhalo moiety to provide intermediate (3). The coupling of (1) and (2) is most efficient in the presence of a catalyst such as lanthanum chloride as described herein. The isoquinoline ring system of intermediate (3) can be further functionalized by employing either Suzuki couplings (Process 1: subjecting (3) to heteroaryl or aryl boronic acids in the presence of a palladium catalyst such as palladium tetra(triphenylphosphine) and a base such as cesium carbonate in solvents such as DMF) or Stille couplings (Process 2: subjecting (3) to heteraryl or aryl tin derivatives in the presence of palladium catalyst such as palladium tetra(triphenylphosphine) in solvents such as toluene).



Palladium reactions can also be employed to couple C4-amino proline elements with functionalized heterocycles. Scheme XX shows intermediate (1) coupling with a functionalized isoquinoline in the presence of a palladium catalyst and a base in a solvent such as toluene. Intermediates like (3) can be converted to compounds of Formula I using the methods described herein.

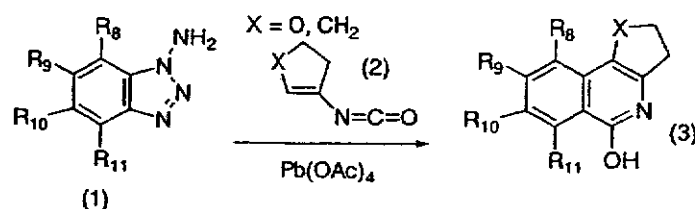


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The construction of functionalized isoquinoline ring systems is also possible employing [4+2] cycloaddition reactions. For example (Scheme XXI) the use of vinyl isocyanates (1) in cycloaddition reactions with benzyne precursors (2) provides functionalized isoquinolones (3). Said isoquinolones can be incorporated into compounds of Formula I using the methods described herein.

15

Scheme XXI



The present invention also provides compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier. Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier, with a pharmaceutically acceptable carrier, e.g., excipient, or vehicle diluent.

The active ingredient, i.e., compound, in such compositions typically comprises from 0.1 weight percent to 99.9 percent by weight of the composition, and often comprises from about 5 to 95 weight percent.

The pharmaceutical compositions of this invention may be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection are preferred. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

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

suitable dispersing or wetting agents and suspending agents. The details concerning the preparation of such compounds are known to those skilled in the art.

When orally administered, the pharmaceutical compositions of this invention
5 may be administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn
10 starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable carriers for the above noted compositions can be found in
15 standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", 19th ed., Mack Publishing Company, Easton, Penn., 1995. Further details concerning the design and preparation of suitable delivery forms of the pharmaceutical compositions of the invention are known to those skilled in the art.

20 Dosage levels of between about 0.01 and about 1000 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.5 and about 250 mg/kg body weight per day of the compounds of the invention are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to
25 about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

30 As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific

compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. Generally, treatment is initiated with small dosages substantially less than
5 the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

10

When the compositions of this invention comprise a combination of a compound of the invention and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80%
15 of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts, solvates or prodrugs are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered in vivo to mammals, such as man, to
20 inhibit HCV NS3 protease or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of other targets in the HCV life cycle such as helicase,
25 polymerase, metalloprotease, or internal ribosome entry site; or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

30 Accordingly, another aspect of this invention provides methods of inhibiting HVC NS3 protease activity in patients by administering a compound of the present

invention or a pharmaceutically acceptable salt or solvate thereof, wherein the substituents are as defined above.

In a preferred embodiment, these methods are useful in decreasing HCV NS3
5 protease activity in the patient. If the pharmaceutical composition comprises only a
compound of this invention as the active component, such methods may additionally
comprise the step of administering to said patient an agent selected from an
immunomodulatory agent, an antiviral agent, a HCV protease inhibitor, or an
inhibitor of other targets in the HCV life cycle such as, for example, helicase,
10 polymerase, or metalloprotease. Such additional agent may be administered to the
patient prior to, concurrently with, or following the administration of the compounds
of this invention.

In an alternate preferred aspect, these methods are useful for inhibiting viral
15 replication in a patient. Such methods can be useful in treating or preventing HCV
disease.

The compounds of the invention may also be used as laboratory reagents.
Compounds may be instrumental in providing research tools for designing of viral
20 replication assays, validation of animal assay systems and structural biology studies
to further enhance knowledge of the HCV disease mechanisms.

The compounds of this invention may also be used to treat or prevent viral
contamination of materials and therefore reduce the risk of viral infection of
25 laboratory or medical personnel or patients who come in contact with such materials,
e.g., blood, tissue, surgical instruments and garments, laboratory instruments and
garments, and blood collection or transfusion apparatuses and materials.

EXAMPLES

The specific examples that follow illustrate the syntheses of the compounds of the instant invention, and are not to be construed as limiting the invention in sphere or scope. The methods may be adapted to variations in order to produce compounds embraced by this invention but not specifically disclosed. Further, variations of the methods to produce the same compounds in somewhat different manner will also be evident to one skilled in the art.

10 Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400 or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash
15 chromatography technique (W.C. Still et al., J. Org. Chem., (1978), 43, 2923).

 All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector and Mass Spectrometry (MS) data were determined with a Micromass Platform for LC in
20 electrospray mode (ES+).

 Unless otherwise noted, in the following examples each compound was analyzed by LC/MS, using one of seven methodologies, having the following conditions.

25 Columns: (Method A) - YMC ODS S7 C18 3.0x50 mm
 (Method B) - YMC ODS-A S7 C18 3.0x50 mm
 (Method C) - YMC S7 C18 3.0x50 mm
 (Method D) - YMC Xterra ODS S7 3.0x50 mm
 (Method E) - YMC Xterra ODS S7 3.0x50 mm
30 (Method F) - YMC ODS-A S7 C18 3.0x50 mm
 (Method G) - YMC C18 S5 4.6x50 mm]

Gradient: 100% Solvent A/0% Solvent B to

0% Solvent A/100% Solvent B

Gradient time: 2 min. (A, B, D, F, G); 8 min. (C, E)

Hold time: 1 min. (A, B, D, F, G); 2 min. (C, E)

Flow rate: 5 mL/min

5 Detector Wavelength: 220 nm

Solvent A: 10% MeOH / 90% H₂O / 0.1% TFA

Solvent B: 10% H₂O / 90% MeOH / 0.1% TFA.

10 The abbreviations used in the present application, including particularly in the illustrative examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

	rt	room temperature
	Boc	tert-butyloxycarbonyl
15	DMSO	dimethylsulfoxide
	EtOAc	ethyl acetate
	t-BuOK	potassium t-butoxide
	Et ₂ O	diethyl ether
	TBME	tert-butylmethyl ether
20	THF	tetrahydrofuran
	CDI	carbonyldiimidazole
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	TFA	trifluoroacetic acid
	NMM	N-methylmorpholine
25	HATU	O-7-azabenzotriazol-1-yl
	HBTU	O-({1H-benzotriazol-1-yl)-N,N,N',N'- tetramethyluronium hexafluorophosphate
	HOBT	N-hydroxybenzotriazole
	PyBrop	bromo-bis-pyrrolidine-phosphonium
30		hexafluorophosphate
	DMF	dimethylformamide
	MeOH	methanol

EDTA	ethylenediaminetetraacetic acid
HRMS	high resolution mass spectrometry
DMAP	4-dimethylaminopyridine
DIPEA	diisopropylethylamine
5 DCM	dichloromethane
DCE	dichloroethane

The compounds and chemical intermediates of the present invention, described in the following examples, were prepared according to the following methods. It should be noted that the following exemplification section is presented in sections. The sections are titled Section A through K. Example numbers and compound numbers are not contiguous throughout the entire Examples portion of the application and hence, each section indicates a "break" in the numbering. The numbering within each section is generally contiguous. Section L describes the biological activity of the compounds. Section M describes a subset of additional compounds that could be made using the methods described herein.

Section A:

Preparation of Intermediates:

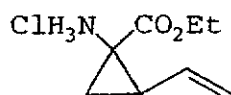
20 Preparation of P1 Intermediates:

The P1 intermediates described in this section can be used to prepare compounds of Formula I by the methods described herein.

I P1 elements:

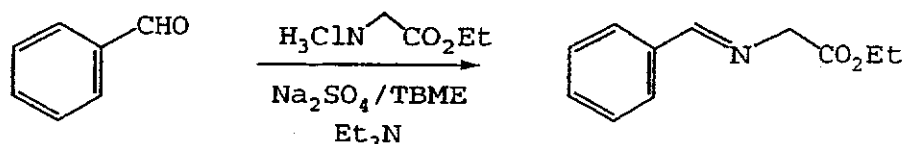
25

1. Preparation of racemic (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester



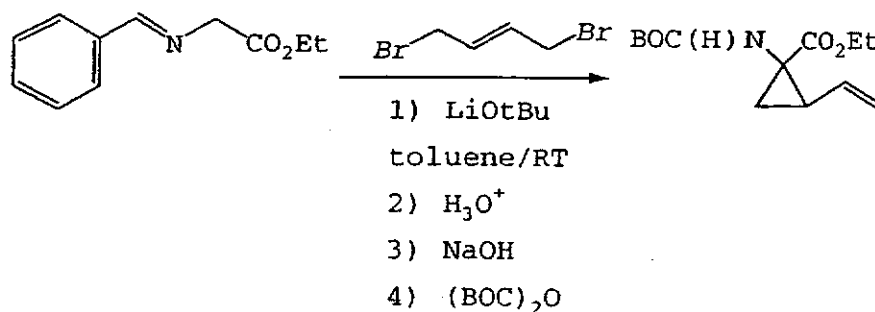
Method A

Step 1



5
 Glycine ethyl ester hydrochloride (303.8 g, 2.16 mole) was suspended in *tert*-butylmethyl ether (1.6 L). Benzaldehyde (231 g, 2.16 mole) and anhydrous sodium sulfate (154.6 g, 1.09 mole) were added and the mixture cooled to 0 °C using an ice-water bath. Triethylamine (455 mL, 3.26 mole) was added dropwise over 30 min and
 10 the mixture stirred for 48 h at rt. The reaction was then quenched by addition of ice-cold water (1 L) and the organic layer was separated. The aqueous phase was extracted with *tert*-butylmethyl ether (0.5 L) and the combined organic phases washed with a mixture of saturated aqueous NaHCO₃ (1 L) and brine (1 L). The solution was dried over MgSO₄, concentrated in vacuo to afford 392.4 g of the *N*-
 15 benzyl imine product as a thick yellow oil that was used directly in the next step. ¹H NMR (CDCl₃, 300 MHz) δ 1.32 (t, *J*=7.1 Hz, 3H), 4.24 (q, *J*=7.1 Hz, 2H), 4.41 (d, *J*=1.1 Hz, 2H), 7.39-7.47 (m, 3H), 7.78-7.81 (m, 2H), 8.31 (s, 1H).

Step 2

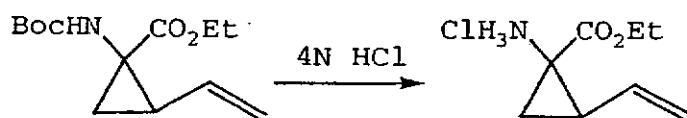


20

To a suspension of lithium *tert*-butoxide (84.06 g, 1.05 mol) in dry toluene (1.2 L), was added dropwise a mixture of the *N*-benzyl imine of glycine ethyl ester (100.4 g, 0.526 mol) and *trans*-1,4-dibromo-2-butene (107.0 g, 0.500 mol) in dry

toluene (0.6 L) over 60 min. After completion of the addition, the deep red mixture was quenched by addition of water (1 L) and *tert*-butylmethyl ether (TBME, 1 L). The aqueous phase was separated and extracted a second time with TBME (1 L). The organic phases were combined, 1 N HCl (1 L) was added and the mixture stirred at room temperature for 2 h. The organic phase was separated and extracted with water (0.8 L). The aqueous phases were then combined, saturated with salt (700 g), TBME (1 L) was added and the mixture cooled to 0 °C. The stirred mixture was then basified to pH 14 by the dropwise addition of 10 N NaOH, the organic layer separated, and the aqueous phase extracted with TBME (2 x 500 mL). The combined organic extracts were dried (MgSO₄) and concentrated to a volume of 1L. To this solution of free amine, was added BOC₂O or di-*tert*-butyldicarbonate (131.0 g, 0.6 mol) and the mixture stirred 4 days at rt. Additional di-*tert*-butyldicarbonate (50 g, 0.23 mol) was added to the reaction, the mixture refluxed for 3 h, and was then allowed cool to room temperature overnight. The reaction mixture was dried over MgSO₄ and concentrated in vacuo to afford 80 g of crude material. This residue was purified by flash chromatography (2.5 Kg of SiO₂, eluted with 1% to 2% MeOH/CH₂Cl₂) to afford 57 g (53%) of racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as a yellow oil which solidified while sitting in the refrigerator: ¹H NMR (CDCl₃, 300 MHz) δ 1.26 (t, *J*=7.1 Hz, 3H), 1.46 (s, 9H), 1.43-1.49 (m, 1H), 1.76-1.82 (br m, 1H), 2.14 (q, *J*=8.6 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 5.12 (dd *J*=10.3, 1.7 Hz, 1H), 5.25 (br s, 1H), 5.29 (dd, *J*=17.6, 1.7 Hz, 1H), 5.77 (ddd, *J*=17.6, 10.3, 8.9 Hz, 1H); MS *m/z* 254.16 (M-1)

Step 3 Preparation of Racemic (1*R*,2*S*)/(1*S*,2*R*) 1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride



N-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (9.39 g, 36.8 mmol) was dissolved in 4 N HCl/dioxane (90 ml, 360 mmol) and

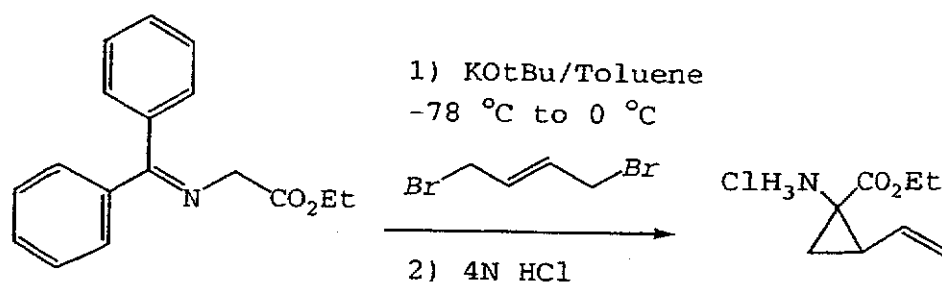
was stirred for 2 h at rt. The reaction mixture was concentrated to supply (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride in quantitative yield (7 g, 100%). ¹H NMR (methanol-*d*₄) δ 1.32 (t, *J*=7.1, 3H), 1.72 (dd, *J*=10.2, 6.6 Hz, 1H), 1.81 (dd, *J*=8.3, 6.6 Hz, 1H), 2.38 (q, *J*=8.3 Hz, 1H), 4.26-4.34 (m, 2H), 5.24 (dd, 10.3, 1.3 Hz, 1H) 5.40 (d, *J*=17.2, 1H), 5.69-5.81 (m, 1H).

10

15

Alternate route for the preparation of Racemic N-Boc-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride

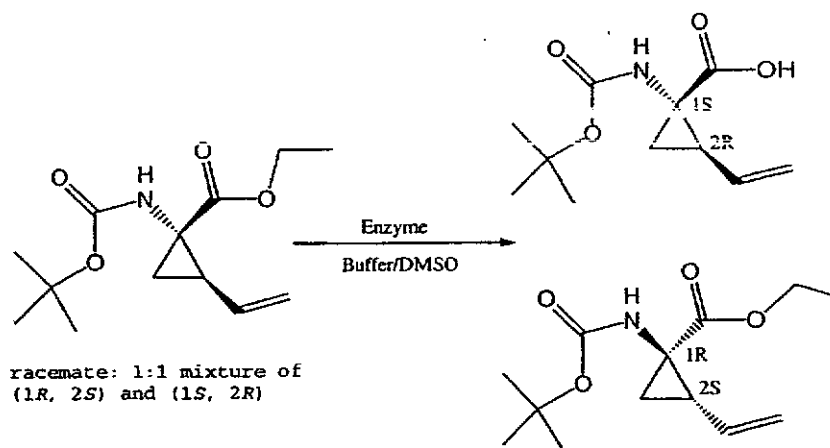
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To a solution of potassium *tert*-butoxide (11.55 g, 102.9 mmol) in THF (450 mL) at -78 °C was added the commercially available *N,N*-dibenzyl imine of glycine ethyl ester (25.0 g, 93.53 mmol) in THF (112 mL). The reaction mixture was warmed to 0 °C, stirred for 40 min, and was then cooled back to -78 °C. To this solution was added *trans*-1,4-dibromo-2-butene (20.0 g, 93.50 mmol), the mixture stirred for 1 h at 0 °C and was cooled back to -78 °C. Potassium *tert*-butoxide (11.55

g, 102.9 mmol) was added, the mixture immediately warmed to 0°C, and was stirred one more hour before concentrating in vacuo. The crude product was taken up in Et₂O (530 mL), 1N aq. HCl solution (106 mL, 106 mmol) added and the resulting biphasic mixture stirred for 3.5 h at rt. The layers were separated and the aqueous
 5 layer was washed with Et₂O (2x) and basified with a saturated aq. NaHCO₃ solution. The desired amine was extracted with Et₂O (3x) and the combined organic extract was washed with brine, dried (MgSO₄), and concentrated in vacuo to obtain the free amine. This material was treated with a 4N HCl solution in dioxane (100 mL, 400
 10 mmol) and concentrated to afford (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride as a brown semisolid (5.3 g, 34% yield) identical to the material obtained from procedure A, except for the presence of a small unidentified aromatic impurity (8%).

15 **Resolution of *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester**

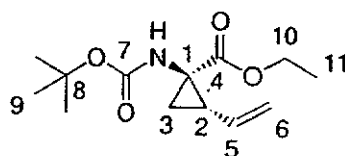
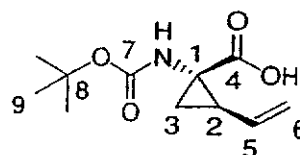


Resolution A

20 To an aqueous solution of sodium phosphate buffer (0.1 M, 4.25 liter ("L"), pH 8) housed in a 12 Liter jacketed reactor, maintained at 39°C, and stirred at 300 rpm was added 511 grams of Acalase 2.4L (about 425 mL) (Novozymes North America Inc.). When the temperature of the mixture reached 39°C, the pH was adjusted to 8.0 by the addition of a 50% NaOH in water. A solution of the racemic *N*-Boc-

(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (85 g) in 850 mL of DMSO was then added over a period of 40 min. The reaction temperature was then maintained at 40°C for 24.5h during which time the pH of the mixture was adjusted to 8.0 at the 1.5h and 19.5h time points using 50% NaOH in water. After 5 24.5h, the enantio-excess of the ester was determined to be 97.2%, and the reaction was cooled to room temperature (26°C) and stirred overnight (16h) after which the enantio-excess of the ester was determined to be 100%. The pH of the reaction mixture was then adjusted to 8.5 with 50% NaOH and the resulting mixture was extracted with MTBE (2 x 2 L). The combined MTBE extract was then washed with 10 5% NaHCO₃ (3 x 100 mL), water (3 x 100 mL), and evaporated *in vacuo* to give the enantiomerically pure *N*-Boc-(1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as light yellow solid (42.55 g; purity: 97% @ 210 nm, containing no acid; 100% enantiomeric excess ("ee").

The aqueous layer from the extraction process was then acidified to pH 2 with 50% 15 H₂SO₄ and extracted with MTBE (2 x 2 L). The MTBE extract was washed with water (3 x 100 mL) and evaporated to give the acid as light yellow solid (42.74 g; purity: 99% @ 210 nm, containing no ester).

1*R*, 2*S*-ester1*S*,2*R*-acid

	ester	acid
High Resoluti onMass Spec	(+) ESI, C ₁₃ H ₂₂ NO ₄ , [M+H] ⁺ , cal. 256.1549, found 256.1542	(-) ESI, C ₁₁ H ₁₆ NO ₄ , [M- H] ⁻ , cal. 226.1079, found 226.1089

NMR observed chemical shift Solvent: CDCl ₃ (proton δ 7.24 ppm, C-13 δ 77.0 ppm) Bruker DRX-500C: proton 500.032 MHz, carbon 125.746 MHz				
Position	Proton (pattern) ppm	C-13 ppm	Proton (pattern) ppm	C-13 ppm
1	----	40.9	----	40.7
2	2.10 (q, J = 9.0 Hz)	34.1	2.17 (q, J = 9.0 Hz)	35.0
3a	1.76 (br)	23.2	1.79 (br)	23.4
3b	1.46 (br)		1.51, (br)	
4	----	170.8	----	175.8
5	5.74 (ddd, J = 9.0, 10.0, 17.0 Hz)	133.7	5.75 (m)	133.4
6a	5.25 (d, J = 17.0 Hz)	117.6	5.28 (d, J = 17.0 Hz)	118.1
6b	5.08 (dd, J = 10.0, 1.5 Hz)		5.12 (d, J = 10.5 Hz)	
7	----	155.8	----	156.2
8	----	80.0	----	80.6
9	1.43 (s)	28.3	1.43 (s)	28.3
10	4.16 (m)	61.3	----	----
11	1.23 (t, J = 7.5 Hz)	14.2	----	----

Resolution B

- To 0.5 mL 100 mM Heps•Na buffer (pH 8.5) in a well of a 24 well plate
- 5 (capacity: 10 ml/well), 0.1 mL of Savinase 16.0L (protease from *Bacillus clausii*) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in

0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40°C. After 18h, enantio-excess of the ester was determined to be 44.3% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after centrifugation, 10 microliter ("µl") of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40°C, after which four mL of ethanol was added to the well. After centrifugation, 10 µl of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

Resolution C

To 0.5 ml 100 mM Heps•Na buffer (pH 8.5) in a well of a 24 well plate (capacity: 10 mL/well), 0.1 ml of Esperase 8.0L, (protease from *Bacillus halodurans*) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in 0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40°C. After 18 hour, enantio-excess of the ester was determined to be 39.6% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after centrifugation, 10 µl of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40°C, after which four mL of ethanol was added to the well. After centrifugation, 10 µl of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

Samples analysis was carried out in the following manner:

1) Sample preparation: About 0.5 ml of the reaction mixture was mixed well with 10 volume of EtOH. After centrifugation, 10 µl of the supernatant was injected onto HPLC column.

2) Conversion determination:

Column: YMC ODS A, 4.6 x 50 mm, S-5 μ m

Solvent: A, 1 mM HCl in water; B, MeCN

- 5 Gradient: 30% B for 1 min; 30% to 45% B over 0.5 min; 45% B for 1.5 min; 45% to 30% B over 0.5 min.

Flow rate: 2 ml/min

UV Detection: 210 nm

Retention time: acid, 1.2 min; ester, 2.8 min.

10

3) Enantio-excess determination for the ester:

Column: CHIRACEL OD-RH, 4.6 x 150 mm, S-5 μ mMobile phase: MeCN/50 mM HClO₄ in water (67/33)

Flow rate: 0.75 ml/min.

- 15 UV Detection: 210 nm.

Retention time:

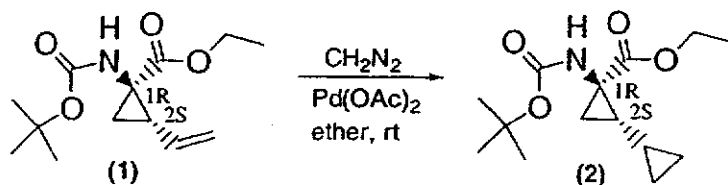
(1S, 2R) isomer as acid: 5.2 min;

Racemate: 18.5 min and 20.0 min;

(1R, 2S) isomer as ester: 18.5 min.

20

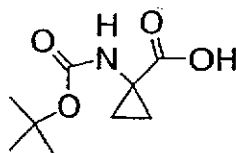
2. Preparation of *N*-Boc-(1*R*,2*S*)-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester



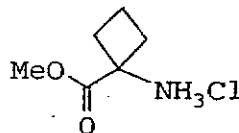
- 25 A solution of *N*-Boc-(1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid (255 mg, 1.0 mmol) in ether (10 mL) was treated with palladium acetate (5 mg, 0.022 mmol). The orange/red solution was placed under an atmosphere of N₂. An excess of diazomethane in ether was added dropwise over the course of 1 h. The resulting solution was stirred at rt for 18 h. The excess diazomethane was removed using a

stream of nitrogen. The resulting solution was concentrated by rotary evaporation to give the crude product. Flash chromatography (10% EtOAc/hexane) provided 210 mg (78%) of *N*-Boc-(1*R*,2*S*)-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester as a colorless oil. LC-MS (retention time: 2.13, similar to method A except: gradient time 3 min, Xterra MS C18 S7 3.0 x 50mm column), MS *m/e* 270 ($M^+ + 1$).

3. 1-*tert*-butoxycarbonylamino-cyclopropane-carboxylic acid is commercially available

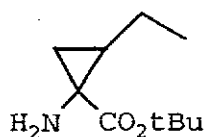


4. Preparation of 1-aminocyclobutanecarboxylic acid methyl ester-hydrochloride



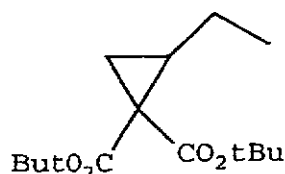
1-aminocyclobutanecarboxylic acid (100 mg, 0.869 mmol)(Tocris) was dissolved in 10 mL of MeOH, HCl gas was bubbled in for 2h. The reaction mixture was stirred for 18 h, and then concentrated in vacuo to give 144 mg of a yellow oil. Trituration with 10 mL of ether provided 100 mg of the titled product as a white solid. ^1H NMR (CDCl_3) δ 2.10-2.25 (m, 1H), 2.28-2.42 (m, 1H), 2.64-2.82 (m, 4H), 3.87 (s, 3H), 9.21 (br s, 3H).

5. Preparation of racemic (1*R*,2*R*)/(1*S*,2*S*) 1-Amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester, shown below.



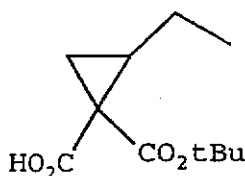
ethyl syn to carboxy

Step 1: Preparation of 2-Ethylcyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester, shown below.



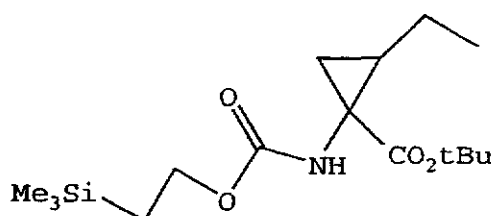
- 5 To a suspension of benzyltriethylammonium chloride (21.0 g, 92.2 mmol) in a 50% aqueous NaOH solution (92.4 g in 185 mL H₂O) was added 1,2-dibromobutane (30.0 g, 138.9 mmol) and di-*tert*-butylmalonate (20.0 g, 92.5 mmol). The reaction mixture was vigorously stirred 18 h at rt, a mixture of ice and water was then added. The crude product was extracted with CH₂Cl₂ (3x) and sequentially washed with water
- 10 (3x), brine and the organic extracts combined. The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The resulting residue was flash chromatographed (100 g SiO₂, 3% Et₂O in hexane) to afford the titled product (18.3 g, 67.8 mmol, 73% yield) which was used directly in the next reaction.

- Step 2: Preparation of racemic 2-Ethylcyclopropane-1,1-dicarboxylic acid *tert*-butyl ester,
- 15 ester, shown below.



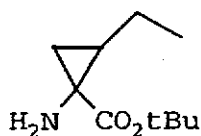
- The product of Step 1 (18.3 g, 67.8 mmol) was added to a suspension of potassium *tert*-butoxide (33.55 g, 299.0 mmol) in dry ether (500 mL) at 0 °C, followed by H₂O (1.35 mL, 75.0 mmol) and was vigorously stirred overnight at rt. The reaction
- 20 mixture was poured in a mixture of ice and water and washed with ether (3x). The aqueous layer was acidified with a 10% aq. citric acid solution at 0°C and extracted with EtOAc (3x). The combined organic layers were washed with water (2x), brine, dried (MgSO₄) and concentrated in vacuo to afford the titled product as a pale yellow oil (10 g, 46.8 mmol, 69% yield).

Step 3: Preparation of (1*R*,2*R*)/(1*S*,2*S*) 2-Ethyl-1-(2-trimethylsilylanylethoxycarbonylamino)cyclopropane-carboxylic acid *tert*-butyl ester, shown below.



- 5 To a suspension, of the product of Step 2 (10 g, 46.8 mmol) and 3 g of freshly activated 4A molecular sieves in dry benzene (160 mL), was added Et₃N (7.50 mL, 53.8 mmol) and DPPA (11 mL, 10.21 mmol). The reaction mixture was refluxed for 3.5 h, 2-trimethylsilyl-ethanol (13.5 mL, 94.2 mmol) was then added, and the reaction mixture was refluxed overnite. The reaction mixture was filtered, diluted
- 10 with Et₂O, washed with a 10% aqueous citric acid solution, water, saturated aqueous NaHCO₃, water (2x), brine (2X), dried (MgSO₄) and concentrated in vacuo. The residue was suspended with 10g of Aldrich polyisocyanate scavenger resin in 120 mL of CH₂Cl₂, stirred at rt overnite and filtered to afford the titled product (8 g, 24.3 mmol; 52%) as a pale yellow oil: ¹H NMR (CDCl₃) δ 0.03 (s, 9H), 0.97 (m, 5H),
- 15 1.20 (bm, 1H), 1.45 (s, 9H), 1.40-1.70 (m, 4H), 4.16 (m, 2H), 5.30 (bs, 1H).

Step 4: Preparation of racemic (1*R*,2*R*)/(1*S*,2*S*) 1-Amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester, shown below.



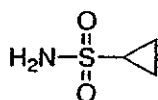
ethyl syn to carboxy

- To the product of Step 3 (3 g, 9 mmol) was added a 1.0 M TBAF solution in THF
- 20 (9.3 mL, 9.3 mmol) and the mixture heated to reflux for 1.5 h, cooled to rt and then diluted with 500 ml of EtOAc. The solution was successively washed with water (2x100 mL), brine (2x100 mL), dried (MgSO₄), concentrated in vacuo to provide the title intermediate

- 25 II PI` elements:

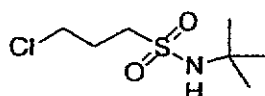
The PI¹ elements prepared below can be used to preapre compounds of Formula I by using the methods described herein.

1. Preparation of cyclopropylsulfonamide:



5

Step 1: Preparation of N-tert-Butyl-(3-chloro)propylsulfonamide

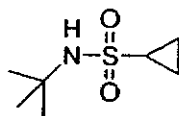


tert-Butylamine (3.0 mol, 315.3 mL) was dissolved in THF (2.5 L). The solution was cooled to -20°C . 3-Chloropropanesulfonyl chloride (1.5 mol, 182.4 mL) was added slowly. The reaction mixture was allowed to warm to rt and stirred for 24 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2.0 L). The resulting solution was washed with 1 N HCl (1.0 L), water (1.0 L), brine (1.0 L) and dried over Na_2SO_4 . It was filtered and concentrated in vacuo to give a slightly yellow solid, which was crystallized from hexane to afford the product as a white solid (316.0 g, 99%).

15

^1H NMR (CDCl_3) δ 1.38 (s, 9H), 2.30-2.27 (m, 2H), 3.22 (t, $J = 7.35$ Hz, 2H), 3.68 (t, $J = 6.2$ Hz, 2H), 4.35 (b, 1H).

Step 2: preparation of Cyclopropanesulfonic acid tert-butylamide

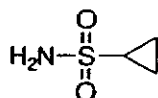


To a solution of N-tert-butyl-(3-chloro)propylsulfonamide (2.14 g, 10.0 mmol) in THF (100 mL) was added n-BuLi (2.5 M in hexane, 8.0 mL, 20.0 mmol) at -78°C . The reaction mixture was allowed to warm up to room temperature over period of 1 h. The volatiles were removed in vacuo. The residue was partitioned between EtOAc and water (200 mL, 200 mL). The separated organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was recrystallized from hexane to yield the desired product as a white solid (1.0 g, 56%).

25

^1H NMR (CDCl_3) δ 0.98-1.00 (m, 2H), 1.18-1.19 (m, 2H), 1.39 (s, 9H), 2.48-2.51 (m, 1H), 4.19 (b, 1H).

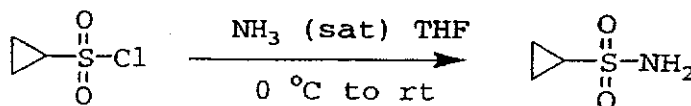
Step 3: preparation of cyclopropylsulfonamide



A solution of cyclopropanesulfonic acid tert-butylamide (110.0 g, 0.62 mol) in TFA (500 mL) was stirred at room temperature for 16 h. The volatile was removed in vacuo. The residue was recrystallized from EtOAc/hexane (60 mL/240 mL) to yield the desired product as a white solid (68.5 g, 91%).

^1H NMR (DMSO- d_6) δ 0.84-0.88 (m, 2H), 0.95-0.98 (m, 2H), 2.41-2.58 (m, 1H), 6.56 (b, 2H).

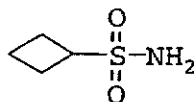
10 2. Alternate procedure for the preparation of cyclopropyl sulfonamide



To a solution of 100 mL of THF cooled to 0 °C was bubbled in gaseous ammonia until saturation was reached. To this solution was added a solution of 5 g (28.45 mmol) of cyclopropylsulfonyl chloride (purchased from Array Biopharma) in 50 mL of THF, the solution warmed to rt overnight and stirred one additional day. The mixture was concentrated until 1-2 mL of solvent remained, applied onto 30 g plug of SiO_2 (eluted with 30% to 60% EtOAc/Hexanes) to afford 3.45g (100%) of cyclopropyl sulfonamide as a white solid. ^1H NMR (Methanol- d_4) δ 0.94-1.07 (m, 4H), 2.52-2.60 (m, 1H); ^{13}C NMR (methanol- d_4) δ 5.92, 33.01.

20

3. Preparation of cyclobutyl sulfonamide

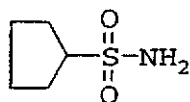


To a solution of 5.0 g (37.0 mmol) of cyclobutyl bromide in 30 mL of anhydrous diethyl ether (Et_2O) cooled to -78 °C was added 44 mL (74.8 mmol) of 1.7M *tert*-butyl lithium in pentanes and the solution slowly warmed to -35 °C over 1.5 h. This mixture was cannulated slowly into a solution of 5.0 g (37.0 mmol) freshly distilled sulfonyl chloride in 100 mL of hexanes cooled to -40 °C, warmed to 0 °C over 1 h and carefully concentrated in vacuo. This mixture was redissolved in Et_2O , washed

25

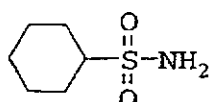
once with some ice-cold water, dried (MgSO_4) and concentrated carefully. This mixture was redissolved in 20 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated in vacuo to a crude yellow solid and was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 1.90 g (38%) of cyclobutylsulfonamide as a white solid. ^1H NMR (CDCl_3) δ 1.95-2.06 (m, 2H), 2.30-2.54 (m, 4H), 3.86 (p, $J=8$ Hz, 1H), 4.75 (brs, 2H); ^{13}C NMR (CDCl_3) δ 16.43, 23.93, 56.29. HRMS m/z (M-H) $^-$ calcd for $\text{C}_4\text{H}_8\text{NSO}_2$: 134.0276, found 134.0282.

10 4 Preparation of cyclopentyl sulfonamide



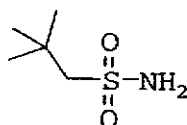
A solution of 18.5 mL (37.0 mmol) of 2M cyclopentyl-magnesium chloride in ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfuryl chloride (obtained from Aldrich) in 100 mL of hexanes cooled to -78 $^\circ\text{C}$. The mixture was warmed to 0 $^\circ\text{C}$ over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et_2O (200 mL), washed once with some ice-cold water (200 mL), dried (MgSO_4) and concentrated carefully. This mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated in vacuo to a crude yellow solid, the residue filtered through 50g of silica gel using 70% EtOAc-hexanes as the eluent and the solution was then concentrated. The residue was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 2.49 g (41%) of cyclopentylsulfonamide as a white solid. ^1H NMR (CDCl_3) δ 1.58-1.72 (m, 2H), 1.74-1.88 (m, 2H), 1.94-2.14 (m, 4H), 3.48-3.59 (m, 1H), 4.80 (bs, 2H); ^{13}C NMR (CDCl_3) δ 25.90, 28.33, 63.54; MS m/e 148 (M-H) $^-$.

5. Preparation of cyclohexyl sulfonamide



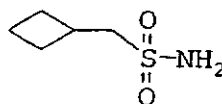
A solution of 18.5 mL (37.0 mmol) of 2M cyclohexylmagnesium chloride (TCI Americas) in ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfonyl chloride in 100 mL of hexanes cooled to -78°C . The mixture was warmed to 0°C over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et_2O (200 mL), washed once with some ice-cold water (200 mL), dried (MgSO_4) and concentrated carefully. This mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated in vacuo to a crude yellow solid, the residue filtered through 50g of silica gel using 70% EtOAc-hexanes as the eluent and was concentrated. The residue was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 1.66 g (30%) of cyclohexylsulfonamide as a white solid: ^1H NMR (CDCl_3) δ 1.11-1.37 (m, 3H), 1.43-1.56 (m, 2H), 1.67-1.76 (m, 1H), 1.86-1.96 (m, 2H), 2.18-2.28 (m, 2H), 2.91 (tt, $J=12$, 3.5 Hz, 1H), 4.70 (bs, 2H); ^{13}C NMR (CDCl_3) δ 25.04, 25.04, 26.56, 62.74; MS m/e 162 (M-1).

6. Preparation of neopentylsulfonamide



Following the procedure for the prep of cyclohexyl sulfonamide, 49 mL (37 mmol) of 0.75M neopentylmagnesium chloride (Alfa) in ether was converted to 1.52g (27%) of neopentylsulfonamide as a white solid. ^1H NMR (CDCl_3) δ 1.17 (s, 9H), 3.12 (s, 2H), 4.74 (brs, 2H); ^{13}C NMR (CDCl_3) δ 29.46, 31.51, 67.38; MS m/e 150 (M-1).

7. Preparation of cyclobutylcarbonyl-sulfonamide

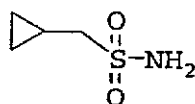


A solution of 12.3 g (83 mmol) of cyclobutylcarbonyl bromide (Aldrich) and 13.7g (91 mmol) of sodium iodide in 150 mL of acetone was refluxed overnight and then cooled to rt. The inorganic solids were filtered off and the acetone and

cyclopropylcarbinyl iodide (8.41 g, 46%) distilled off at ambient and 150 torr at 80 °C, respectively.

A solution of 4.0 g (21.98 mmol) of cyclobutyl carbinyl iodide in 30 mL of anhydrous diethyl ether (Et₂O) cooled to -78 °C was cannulated into a solution of 17 mL (21.98 mmol) of 1.3M sec-butyl lithium in cyclohexanes and the solution was stirred for 5 min. To this mixture was cannulated a solution of 3.0 g (21.98 mmol) of freshly distilled sulfuryl chloride in 110 mL of hexanes cooled to -78 °C, the mixture warmed to rt over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et₂O, washed once with some ice-cold water, dried (MgSO₄) and concentrated carefully. This mixture was redissolved in 30 mL of THF, added dropwise to 500 mL of saturated NH₃ in THF and was allowed to stir overnight. The mixture was concentrated in vacuo to a crude yellow solid and was recrystallized from the minimum amount of CH₂Cl₂ in hexanes with 1-2 drops of MeOH to afford 1.39 g (42%) of cyclobutyl carbinylsulfonamide as a white solid. ¹H NMR (CDCl₃) δ 1.81-2.03 (m, 4H), 2.14-2.28 (m, 2H), 2.81-2.92 (m, 1H), 3.22 (d, *J*=7 Hz, 2H), 4.74 (brs, 2H); ¹³C NMR (CDCl₃) δ 19.10, 28.21, 30.64, 60.93; MS *m/e* 148 (M-1). time: 1.73, method B), 818 (M⁺+H)

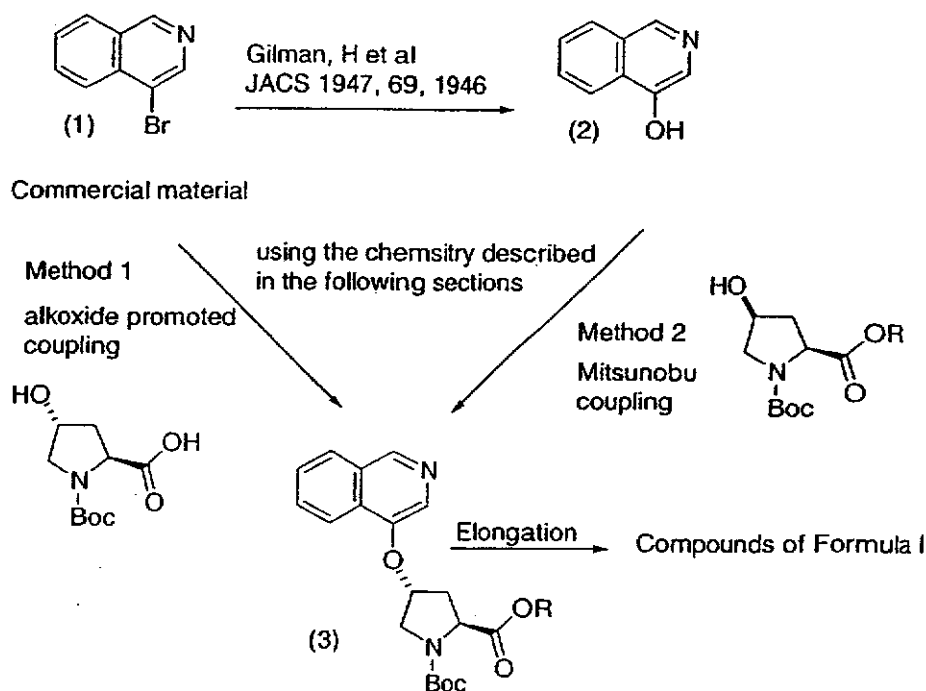
8: Preparation of cyclopropylcarbinyl-sulfonamide



Using the procedure employed for the preparation of cyclobutylcarbinyl-sulfonamide, cyclopropylcarbinyl sulfonamide was prepared from cyclopropylcarbinyl bromide (Aldrich) (see also *JACS* 1981, p.442-445). ¹H NMR (CDCl₃) δ 0.39-0.44 (m, 2H), 0.67-0.76 (m, 2H), 1.13-1.27 (m, 1H), 3.03 (d, *J*=7.3 Hz, 2H), 4.74 (brs, 2H); ¹³C NMR (CDCl₃) δ 4.33, 5.61, 59.93; MS *m/e* 134 (M-1).

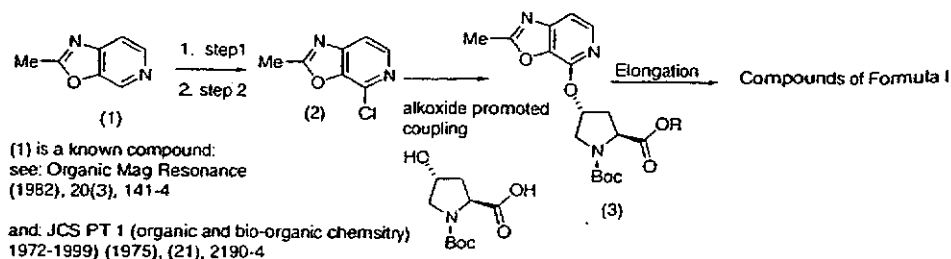
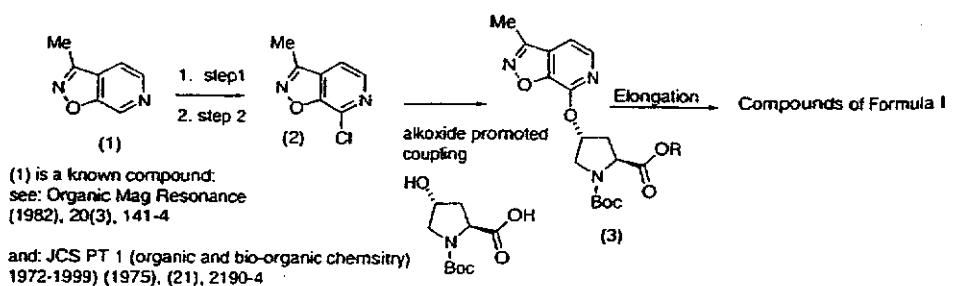
III Heterocycles to be used as starting material in the construction of P2 elements for subsequent incorporation into compounds of Formula I.

1. Isoquinolines



Isoquinoline (1) and substituted analogues thereof, can be incorporated into P2 elements using the two methods outline above and described in detail herein. Said P2 elements (3) can then be converted into compounds of Formula I using procedures analogous to those described herein for similar isoquinoline analogues.

2. Isoxazolepyridine and Oxazolepyridine(1)



Isoxazole and oxazole heterocycle (1) and analogues thereof can be prepared using known chemistry and incorporated into compounds of Formula I using the chemistry described herein for similar isoxazolepyridine intermediates as shown in section B.

5 **Section B:**

In Section B the following conditions were used for LC/MS analysis.

Columns: Method A: YMC ODS-A C18 S7 (4.6 x 33 mm)

 Method B: YMC Xterra ODS S7 (3.0 x 50mm)

 Method C: Xterra ms C18 (4.6 x 33mm)

10 Method D: YMC ODS-A C18 S3 (4.6 x 33 mm)

Gradient: 100% solvent A/ 0% solvent B to 0% solvent A/ 100% solvent B

Gradient time: 3 min.

Hold Time: 1 min.

Flow Rate: 5 mL/min.

15 Detector Wavelength: 220 nm.

Solvents: Solvent A: 10% MeOH/ 90% water/ 0.1% TFA. Solvent B: 90% MeOH/
10% water/ 0.1% TFA.

The following conditions were used for prep-HPLC separation.

Columns: Phenomenex-Luna 30X100 mm, S5

20 Gradient: 60% solvent A/ 40% solvent B to 0% solvent A/ 100% solvent B

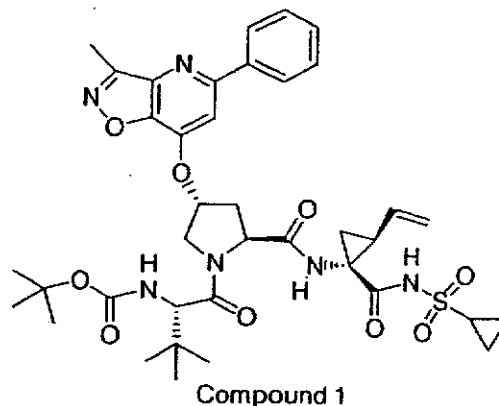
Gradient time: 15 min.

Stop Time: 20 min.

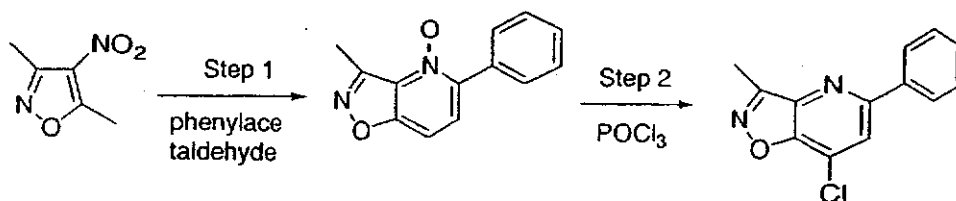
Flow Rate: 30 mL/min.

Detector Wavelength: 220 nm.

25 Solvents: Solvent A: 10% MeOH/ 90% water/ 0.1% TFA. Solvent B: 90% MeOH/
10% water/ 0.1% TFA.

Example 1: Preparation of Compound 1.

Scheme 1

**Step 1:**

A mixture of 3,5-dimethyl-4-nitro-isoxazole (1.42 g, 10.0 mmol), phenylacetaldehyde (1.32 g, 11.0 mmol) in piperidine (1 mL) and ethanol (10 mL) was heated to reflux for 16 h. After cooling down to the ambient temperature, the product precipitated out was collected by filtration. The cake was washed with cold ethanol thoroughly to afford 1.20 g (53%) of the desired product as a white solid.

¹H NMR (CDCl₃) δ 2.87 (s, 3H), 7.46-7.50 (m, 3H), 7.56 (d, *J*=8.5 Hz, 1H), 7.7-7.80 (m, 2H);

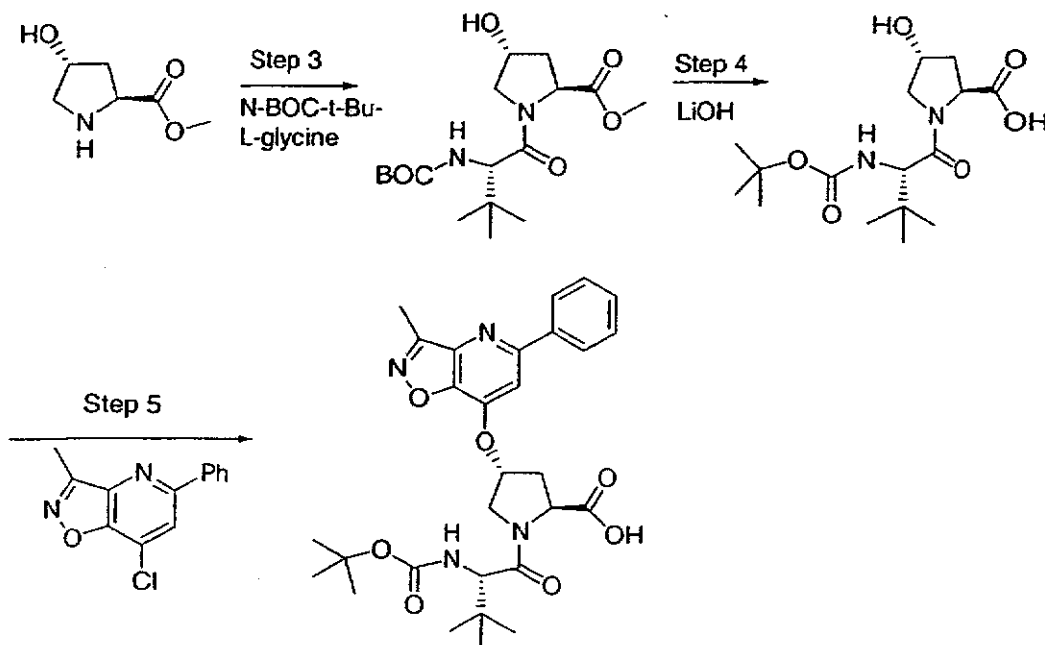
LC-MS (retention time: 1.19 min, method B), MS *m/z* 227 (*M*⁺+H).

Step 2:

A solution of 3-methyl-5-phenyl-isoxazolo[4,5-b]pyridine 4-oxide (1.00 g, 4.40 mmol) and POCl₃ (2.71 g, 17.7 mmol) in chloroform (10 mL) was heated to reflux for 1 h. After cooling down to the ambient temperature, the final solution was diluted with chloroform (50 mL) and washed with NaHCO₃ (aq.) (two 50 mL portions) and brine, dried over MgSO₄, filtered, evaporated. The residue was purified by flash chromatography (4:1 hexane-EtOAc) to afford 790 mg (73%) of the desired product as a white solid.

^1H NMR (CDCl_3) δ 2.72 (s, 3H), 7.46-7.54 (m, 3H), 7.91 (s, 1H), 8.00-8.03 (m, 2H);
LC-MS (retention time: 1.76 min, method B), MS m/z 245, 247 ($\text{M}^+ + \text{H}$).

Scheme 2



5 Step 3:

To a mixture of 4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester (H-Hyp-OMe HCl) (1.81 g, 10.0 mmol), HATU (5.70 g, 15.0 mmol), and N-BOC-t-butyl-L-glycine (2.42 g, 10.5 mmol) in CH_2Cl_2 (100 mL) was added DIPEA (3.47 g, 31.0 mmol) at 0°C . After stirring at the ambient temperature for 12 h, the formed solution was diluted with CH_2Cl_2 (100 mL), washed with iced 5% citric acid (aq). The organic layer was washed with 5% citric acid, 1M NaOH, brine respectively, dried over MgSO_4 , and filtered. The filtrate was evaporated in vacuo to provide 3.55 g (99%) of the desired product as an off-white foam. This product was used for the next reaction as crude without further purification.

15

^1H NMR (CD_3OD) δ 1.04 (s, 9H), 1.43 (s, 9H), 1.99-2.03 (m, 1H), 2.20-2.30 (m, 1H), 3.69 (s, 3H), 3.70-3.79 (m, 2H), 4.28 (b, 1H), 4.46 (b, 1H), 4.74-4.80 (m, 1H);
LC-MS (retention time: 1.28 min, method B), MS m/z 359 ($\text{M}^+ + \text{H}$).

Step 4:

A mixture of the product of Step 3 (3.55 g, 9.9 mmol) in THF (50 mL), MeOH (50 mL) and LiOH monohydrate (0.83 g, 19.9 mmol in 50 mL H₂O) was stirred at the ambient temperature over night. After removal of the volatiles in vacuo, the residue was dissolved in 0.1 M NaOH (100 mL). This aqueous solution was washed with ether (50 mL), acidified by 1M HCl to pH4. Extracted with EtOAc (100 mL). The organic layer was washed with 5% citric acid and brine, dried over MgSO₄, evaporated to dryness to give 3.20g (95%) of the desired product as a white foam. This product was used as crude without further purification.

10

¹H NMR (CD₃OD) δ 1.02 (s, 9H), 1.43 (s, 9H), 2.01-2.09 (m, 1H), 2.25-2.32 (m, 1H), 3.70-3.85 (m, 2H), 4.26-4.30 (m, 1H), 4.46-4.51 (m, 2H), 6.37-6.41 (m, 1H); LC-MS (retention time: 1.14 min, method B), MS *m/z* 345 (M⁺+H).

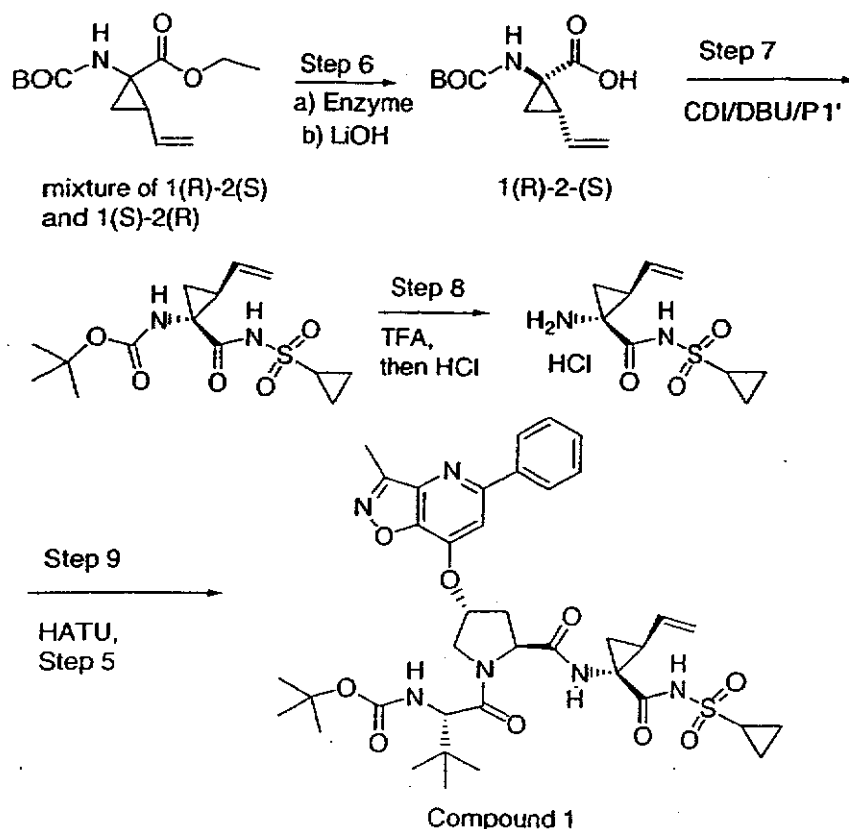
15 Step 5:

To a solution of the product of Step 4 (1.01 g, 2.93 mmol) in DMSO (30 mL) was added potassium *tert*-butoxide (1.02 g, 9.08 mmol). The formed solution was stirred at the ambient temperature for 1 h before addition of 7-chloro-3-methyl-5-phenyl-isoxazolo[4,5-*b*]pyridine (0.75 g, 3.08 mmol). The final solution was stirred for 12 h. Then was quenched with iced water, acidified with 1M HCl to pH 4, extracted with EtOAc (two 200 mL portions). The organic layers were washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC (60%B—100%B, 15 min gradient) to afford 305 mg (19%) of the desired product as a pale yellow solid.

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¹H NMR (CD₃OD) δ 1.02 (s, 9H), 1.17 (s, 9H), 2.37-2.47 (m, 1H), 2.64 (s, 3H), 2.85-2.93 (m, 1H), 4.00-4.08 (m, 1H), 4.14 (b, 1H), 4.49-4.55 (m, 1H), 4.62-4.71 (m, 1H), 5.70 (m, 1H), 7.45-7.53 (m, 3H), 7.56 (s, 1H), 8.03-8.06 (m, 2H); LC-MS (retention time: 1.89 min, method B), MS *m/z* 553 (M⁺+H).

Scheme 3



Step 6a

As described in section A.

Step 6b:

- 5 To a solution of 1(R)-tert-butoxycarbonylamino-2(S)-vinyl-cyclopropanecarboxylic acid ethyl ester, the product of Step 6a (3.28 g, 13.2 mmol) in THF (7 mL) and methanol (7 mL) was added a suspension of LiOH (1.27 g, 53.0 mmol) in water (14 mL). The mixture was stirred overnight at room temperature and quenched with 1N NaOH (15 mL) and water (20 mL). The resulting mixture was
- 10 washed with EtOAc (20 mL), and the organic phase was extracted with 20 mL 0.5N NaOH. The combined aqueous phases were acidified with 1N HCl until pH 4 and extracted with EtOAc (3 x 40mL). The combined organic extracts were washed with brine and dried (MgSO₄) to yield the title compound as a white solid (2.62 g, 87%).

¹H NMR: (DMSO-d₆) δ 1.22-1.26 (m, 1H), 1.37 (s, 9H), 1.50-1.52 (m, 1H), 2.05 (q, J=9 Hz, 1H), 5.04 (d, J=10 Hz, 1H), 5.22 (d, J=17 Hz, 1H), 5.64-5.71 (m, 1H), 7.18, 7.53 (s, NH (rotamers)), 12.4 (br s, 1H);

LC-MS (retention time: 1.67 min, method B), MS *m/z* 228 (M⁺+H).

5

Step 7:

A solution of the product of Step 6 (2.62 g, 11.5 mmol) and CDI (2.43 g, 15.0 mmol) in THF (40 mL) was heated at reflux for 50 min under nitrogen. The solution was cooled to room temperature and transferred by cannula to a solution of cyclopropylsulfonamide (1.82 g, 15.0 mmol) in THF (10 mL). To the resulting solution was added DBU (2.40 mL, 16.1 mmol) and stirring was continued for 20 h. The mixture was quenched with 1N HCl to pH 1 and THF was evaporated in vacuo. The suspension was extracted with EtOAc (2 x 50 mL) and the combined organic extracts dried (Na₂SO₄). Purification by recrystallization from hexanes-EtOAc (1:1) afforded the title compound (2.4 g) as a white solid. The mother liquor was purified by a Biotage 40S column (eluted 9% acetone in DCM) to give a second batch of the title compound (1.1 g). Both batches were combined (total yield 92%).

¹H NMR: (DMSO-d₆) δ 0.96-1.10 (m, 4H), 1.22 (dd, J=5.5, 9.5 Hz, 1H), 1.39 (s, 9H), 1.70 (t, J=5.5 Hz, 1H), 2.19-2.24 (m, 1H), 2.90 (m, 1H), 5.08 (d, J=10 Hz, 1H), 5.23 (d, J=17 Hz, 1H), 5.45 (m, 1H), 6.85, 7.22 (s, NH (rotamers));

LC-MS (retention time: 1.70 min, method B), MS *m/z* 331 (M⁺+H).

Step 8:

A solution of the product of Step 7 (3.5 g, 10.6 mmol) in DCM (35 mL) and TFA (32 mL) was stirred at room temperature for 1.5 h. The volatiles were removed in vacuo and the residue suspended in 1N HCl in diethyl ether (20 mL) and concentrated in vacuo. This procedure was repeated once. The resulting mixture was triturated from pentane and filtered to give the title compound as a hygroscopic, off-white solid (2.60 g, 92%).

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¹H NMR: (DMSO-d₆) δ 1.01-1.15 (m, 4H), 1.69-1.73 (m, 1H), 1.99-2.02 (m, 1H), 2.38 (q, J=9 Hz, 1H), 2.92-2.97 (m, 1H), 5.20 (d, J=11 Hz, 1H), 5.33 (d, J=17 Hz, 1H), 5.52-5.59 (m, 1H), 9.17 (br s, 3H);

LC-MS (retention time: 0.24 min, method B), MS *m/z* 231 (M⁺+H).

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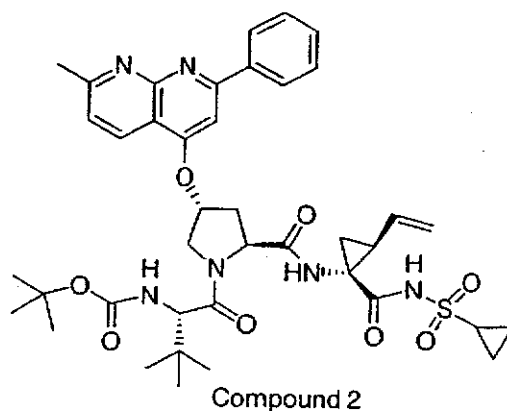
Step 9:

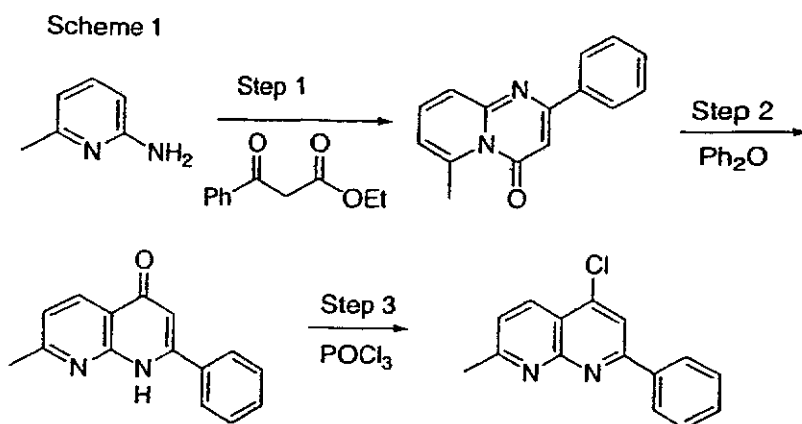
To an iced mixture of the product of Step 5 (70 mg, 0.13 mmol), (1*R*,2*S*)-cyclopropanesulfonic acid (1-amino-2-vinyl-cyclopropanecarbonyl)amide hydrochloride, the product of Step 8 (37 mg, 0.14 mmol) and HATU (72 mg, 0.19 mmol) in DCM (2 mL) was added diisopropylethylamine (50 mg, 0.39 mmol). The formed solution was allowed to warm up to the ambient temperature for 12 h and evaporated *in vacuo*. The residue was purified by prep-HPLC (60%B—100%B, 15 min gradient) to afford 52 mg (54%) of Compound 1 as a grayish solid.

15 ¹H NMR (CD₃OD) δ 0.96-1.09 (m, 12H), 1.16-1.25 (m, 10H), 1.44-1.48 (m, 1H), 1.87-1.91 (m, 1H), 2.20-2.40 (m, 2H), 2.63-2.65 (m, 4H), 2.89-2.98 (m, 1H), 4.08-4.20 (m, 2H), 4.44-4.65 (m, 2H), 5.13 (d, J=11.7 Hz, 1H), 5.32 (d, J=15 Hz, 1H), 5.72-5.85 (b, 2H), 6.62 (d, J=15.0 Hz, 1H), 7.46-7.53 (m, 3H), 7.58 (s, 1H), 8.04-8.07 (m, 2H);

20 LC-MS (retention time: 1.92 min, method B), MS *m/z* 765 (M⁺+H).

Example 2: Preparation of Compound 2.





Step 1:

A mixture of 2-amino-6-methylpyridine (1.08 g, 10.0 mmol), ethyl benzoylacetate (2.30 g, 12.0 mmol) and polyphosphoric acid (6.00 g, 61.2 mmol) was heated to 110°C for 5 h. After cooling to the ambient temperature, the mixture was poured into iced water (20 mL) and neutralized to pH 7 with 10 M NaOH. Extracted with CHCl₃. The organic layer was washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by flash chromatography (1:1 hexane-EtOAc) to afford 510 mg (22%) of the desired product as a pale yellow solid.

¹H NMR (CDCl₃) δ 3.08 (s, 3H), 6.64 (d, *J*=7.0 Hz, 1H), 6.71 (s, 1H), 7.42-7.52 (m, 5H), 8.04-8.06 (m, 2H);

LC-MS (retention time: 1.21 min, method B), MS *m/z* 237 (M⁺+H).

Step 2:

A solution of 6-methyl-2-phenyl-pyrido[1,2a]pyrimidin-4-one (489 mg, 2.07 mmol) in melted diphenyl ether (5 mL) was heated to gentle reflux for 5 h. After cooling to the ambient temperature, the formed suspension was diluted with diethyl ether (10 mL), filtered. The cake was washed with diethyl ether thoroughly to afford 450 mg (92%) of the desired product as a brownish solid.

LC-MS (retention time: 1.25 min, method B), MS *m/z* 237 (M⁺+H).

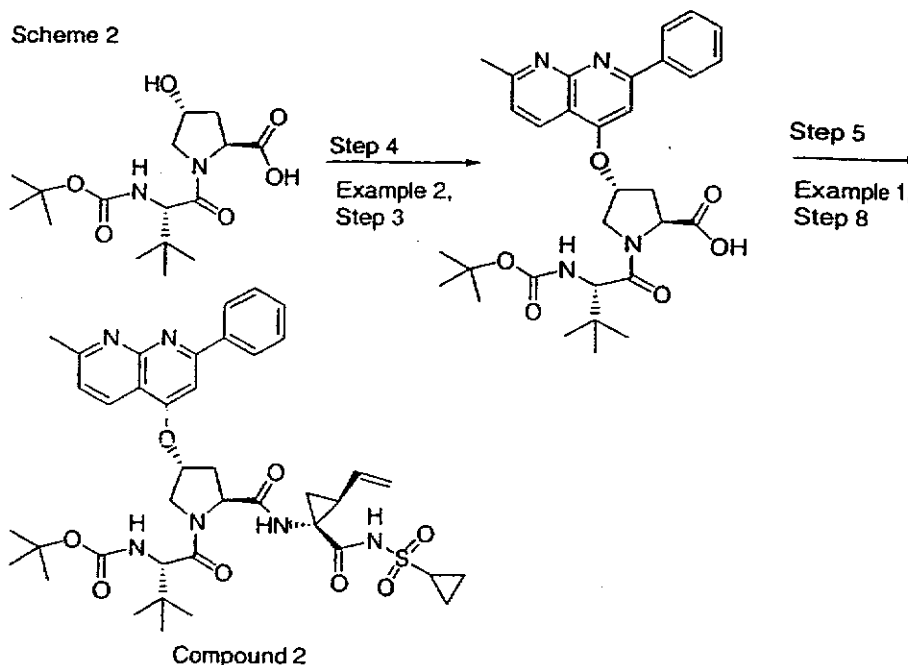
Step 3:

A suspension of 7-methyl-2-phenyl-1H-[1,8]naphthyridin-4-one (450 mg, 1.91 mmol) in POCl₃ (10 mL) was heated to gentle reflux for 3 h. Evaporated in

vacuo. The residue was poured into iced water (20 mL) and neutralized to pH 10 with 10 M NaOH. Extracted with CHCl_3 . The organic layer was washed with brine, dried over MgSO_4 , filtered, evaporated. The residue was purified by flash chromatography (2:1 hexane-EtOAc) to afford 450 mg (92%) of the desired product as a pink solid.

^1H NMR (CD_3OD) δ 2.80 (s, 3H), 7.54-7.56 (m, 3H), 7.61 (d, $J=8.4$ Hz, 1H), 8.25-8.30 (m, 3H), 8.58 (d, $J=8.4$ Hz, 1H);

LC-MS (retention time: 1.39 min, method B), MS m/z 255, 257 ($\text{M}^+ + \text{H}$).



Step 4:

This product was prepared by the same procedure as described in Example 1, Step 5, except using 4-chloro-7-methyl-2-phenyl-[1,8]naphthyridine from Example 2, Step 3 instead.

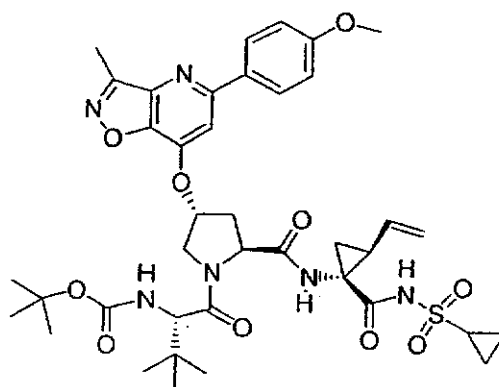
LC-MS (retention time: 1.55 min, method B), MS m/z 563 ($\text{M}^+ + \text{H}$).

Step 5:

Compound 2 was prepared by the same procedure as described in Example 1, Step 9, except using the product of Example 2, Step 4 instead.

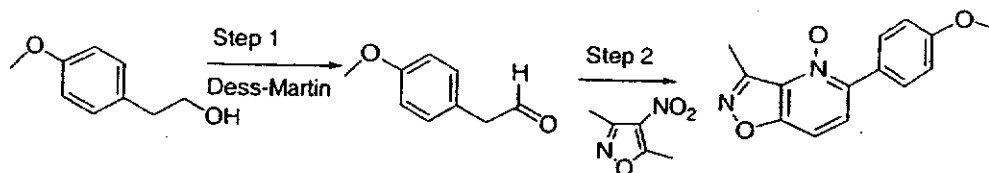
^1H NMR (CD_3OD) δ 1.01-1.10 (m, 12H), 1.21-1.26 (m, 10H), 1.40-1.45 (m, 1H), 1.86-1.91 (m, 1H), 2.20-2.29 (m, 1H), 2.39-2.49 (m, 1H), 2.72-2.81 (m, 1H), 2.92-2.95 (m, 4H), 4.10-4.16 (m, 2H), 4.55-4.65 (m, 2H), 5.14 (d, $J=12.0$ Hz, 1H), 5.30 (d, $J=15.0$ Hz, 1H), 5.67-5.82 (m, 2H), 7.60-7.80 (m, 3H), 7.78 (d, $J=8.6$ Hz, 1H), 7.87 (s, 1H), 8.26-8.29 (m, 2H), 8.95 (d, $J=8.4$ Hz, 1H);
 LC-MS (retention time: 1.62 min, method B), MS m/z 775 ($\text{M}^+\text{+H}$).

Example 3: Preparation of Compound 3.



Compound 3

Scheme 1



Step 1:

To a solution of 4-methoxyphenethyl alcohol (1.52 g, 10.0 mmol) in CH_2Cl_2 (50 mL) at 0°C was added Dess-Martin reagent (4.45 g, 10.5 mmol) in one portion.

The formed mixture was allowed to warm to the ambient temperature for 1 h. Washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (aq) and 1M NaOH, brine respectively. Dried over MgSO_4 , evaporated in vacuo to give 1.50 g (100%) of the desired aldehyde as a viscous oil. This product was used as crude without any further purification.

Step 2:

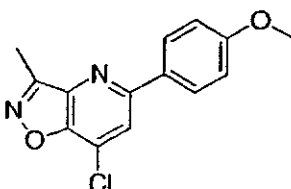
A solution of 3,5-dimethyl-4-nitro-isoxazole (142 mg, 1.0 mmol), 4-methoxy-phenylacetaldehyde from Example 3, Step 1 (180 mg, 1.1 mmol) in piperidine (0.1 mL) and ethanol (2 mL) was heated to reflux for 12 h. After cooling down to the ambient temperature, the product precipitated out was collected by filtration. The cake was washed with cold ethanol thoroughly to afford 130 mg (51%) of the desired product as a grayish solid.

^1H NMR (CDCl_3) δ 2.88 (s, 3H), 3.87 (s, 3H), 7.02 (d, $J=8.5$ Hz, 2H), 7.50 (d, $J=9.0$ Hz, 1H), 7.57 (d, $J=9.0$ Hz, 1H), 7.81 (d, $J=8.5$ Hz, 2H);

LC-MS (retention time: 1.24 min, method B), MS m/z 257 ($\text{M}^+ + \text{H}$).

10

Step 3:

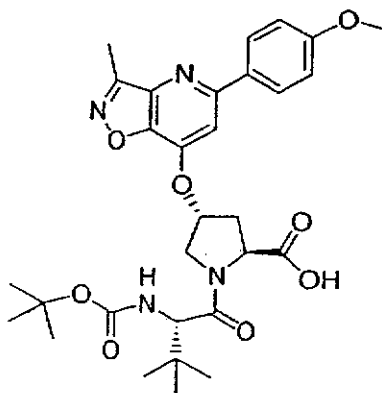


This product was prepared by the same procedure as described in Example 1, Step 2, except using the product of Example 3, Step 2 instead.

^1H NMR (CDCl_3) δ 2.70 (s, 3H), 3.87 (s, 3H), 7.00-7.03 (m, 2H), 7.84 (s, 1H), 7.96-7.98 (m, 2H);

LC-MS (retention time: 1.96 min, method B), MS m/z 275, 277 ($\text{M}^+ + \text{H}$).

Step 4:



20

This product was prepared by the same procedure as described in Example 1, Step 5, except using the product of Example 3, Step 3 instead.

^1H NMR (CD_3OD) δ 1.02 (s, 9H), 1.18 (s, 9H), 2.39-2.43 (m, 1H), 2.63 (s, 3H), 2.75-2.80 (m, 1H), 3.87 (s, 3H), 4.00-4.08 (m, 1H), 4.17 (b, 1H), 4.49-4.55 (m, 1H), 4.62-4.71 (m, 1H), 5.68 (b, 1H), 7.05 (d, $J=8.5$ Hz, 2H), 7.49 (s, 1H), 8.00 (d, $J=8.5$ Hz, 2H);

- 5 LC-MS (retention time: 1.89 min, method B), MS m/z 583 ($\text{M}^+ + \text{H}$).

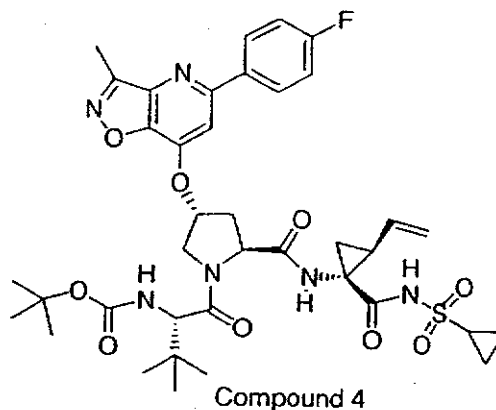
Step 5:

Compound 3 was prepared by the same procedure as described in Example 1, Step 9, except using the product of Example 3, Step 4 instead.

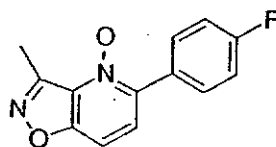
- 10 ^1H NMR (CD_3OD) δ 1.01-1.09 (m, 12H), 1.17-1.26 (m, 10H), 1.44-1.47 (m, 1H), 1.87-1.91 (m, 1H), 2.20-2.40 (m, 2H), 2.63-2.65 (m, 4H), 2.89-2.98 (m, 1H), 3.87 (s, 3H), 4.08-4.20 (m, 2H), 4.44-4.65 (m, 2H), 5.13 (d, $J=11.7$ Hz, 1H), 5.32 (d, $J=15.0$ Hz, 1H), 5.72-5.85 (m, 2H), 7.05 (d, $J=8.5$ Hz, 2H), 7.06 (s, 1H), 8.01 (d, $J=8.5$ Hz, 2H);

- 15 LC-MS (retention time: 1.96 min, method B), MS m/z 795 ($\text{M}^+ + \text{H}$).

Example 4: Preparation of Compound 4.



Step 1:

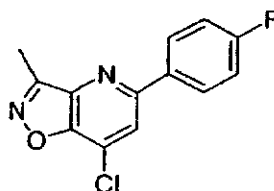


20

This product was prepared by the same procedure as described in Example 3, Step 1&2, except using 4-fluorophenethyl alcohol instead.

LC-MS (retention time: 1.18 min, method B), MS m/z 245 ($\text{M}^+ + \text{H}$).

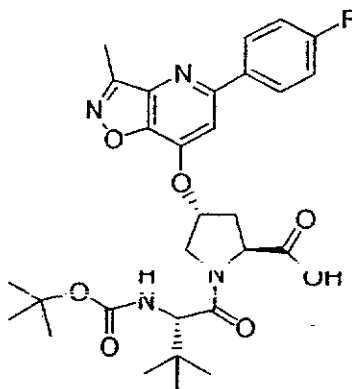
Step 2:



This product was prepared by the same procedure as described in Example 1, Step 2,
5 except using the product of Example 4, Step 1 instead.

^1H NMR (CDCl_3) δ 2.71 (s, 3H), 7.17-7.20 (m, 2H), 7.86 (s, 1H), 8.00-8.02 (m, 2H);
LC-MS (retention time: 1.71 min, method B), MS m/z 263, 265 ($\text{M}^+ + \text{H}$).

Step 3:



10

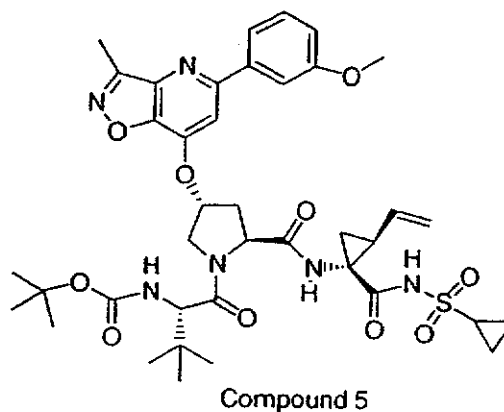
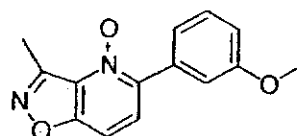
This product was prepared by the same procedure as described in Example 1, Step 5,
except using the product of Example 4, Step 2 instead.

LC-MS (retention time: 1.91 min, method B), MS m/z 571 ($\text{M}^+ + \text{H}$).

15 Step 4:

Compound 4 was prepared by the same procedure as described in Example 1, Step 9,
except using the product of Example 4, Step 3 instead.

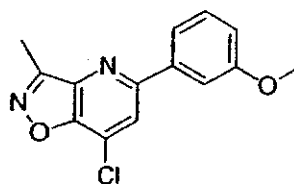
^1H NMR (CD_3OD) δ 1.01-1.09 (m, 12H), 1.17-1.26 (m, 10H), 1.44-1.47 (m, 1H),
1.87-1.91 (m, 1H), 2.20-2.40 (m, 2H), 2.63-2.65 (m, 4H), 2.89-2.98 (m, 1H), 4.08-
20 4.20 (m, 2H), 4.44-4.65 (m, 2H), 5.13 (d, $J=11.7$ Hz, 1H), 5.32 (d, $J=15.0$ Hz, 1H),
5.72-5.85 (m, 2H), 7.20-7.26 (m, 2H), 7.60 (s, 1H), 8.09-8.14 (m, 2H), 9.26 (b, 1H);
LC-MS (retention time: 1.91 min, method B), MS m/z 783 ($\text{M}^+ + \text{H}$).

Example 5: Preparation of Compound 5.**5 Step 1:**

This product was prepared by the same procedure as described in Example 3, Step 1&2, except using 3-methoxy-phenethyl alcohol instead.

LC-MS (retention time: 1.03 min, method B), MS m/z 257 ($M^+ + H$).

10

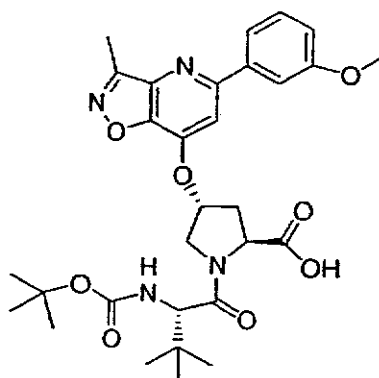
Step 2:

This product was prepared by the same procedure as described in Example 1, Step 2, except using the product of Example 5, Step 1 instead.

15 ^1H NMR ($CDCl_3$) δ 2.72 (s, 3H), 3.90 (s, 3H), 7.00-7.02 (m, 1H), 7.41 (t, $J=8.0$ Hz, 1H), 7.55 (d, $J=7.5$ Hz, 1H), 7.59 (d, $J=2.0$ Hz, 1H), 7.89 (s, 1H);

LC-MS (retention time: 1.89 min, method B), MS m/z 275, 277 ($M^+ + H$).

Step 3:



This product was prepared by the same procedure as described in Example 1, Step 5, except using the product of Example 5, Step 2 instead.

¹H NMR (CD₃OD) δ 1.02 (s, 9 H), 1.18 (s, 9H), 2.37-2.47 (m, 1H), 2.64 (s, 3H),
 5 2.85-2.93 (m, 1H), 3.88 (s, 3H), 4.00-4.08 (m, 1H), 4.14 (b, 1H), 4.49-4.55 (m, 1H),
 4.62-4.71 (m, 1H), 5.71 (b, 1H), 7.02-7.04 (m, 1H), 7.40 (t, *J*=8.0 Hz, 1H), 7.58-7.62
 (m, 3H);

LC-MS (retention time: 1.90 min, method B), MS *m/z* 583 (M⁺+H).

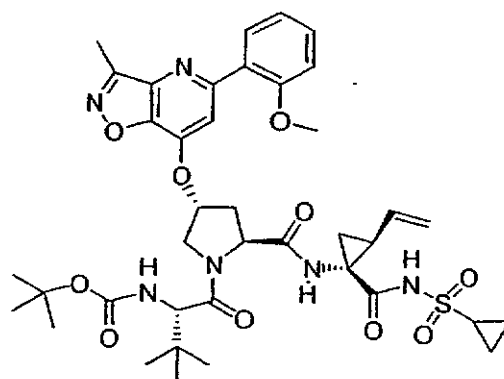
10 Step 4:

Compound 5 was prepared by the same procedure as described in Example 1, Step 9, except using the product of Example 5, Step 3 instead.

¹H NMR (CD₃OD) δ 1.01-1.09 (m, 12H), 1.17-1.29 (m, 10H), 1.44-1.47 (m, 1H),
 1.87-1.91 (m, 1H), 2.20-2.40 (m, 2H), 2.63-2.65 (m, 4H), 2.89-2.98 (m, 1H), 3.89 (s,
 15 3H), 4.08-4.20 (m, 2H), 4.44-4.65 (m, 2H), 5.13 (d, *J*=11.7 Hz, 1H), 5.32 (d, *J*=15.0
 Hz, 1H), 5.72-5.85 (m, 2H), 7.02-7.05 (m, 1H), 7.41 (t, *J*=8.0 Hz, 1H), 7.55-7.61 (m,
 3H);

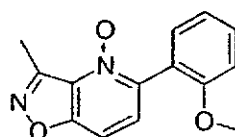
LC-MS (retention time: 1.96 min, method B), MS *m/z* 795 (M⁺+H).

20 Example 6: Preparation of Compound 6.



Compound 6

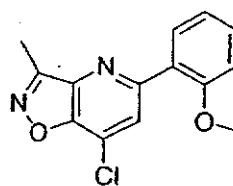
Step 1:



- 5 This product was prepared by the same procedure as described in Example 3, Step 1&2, except using 2-methoxy-phenethyl alcohol instead.

LC-MS (retention time: 1.10 min, method B), MS m/z 257 ($M^+ + H$).

Step 2:



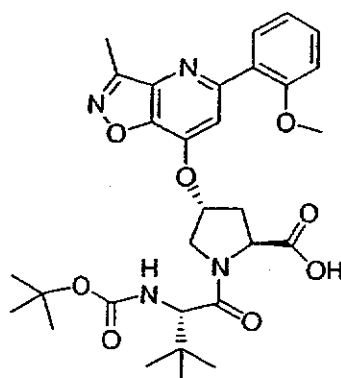
10

This product was prepared by the same procedure as described in Example 1, Step 2, except using the product of Example 6, Step 1 instead.

$^1\text{H NMR}$ (CDCl_3) δ 2.721 (s, 3H), 3.88 (s, 3H), 7.03 (d, $J=8.0$ Hz, 1H), 7.11 (t, $J=7.5$ Hz, 1H), 7.41-7.44 (m, 1H), 7.79-7.81 (m, 1H), 8.04 (s, 1H);

- 15 LC-MS (retention time: 1.92 min, method B), MS m/z 275, 277 ($M^+ + H$).

Step 3:



This product was prepared by the same procedure as described in Example 1, Step 5, except using the product of Example 6, Step 2 instead.

- ¹H NMR (CD₃OD) δ 1.02 (s, 9 H), 1.20 (s, 9H), 2.37-2.47 (m, 1H), 2.63 (s, 3H),
 5 2.85-2.93 (m, 1H), 3.89 (s, 3H), 4.00-4.08 (m, 1H), 4.14 (b, 1H), 4.49-4.55 (m, 1H),
 4.62-4.71 (m, 1H), 5.56 (b, 1H), 7.09 (t, *J*=7.5 Hz, 1H), 7.15 (d, *J*=8.5 Hz, 1H), 7.41-
 7.44 (m, 1H), 7.52 (s, 1H), 7.67 (d, *J*=8.0 Hz, 1H);
 LC-MS (retention time: 1.76 min, method B), MS *m/z* 583 (M⁺+H).

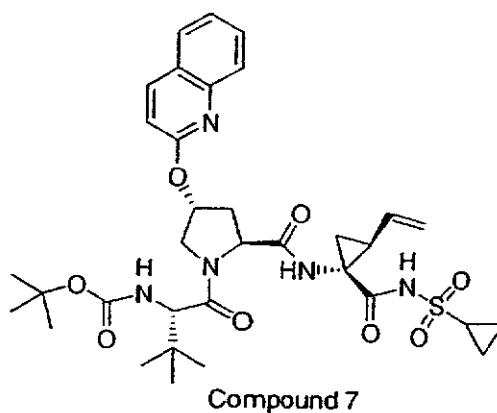
10 Step 4:

Compound 6 was prepared by the same procedure as described in Example 1, Step 9, except using the product of Example 6, Step 3 instead.

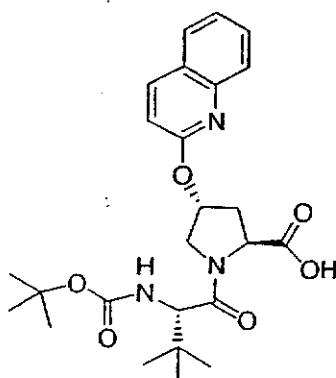
- ¹H NMR (CD₃OD) δ 1.01-1.08 (m, 12H), 1.17-1.26 (m, 10H), 1.44-1.47 (m, 1H),
 1.87-1.91 (m, 1H), 2.20-2.40 (m, 2H), 2.63-2.65 (m, 4H), 2.89-2.98 (m, 1H), 3.88 (s,
 15 3H), 4.08-4.12 (m, 1H), 4.19 (b, 1H), 4.44-4.65 (m, 2H), 5.13 (d, *J*=11.7 Hz, 1H),
 5.32 (d, *J*=15.0 Hz, 1H), 5.59 (b, 1H), 5.72-5.80 (m, 1H), 7.09 (t, *J*=7.5 Hz, 1H), 7.15
 (d, *J*=8.5 Hz, 1H), 7.41-7.45 (m, 1H), 7.66 (s, 1H), 7.66-7.67 (m, 1H);
 LC-MS (retention time: 1.93 min, method B), MS *m/z* 795 (M⁺+H).

20 Example 7: Preparation of Compound 7.

87



Step 1:



- 5 This product was prepared by the same procedure as described in Example 1, Step 5, except using 2-chloro-quinoline instead.

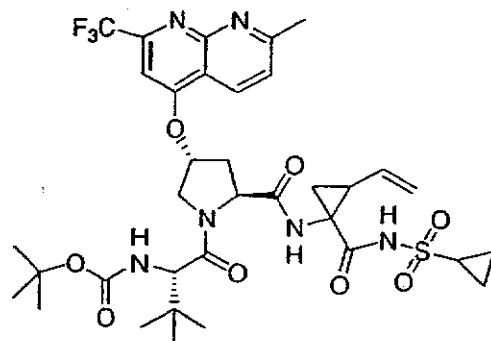
LC-MS (retention time: 1.73 min, method B), MS m/z 472 ($M^+ + H$).

Step 2:

- 10 Compound 7 was prepared by the same procedure as described in Example 1, Step 9, except using the product of Example 7, Step 1 instead.

- ^1H NMR (CD_3OD) δ 1.01-1.08 (m, 12H), 1.17-1.26 (m, 10H), 1.44-1.47 (m, 1H), 1.87-1.91 (m, 1H), 2.23-2.30 (m, 2H), 2.52-2.57 (m, 1H), 2.89-2.98 (m, 1H), 4.10-4.14 (m, 1H), 4.09-4.15 (m, 2H), 4.47-4.51 (m, 1H), 5.13 (d, $J=10.0$ Hz, 1H), 5.32 (d, $J=17.0$ Hz, 1H), 5.73-5.78 (m, 1H), 5.92 (b, 1H), 6.90-6.92 (m, 1H), 7.42 (t, $J=7.5$ Hz, 1H), 7.64 (t, $J=7.5$ Hz, 1H), 7.78-7.82 (m, 2H), 8.13 (d, $J=7.5$ Hz, 1H), 9.18 (d, 1H);

LC-MS (retention time: 1.75 min, method B), MS m/z 684 ($M^+ + H$).

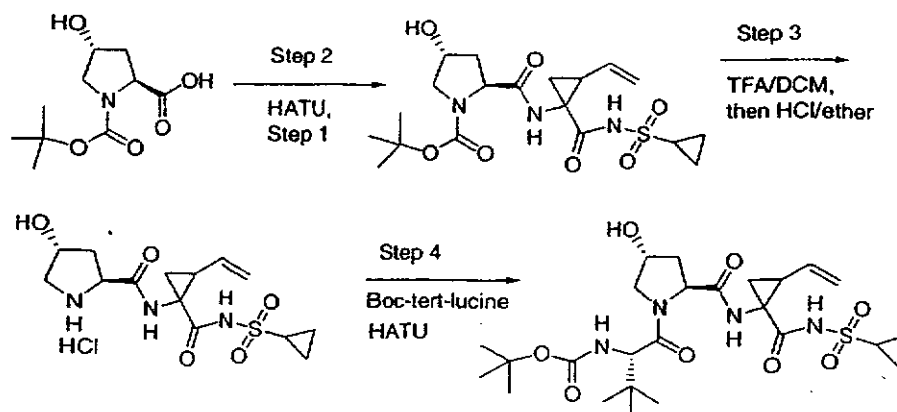
Example 8: Preparation of Compound 8.**Compound 8****Scheme 1**

5

Step 1:

This product was prepared by the same procedure as described in Example 1, Step 6b through 8, without using Step 6a, an enzymatic resolution step.

LC-MS (retention time: 0.24 min, method B), MS m/z 231 ($M^+ + H$).

Scheme 2

10

Step 2:

To an iced mixture of N-BOC-4-trans-hydroxy-L-proline (1.58 g, 6.83 mmol), cyclopropanesulfonic acid (1-amino-2-vinyl-cyclopropanecarbonyl)-amide

hydrochloride (Example 8, Step 1) (2.00 g, 7.52 mmol) and HATU (3.89 g, 10.2 mmol) in CH_2Cl_2 (100 mL) was added diisopropylethylamine (4.41 g, 34.2 mmol). The formed solution was allowed to warm up to the ambient temperature for 12 h. Diluted with EtOAc (200 mL), washed with 5% H_3PO_4 and brine, dried over MgSO_4 ,
5 filtered, evaporated. The residue was purified by flash chromatography (gradient, 2:1—1:1 hexane-acetone) to yield 1.25 g (41%) of the desired product.

^1H NMR ($\text{DMSO}-d_6$) δ 1.00-1.08 (m, 4H), 1.34-1.40 (m, 1:2, 10H), 1.62-1.70 (m, 1H), 1.76-1.87 (m, 1H), 2.02-2.21 (m, 2H), 2.81-2.95 (m, 1H), 3.20-3.45 (m, 2H), 4.04-4.09 (m, 1H), 4.26 (b, 1H), 5.08-5.12 (m, 1H), 5.26 (d, $J=17.1$ Hz, 1H), 5.59-
10 5.69 (m, 1H), 8.59, 8.87 (rotamers, 1:2, 1H), 10.48-11.15 (rotamers, 2:1, 1H);
LC-MS (retention time: 1.25 min, method B), MS m/e 444 (M^++H).

Step 3:

This product was prepared by the same procedure as described in Example 1,
15 Step 8, except using the product of Example 8, Step 2 instead.
LC-MS (retention time: 1.02 min, method B), MS m/e 344 (M^++H).

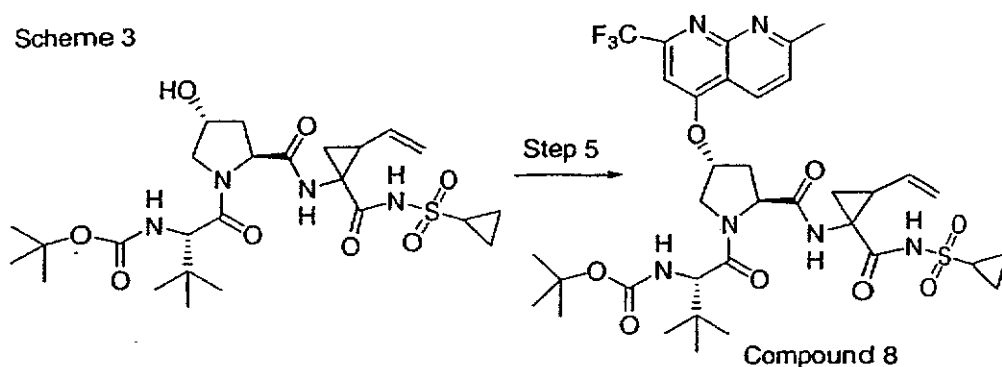
Step 4:

To an iced mixture of N-BOC-4-trans-hydroxy-L-proline (1.58 g, 6.83
20 mmol), cyclopropanesulfonic acid (1-amino-2-vinyl-cyclopropanecarbonyl)-amide
hydrochloride (Example 8, Step 3) (2.00 g, 7.52 mmol) and HATU (3.89 g, 10.2
mmol) in CH_2Cl_2 (100 mL) was added diisopropylethylamine (4.41 g, 34.2 mmol).
The formed solution was allowed to warm up to the ambient temperature for 12 h.
Diluted with EtOAc (200 mL), washed with 5% H_3PO_4 and brine, dried over MgSO_4 ,
25 filtered, evaporated. The residue was purified by flash chromatography (gradient,
2:1—1:1 hexane-acetone) to yield 1.25 g (41%) of the desired product.

^1H NMR (CD_3OD) δ 0.99-1.07 (m, 11H), 1.35-1.44 (m, 13H), 1.75-1.87 (m, 1H),
2.09-2.22 (m, 2H), 2.88-2.94 (m, 1H), 3.74-3.82 (m, 2H), 4.28-4.30 (m, 1H), 4.33-
4.38 (m, 1H), 4.48 (b, 1H), 5.11-5.13 (m, 1H), 5.30 (d, $J=15.0$ Hz, 1H), 5.70-5.78 (m,
30 1H), 6.51-6.61 (m, 1H);

LC-MS (retention time: 1.26 min, method B), MS m/e 557 (M^++H).

Scheme 3

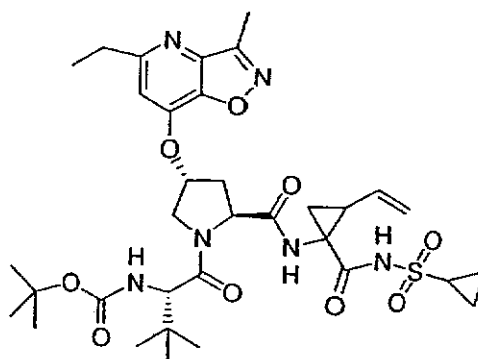
**Step 5:**

To a solution of the product of Example 8, Step 4 (56 mg, 0.1 mmol) in DMSO (2 mL) was added potassium tert-butoxide (49 mg, 0.44 mmol). The formed solution was stirred at the ambient temperature for 1 h before addition of 4-chloro-7-methyl-2-trifluoromethyl-[1,8]naphthyridine (P. Ferrarini et al, *J Heterocyclic Chem*, 1983, p1053) (30 mg, 0.12 mmol). The final solution was stirred for 12 h. Quenched with iced water, acidified with 1M HCl to pH 4, extracted with EtOAc (20 mL, X2). The organic layers were washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC to yield 16 mg (21%) of Compound 8 as a pink solid.

¹H NMR (CD₃OD) δ 0.92-0.99 (m, 11H), 1.01-1.04 (m, 11H), 1.22-1.45 (m, 2H), 1.76-1.85 (m, 1H), 2.18-2.40 (m, 2H), 2.76 (s, 3H), 2.86-2.97 (m, 1H), 4.00-4.11 (m, 2H), 4.48-4.58 (m, 2H), 5.09-5.12 (m, 1H), 5.28-5.31 (m, 1H), 5.59 (b, 1H), 5.69-5.78 (m, 1H), 6.39-6.48 (m, 1H), 7.58-7.64 (m, 2H), 8.08 (s, 1H), 8.64-8.68 (m, 1H), 8.85-8.91 (m, 1H);

LC-MS (retention time: 1.89 min, method B), MS m/e 767 (M⁺+H).

Example 9: Preparation of Compound 9.

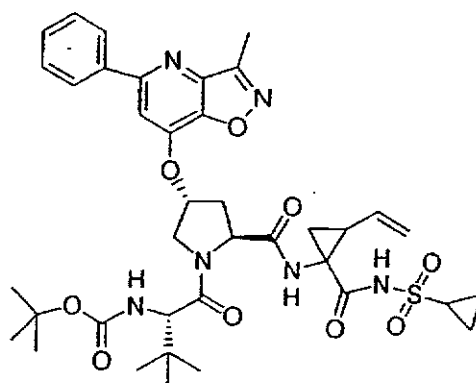


Compound 9

Compound 9 was prepared by the same procedure as described in Example 8, Step 5, except using 7-chloro-5-ethyl-3-methyl-isoxazolo[4,5-b]pyridine (R. Nesi et al, *Synth Comm.* 1992, 22(16), 2349) instead.

- 5 ¹H NMR (CD₃OD) δ 1.01-1.09 (m, 11H), 1.21-1.25 (m, 11H), 1.36 (t, J=7.8 Hz, 3H), 1.38-1.47 (m, 2H), 1.80-1.90 (m, 1H), 2.20-2.31 (m, 2H), 2.59 (s, 3H), 2.90-3.00 (m, 3H), 4.01-4.18 (m, 2H), 4.41-4.51 (m, 2H), 5.11-5.15 (m, 1H), 5.27-5.32 (m, 1H), 5.58 (b, 1H), 5.70-5.80 (m, 1H), 7.11 (s, 1H), 7.72, 7.98 (1:1, 1H), 9.00, 9.22 (1:1, 1H);
- 10 LC-MS (retention time: 1.75 min, method B), MS m/e 717 (M⁺+H).

Example 10: Preparation of Compound 10.



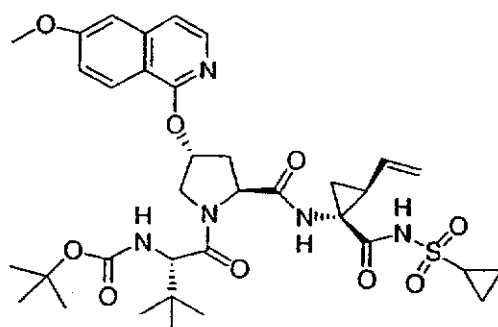
Compound 10

- Compound 10 was prepared by the same procedure as described in Example 8, Step 5, except using 7-chloro-5-phenyl-3-methyl-isoxazolo[4,5-b]pyridine (Example 1, Step 2) instead.
- 15

^1H NMR (CD_3OD) δ 1.00-1.09 (m, 12H), 1.16-1.25 (m, 10H), 1.44-1.48 (m, 1H), 1.79-1.89 (m, 1H), 2.20-2.40 (m, 2H), 2.64-2.66 (m, 4H), 2.89-2.98 (m, 1H), 4.08-4.20 (m, 2H), 4.44-4.55 (m, 2H), 5.11-5.16 (m, 1H), 5.27-5.31 (m, 1H), 5.72-5.74 (m, 2H), 7.20-7.35 (m, 1H), 7.46-7.51 (m, 2H), 7.55-7.68 (m, 1H), 8.05-8.06 (m, 2H);

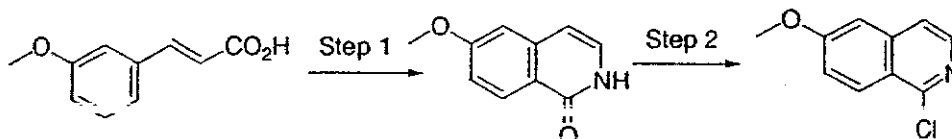
5 LC-MS (retention time: 1.97 min, method B), MS m/z 765 ($\text{M}^+ + \text{H}$).

Example 11: Preparation of Compound 11.



Compound 11

Scheme 1



10

Step 1:

To a solution of 3-methoxy cinnamic acid (11.04 g, 62 mmol) and triethylamine (12.52 g, 124 mmol) in acetone (80 mL) was added ethyl chloroformate (approximately 1.5 equivalents) dropwise at 0°C . After stirring at this temperature for 1 h, aqueous NaN_3 (6.40 g, 100 mmol in 35 mL H_2O) was added dropwise and the reaction mixture was stirred for 16 h at the ambient temperature. Water (100 mL) was added to the mixture and the volatile was removed in vacuo. The resulting slurry was extracted with toluene (3X50 mL) and the combined organic layers were dried over MgSO_4 . This dried solution was added dropwise to a heated solution of diphenylmethane (50 mL) and tributylamine (30 mL) at 190°C . The toluene was distilled off as added. After complete addition, the reaction temperature was raised to 210°C for 2 h. After cooling, the precipitated product was collected by filtration,

20

washed with hexane (2X50 mL), and dried to yield the desired product as a white solid (5.53 g, 51%) (Nicolas Briet *at el*, *Tetrahedron*, 2002, 5761-5766).

LC-MS (retention time: 0.82 min, method B), MS m/z 176 ($M^+ + H$).

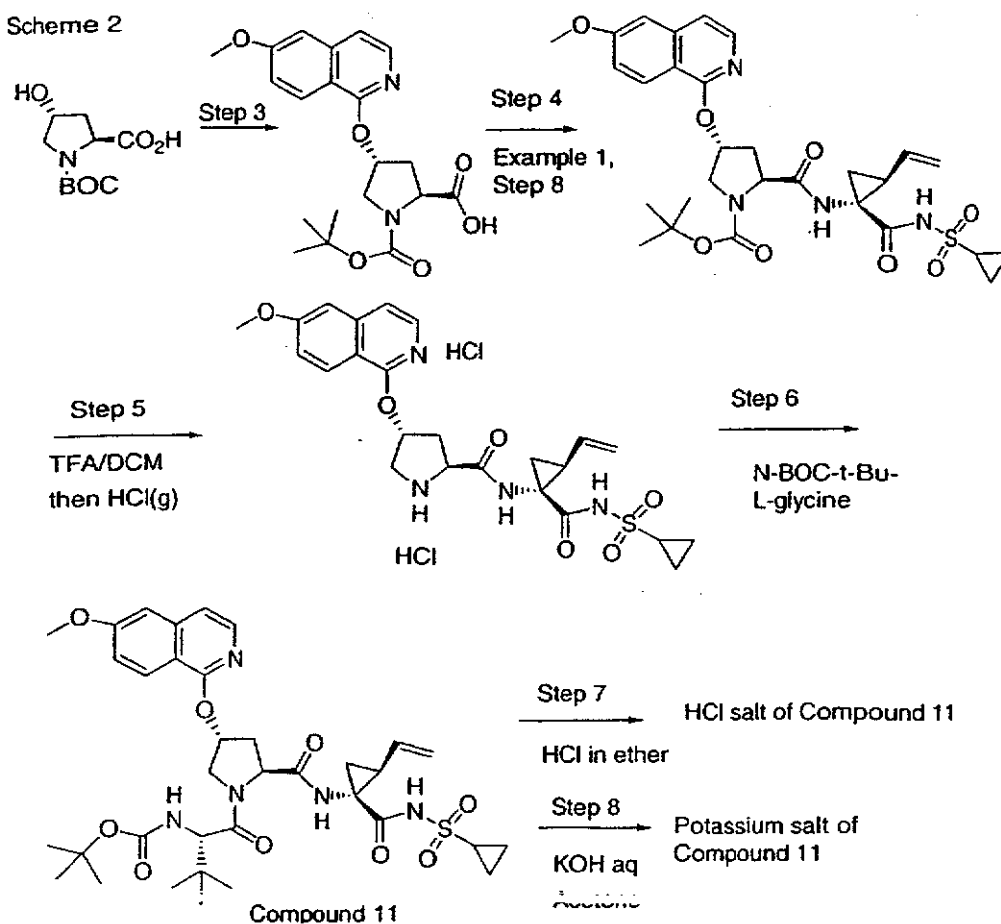
5 Step 2:

6-Methoxy-2*H*-isoquinolin-1-one (5.0 g, 28.4 mmol) in POCl₃ (10 mL) was heated to gentle reflux for 3 h the evaporated *in vacuo* (Nicolas Briet *at el*, *Tetrahedron*, 2002, 5761-5766). The residue was poured into iced water (20 mL) and neutralized to pH 10 with 10 M NaOH. Extracted with CHCl₃. The organic layer was washed with
10 brine, dried over MgSO₄, filtered, evaporated. The residue was purified by flash chromatography (1:1 hexane-EtOAc) to afford 4.41 g (80%) of the desired product as a white solid.

¹H NMR (CD₃OD) δ 3.98 (s, 3H), 7.34-7.38 (m, 2 H), 7.69 (d, $J=5.5$ Hz, 1H), 8.10 (d, $J=6.0$ Hz, 1H), 8.23 (d, $J=9.5$ Hz, 1H);

15 LC-MS (retention time: 1.42 min, method B), MS m/z 194 ($M^+ + H$).

Scheme 2



Step 3:

To a solution of N-BOC-3-(*R*)-hydroxy-L-proline (892 mg, 3.89 mmol) in DMSO (40 mL) at the ambient temperature was added potassium tert-butoxide (1.34 g, 12.0 mmol) in one portion. The formed suspension was stirred at this temperature for 30 min before being cooled to 10°C. 1-chloro-6-methoxyisoquinoline (example 11, Step 2) (785 mg, 4.05 mmol) was added as solid in one portion and the final mixture was stirred at the ambient temperature for 12 h. Quenched with iced 5% citric acid (aq), extracted with EtOAc (100 mL). The aqueous phase was extracted with EtOAc again. The combined organic layers were washed with 5% citric acid (aq) and brine respectively, dried over MgSO₄, filtered. The filtrate was evaporated in vacuo to dryness to yield 1.49 g (99%) of the desired product as an off-white foam. This material was used in the next step reaction as crude without further purification.

^1H NMR (CD_3OD) δ 1.42, 1.44 (rotamers, 9H), 2.38-2.43 (m, 1H), 2.66-2.72 (m, 1H), 3.80-3.87 (m, 2H), 3.92 (s, 3H), 4.44-4.52 (m, 1H), 5.73 (b, 1H), 7.16-7.18 (m, 2H), 7.24-7.25 (m, 1H), 7.87-7.88 (m, 1H), 8.07 (d, $J=8.5$ Hz, 1H);
LC-MS (retention time: 1.62 min, method B), MS m/z 389 ($\text{M}^+ + \text{H}$).

5

Step 4:

To a mixture of the product of Example 11, Step 3 (1.49 g, 3.84 mmol), HATU (2.19 g, 5.76 mmol), and cyclopropanesulfonic acid (1-(R)-amino-2-(S)-vinyl-cyclopropanecarbonyl)-amide HCl salt (Example 1, Step 8) (1.12 g, 4.22 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (1.29 g, 11.5 mmol) at 0°C . After stirring at the ambient temperature for 12 h, the formed solution was diluted with CH_2Cl_2 (50 mL), washed with iced 5% citric acid (aq). The organic layer was washed with 5% citric acid (aq) and brine respectively, dried over MgSO_4 , and filtered. The filtrate was evaporated in vacuo to dryness. The residue was recrystallized from methanol to yield 1.60 g (70%) of the desired product as a white solid.

15

^1H NMR (CD_3OD) δ 1.05-1.08 (m, 2H), 1.16-1.20 (m, 1H), 1.24-1.27 (m, 1H), 1.42-1.45 (m, 10H), 1.88 (dd, $J=8.09, 5.34$ Hz, 1H), 2.24-2.30 (m, 2H), 2.53-2.57 (m, 1H), 2.94-2.98 (m, 1H), 3.80 (d, $J=12.5$ Hz, 1H), 3.86-3.89 (m, 1H), 3.93 (s, 3H), 4.40-4.42 (m, 1H), 5.13 (d, $J=10.5$ Hz, 1H), 5.32 (d, $J=18.0$ Hz, 1H), 5.72-5.81 (m, 2H), 7.17-7.20 (m, 2 H), 7.26 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.07 (d, $J=9.0$ Hz, 1H);

20

LC-MS (retention time: 1.74 min, method B), MS m/z 601 ($\text{M}^+ + \text{H}$).

Step 5:

To an iced solution of the product of Example 11, Step 4 (1.50 g, 2.50 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The formed solution was allowed to warm to the ambient temperature for 2 h. The solvent was removed *in vacuo*. The residue was triturated with 1M HCl in ether. Filtered, washed with ether to yield 1.43 g (99.8%) of the desired product as a hygroscopic white solid.

25

^1H NMR (CD_3OD) δ 1.03-1.208 (m, 4H), 1.26-1.31 (m, 1H), 1.37-1.40 (m, 1H), 1.95-1.97 (m, 1H), 2.32-2.37 (m, 1H), 2.42-2.48 (m, 1H), 2.95-2.99 (m, 1H), 3.88 (d, $J=12.5$ Hz, 2H), 3.98 (s, 3H), 4.40-4.42 (m, 1H), 5.16 (d, $J=10.5$ Hz, 1H), 5.33 (d,

30

$J=18.0$ Hz, 1H), 5.62-5.69 (m, 1H), 5.97 (b, 1H), 7.30-7.34 (m, 2H), 7.47 (d, $J=6.0$ Hz, 1H), 7.90 (d, $J=6.5$ Hz, 1H), 8.34 (d, $J=9.0$ Hz, 1H), 9.14 (b, 1H);
LC-MS (retention time: 1.12 min, method B), MS m/z 501 ($M^+ + H$).

5 Step 6:

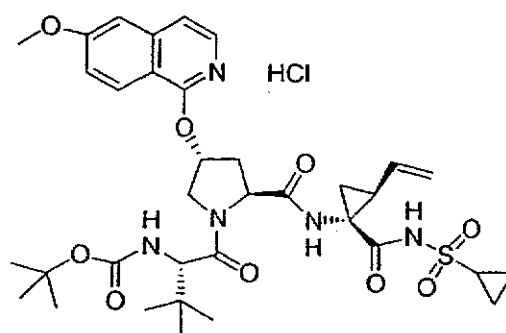
To a mixture of the product of Example 11, Step 5 (1.49 g, 3.84 mmol), HATU (2.19 g, 5.76 mmol), and N-BOC-t-butyl-L-glycine (1.12 g, 4.22 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (1.29 g, 11.5 mmol) at $0^\circ C$. After stirring at the ambient temperature for 12 h, the formed solution was diluted with CH_2Cl_2 (50 mL),
10 washed with iced 5% citric acid (aq). The organic layer was washed with 5% citric acid (aq) and brine respectively, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to dryness. The residue was purified by prep-HPLC (40%B to 100%B, 15 min gradient time) to yield 1.60 g (70%) of Compound 11 as a white solid.

15 ^1H NMR (CD_3OD) δ 1.00-1.08 (m, 12H), 1.23-1.25 (m, 1H), 1.27 (s, 9H), 1.40-1.45 (m, 1H), 1.85-1.88 (m, 1H), 2.20-2.30 (m, 2H), 2.55-2.61 (m, 1H), 2.91-2.97 (m, 1H), 3.92 (s, 3H), 4.02-4.06 (m, 1H), 4.21-4.24 (m, 1H), 4.40-4.42 (m, 1H), 4.49-4.51 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.28 (d, $J=18.0$ Hz, 1H), 5.69-5.74 (m, 1H), 5.81 (b, 1H), 6.60 (d, $J=10.0$ Hz, 1H), 7.08-7.10 (m, 1H), 7.18 (s, 1H), 7.25 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.09 (d, $J=9.0$ Hz, 1H);
20

LC-MS (retention time: 1.75 min, method B), MS m/z 714 ($M^+ + H$);

Anal. Calcd for $C_{35}H_{47}N_5O_9S \cdot 0.5 H_2O$: C, 58.16; H, 6.69; N, 9.69, Found: C, 58.01; H, 6.46; N, 9.55.

25 Step 7:



To a solution of Compound 11 (71 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at -78°C was added 1M HCl in ether (0.2 mL, 0.2 mmol). After stirring at this temperature for 10 min, the volatile was removed in vacuo without heating bath. The residue was triturated with ether, filtered, washed with ether and dried to yield 61 mg (85%) of the desired HCl salt of Compound 11 as a very fine solid.

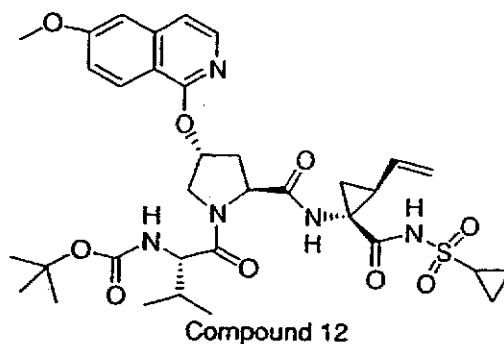
^1H NMR (CD_3OD) δ 1.00-1.08 (m, 12H), 1.19 (s, 9H), 1.23-1.25 (m, 1 H), 1.40-1.45 (m, 1H), 1.85-1.91 (m, 1H), 2.20-2.26 (m, 1H), 2.31-2.42 (m, 1 H), 2.65-2.78 (m, 1H), 2.92-2.97 (m, 1H), 4.00 (s, 3H), 4.10-4.16 (m, 2H), 4.51-4.64 (m, 2H), 5.13 (d, $J=10.5$ Hz, 1H), 5.30 (d, $J=18$ Hz, 1H), 5.69-5.79 (m, 1H), 5.84 (b, 1H), 7.28 (d, $J=9.3$ Hz, 1H), 7.40 (s, 1H), 7.55 (d, $J=6.3$ Hz, 1H), 7.89-7.92 (m, 1H), 8.29 (d, $J=9.0$ Hz, 1H), 9.21 (b, 1 H);

LC-MS (retention time: 1.75 min, method B), MS m/z 714 ($\text{M}^+ + \text{H}$).

Anal. Calcd for $\text{C}_{35}\text{H}_{47}\text{N}_5\text{O}_9\text{S} \cdot 1.0 \text{ HCl}$: C, 56.02; H, 6.44; N, 9.33; Cl, 4.72; S, 4.27. Found: C, 55.80; H, 6.42; N, 9.15; Cl, 4.56; S, 4.09.

Step 8:

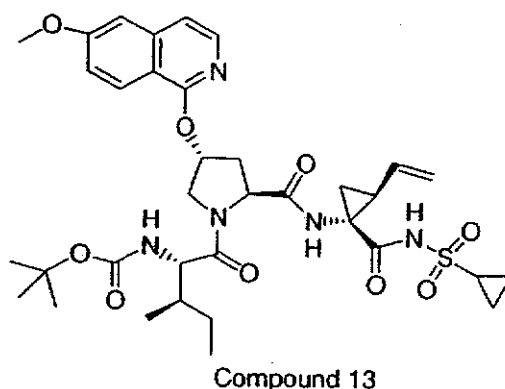
To a 25 ml 2 neck flask was added a stir bar, septa and N_2 gas adapter. Compound 11 (99.7 mg, 0.140 mmol) was weighed out and added to the reaction flask. The reaction flask was purged and placed under a N_2 atmosphere. 850 μl of acetone was added to the flask to provide a clear solution. To this solution at room temperature was added 780 μl of a .179 M solution of KOH (aq.) prepared by the dissolution of solid KOH (502.8 mg, 8.97 mmol) in 50 ml of H_2O . The solution warmed slightly upon addition of the KOH but remained clear. The clear solution was allowed to stir at RT for 2 hours. The product crystallized out of solution and was isolated by filtration. The cake was washed with cold acetone to afford 42 mg (40% yield) of the desired product as fine white needles: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 0.52 - 0.65 (m, 2H), 0.66 - 0.82 (m, 2H), 0.96 (s, 9H), 1.21 - 1.24 (m, 10H), 1.44 - 1.63 (m, 1H), 1.72 - 1.92 (m, 1H), 2.30 - 2.42 (m, 1H), 2.46 (d, $J=7.93$ Hz, 1H), 2.60 - 2.85 (m, 1H), 3.89 (s, 3H), 3.93 - 4.05 (m, 1H), 4.07 - 4.24 (m, 1H), 4.41 (t, $J=8.39$ Hz, 1H), 4.79 - 4.95 (m, 1H), 4.97 - 5.17 (m, 1H), 5.71 (b, 1H), 5.80 - 6.10 (m, 1H), 6.64 (d, $J=8.54$ Hz, 1H), 7.10 (d, $J=8.85$ Hz, 1H), 7.24 - 7.37 (m, 2H), 7.90 - 7.96 (m, 1H), 7.99 - 8.04 (b, 1H), 8.06 (d, $J=9.15$ Hz, 1H). Elemental analysis for $\text{C}_{35}\text{H}_{46}\text{KN}_5\text{O}_9\text{S} \cdot \text{H}_2\text{O}$; calc. C, 54.60; H, 6.28; K, 5.08; N, 9.10 actual C, 54.88; H, 6.23; K, 5.05; N, 9.01; MS m/e 714 (MH^+);

Example 12: Preparation of Compound 12.

Compound 12 was prepared by the same procedure as described in Example 11, Step
 5 6, except using N-BOC-L-valine instead.

¹H NMR (CD₃OD) δ 0.94-0.98 (m, 6H), 1.07-1.09 (m, 3H), 1.21-1.25 (m, 10H),
 1.40-1.43 (m, 1H), 1.88-1.89 (m, 1H), 2.05-2.09 (m, 1H), 2.22-2.35 (m, 2H), 2.57-
 2.61 (m, 1H), 2.94-2.97 (m, 1H), 3.92 (s, 3H), 4.03-4.06 (m, 2H), 4.47-4.55 (m, 2H),
 5.12 (d, *J*=10.5 Hz, 1H), 5.32 (d, *J*=18.1 Hz, 1H), 5.74-5.81 (m, 1H), 5.86 (b, 1H),
 10 7.10 (d, *J*=9.0 Hz, 1H), 7.18 (s, 1H), 7.25 (d, *J*=6.0 Hz, 1H), 7.88 (d, *J*=6.0 Hz, 1H),
 8.10 (d, *J*=9.0 Hz, 1H);

LC-MS (retention time: 1.71 min, method B), MS *m/z* 700 (M⁺+H).

Example 13: Preparation of Compound 13.

15

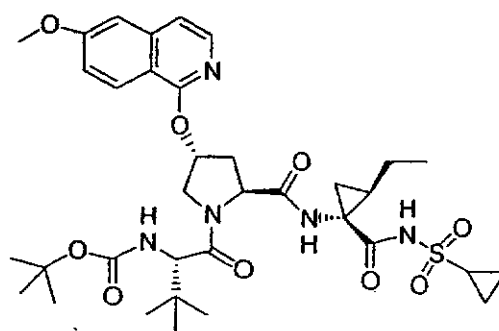
Compound 13 was prepared by the same procedure as described in Example 11, Step
 6, except using N-BOC-L-alloseucine instead.

¹H NMR (CD₃OD) δ 0.89-0.96 (m, 6H), 1.07-1.18 (m, 5H), 1.28 (s, 9H), 1.42-1.45
 (m, 1H), 1.50-1.54 (m, 1H), 1.87-1.89 (m, 2H), 2.23-2.34 (m, 2H), 2.57-2.61 (m,

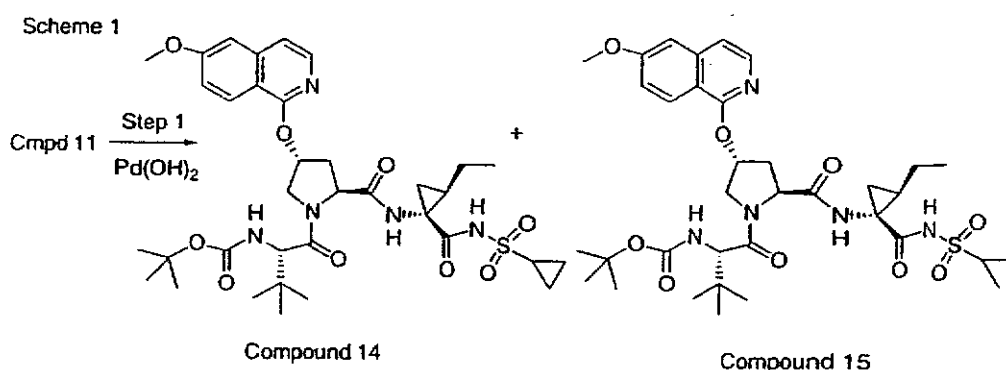
1H), 2.92-2.95 (m, 1H), 3.92 (s, 3H), 4.05-4.07 (m, 1H), 4.22-4.24 (m, 1H), 4.37-4.40 (m, 1H), 4.54-4.56 (m, 1H), 5.13 (d, $J=10.5$ Hz, 1H), 5.32 (d, $J=18.0$ Hz, 1H), 5.75-5.82 (m, 1H), 5.86 (b, 1H), 7.12 (d, $J=9.0$ Hz, 1H), 7.19 (s, 1H), 7.24 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.10 (d, $J=9.0$ Hz, 1H);

5 LC-MS (retention time: 1.77 min, method B), MS m/z 714 ($M^+ + H$).

Example 14: Preparation of Compound 14.



Compound 14



10 Step 1:

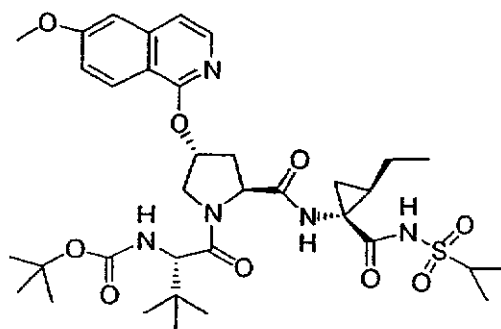
A mixture of Compound 11 (150 mg, 0.21 mmol) and Pearlmann's catalyst ($Pd(OH)_2$, 15 mg) in EtOAc (10 mL) was placed on Parr shaker for 20 min under 10 psi H_2 . Filtered through celite. The filtrate was evaporated in vacuo. The residue was purified by prep-HPLC to provide 67 mg (45%) of Compound 14 as a white solid.

15 ^1H NMR (CD_3OD) δ 0.96-0.99 (m, 4H), 1.04 (s, 9H), 1.07-1.09 (m, 2H), 1.21-1.24 (m, 2H), 1.27 (s, 9H), 1.51-1.65 (m, 4H), 2.25-2.27 (m, 1H), 2.55-2.61 (m, 1H), 2.94-2.98 (m, 1H), 3.92 (s, 3H), 4.02-4.06 (m, 1H), 4.21-4.24 (m, 1H), 4.40-4.42 (m, 1H), 4.49-4.51 (m, 1H), 5.81 (b, 1H), 6.59 (d, $J=10.0$ Hz, 1H), 7.08-7.10 (m, 1H), 7.18 (d,

$J=1.5$ Hz, 1H), 7.24 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.08 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.76 min, method B), MS m/z 716 ($M^+ + H$).

5 Example 15: Preparation of Compound 15.



Compound 15

Compound 15 was isolated from the same reaction of making Compound 14 with a slightly longer retention time as a by-product in 15% yield.

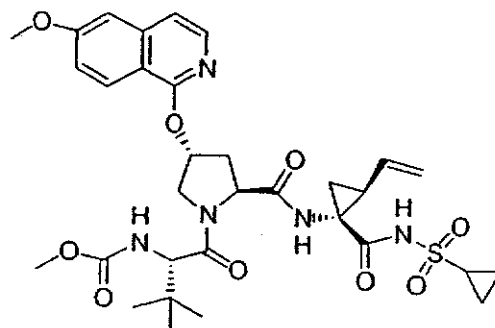
^1H NMR (CD_3OD) δ 0.92-1.10 (m, 17H), 1.26-1.36 (m, 13H), 1.64-1.72 (m, 1H),

1.90-1.96 (m, 1H), 2.30-2.40 (m, 1H), 2.63-2.67 (m, 1H), 2.96-3.00 (m, 1H), 3.92 (s, 3H), 4.03-4.07 (m, 1H), 4.24 (b, 1H), 4.40-4.42 (m, 1H), 4.49-4.51 (m, 1H), 5.83 (b, 1H), 7.08-7.11 (m, 1H), 7.19 (d, $J=2.0$ Hz, 1H), 7.25 (d, $J=6.0$ Hz, 1H), 7.89 (d, $J=6.0$ Hz, 1H), 8.10 (d, $J=9.0$ Hz, 1H), 8.51 (b, 1H);

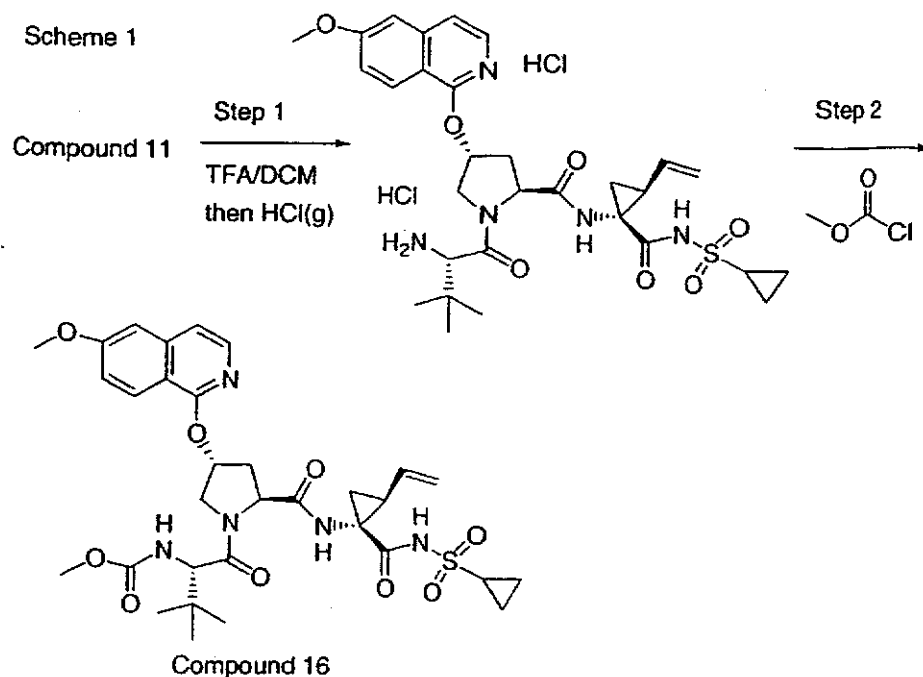
LC-MS (retention time: 1.83 min, method B), MS m/z 718 ($M^+ + H$).

15

Example 16: Preparation of Compound 16.



Compound 16



Step 1:

To a solution of Compound 11 (420 mg, 0.59 mmol) in DCM (5 mL) at 0°C was added TFA (5 mL). After stirring at this temperature for 2 h, the volatile was removed in vacuo. The residue was triturated with 1M HCl in ether (5 mL), filtered, washed with ether and dried to yield 360 mg (89%) of the desired HCl salt as a very fine solid.

LC-MS (retention time: 1.28 min, method B), MS m/z 614 ($M^+ + H$).

Step 2:

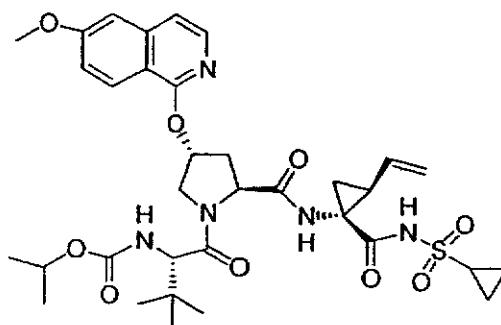
To a suspension of the product of Example 16, Step 1 (39 mg, 0.06 mmol), and DIPEA (20 mg, 0.18 mmol) in DCM (1 mL) at 0°C was added methyl chloroformate (6.8 mg, 0.072 mmol). After stirring at this temperature for 2 h, the volatile was removed in vacuo. The residue was purified by prep-HPLC to give 21 mg (58 %) of Compound 16 as a white crystal.

^1H NMR (CD_3OD) δ 1.05-1.09 (m, 11H), 1.22-1.25 (m, 2H), 1.41-1.44 (m, 1H), 1.86-1.89 (m, 1H), 2.22-2.32 (m, 2H), 2.59-2.63 (m, 1H), 2.89-2.93 (m, 1H), 3.48 (s, 3H), 3.92 (s, 3H), 4.06-4.10 (m, 1H), 4.31-4.33 (m, 1H), 4.38-4.40 (m, 1H), 4.50-4.52 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.30 (d, $J=18.0$ Hz, 1H), 5.71-5.80 (m, 1H),

5.85 (b, 1H), 6.95 (d, $J=10.0$ Hz, 1H), 7.13-7.16 (m, 1H), 7.19 (s, 1H), 7.25 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.09 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.54 min, method B), MS m/z 672 ($M^+ + H$).

5 Example 17: Preparation of Compound 17.

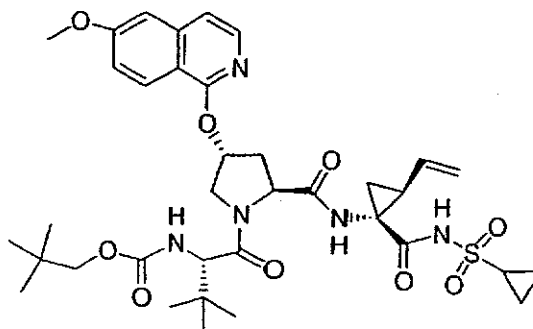


Compound 17

Compound 17 was prepared by the same procedure as described in Example 16, Step 2, except using isopropyl chloroformate instead.

- ¹H NMR (CD₃OD) δ 1.00-1.09 (m, 15H), 1.13-1.16 (m, 2H), 1.24-1.26 (m, 2H),
 10 1.40-1.45 (m, 1H), 1.86-1.89 (m, 1H), 2.21-2.31 (m, 2H), 2.55-2.61 (m, 1H), 2.91-
 2.97 (m, 1H), 3.92 (s, 3H), 4.04-4.08 (m, 1H), 4.30 (b, 1H), 4.40 (d, $J=10$ Hz, 1H),
 4.49-4.54 (m, 2H), 5.12 (d, $J=10.5$ Hz, 1H), 5.29 (d, $J=18.0$ Hz, 1H), 5.71-5.77 (m,
 1H), 5.84 (b, 1H), 6.80 (d, $J=10.0$ Hz, 1H), 7.11 (d, $J=9.0$ Hz, 1H), 7.19 (s, 1H), 7.25
 (d, $J=6.0$ Hz, 1H), 7.88 (d, $J=6.0$ Hz, 1H), 8.08 (d, $J=9.0$ Hz, 1H);
 15 LC-MS (retention time: 1.74 min, method B), MS m/z 700 ($M^+ + H$).

Example 18: Preparation of Compound 18.

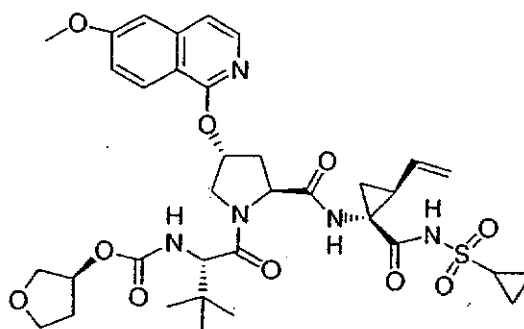


Compound 18

Compound 18 was prepared by the same procedure as described in Example 16, Step 2, except using neopentyl chloroformate instead.

- ¹H NMR (CD₃OD) δ 0.61 (b, 1H), 0.84 (s, 8H), 1.05-1.09 (m, 11H), 1.23-1.25 (m, 2H), 1.39-1.44 (m, 1H), 1.85-1.88 (m, 1H), 2.20-2.30 (m, 2H), 2.56-2.62 (m, 1H),
 5 2.91-2.97 (m, 1H), 3.38 (d, *J*=9.0 Hz, 1H), 3.55 (d, *J*=9.0 Hz, 1H), 3.92 (s, 3H), 4.02-4.06 (m, 1H), 4.32 (d, *J*=9.5 Hz, 1H), 4.41 (d, *J*=9.0 Hz, 1H), 4.49-4.51 (m, 1H), 5.12 (d, *J*=10.5 Hz, 1H), 5.28 (d, *J*=18.0 Hz, 1H), 5.69-5.74 (m, 1H), 5.81 (b, 1H), 6.90 (d, *J*=10.0 Hz, 1H), 7.08-7.10 (m, 1H), 7.19 (s, 1H), 7.26 (d, *J*=6.0 Hz, 1H), 7.88 (d, *J*=6.0 Hz, 1H), 8.07 (d, *J*=9.0 Hz, 1H);
 10 LC-MS (retention time: 1.84 min, method B), MS *m/z* 728 (M⁺+H).

Example 19: Preparation of Compound 19.

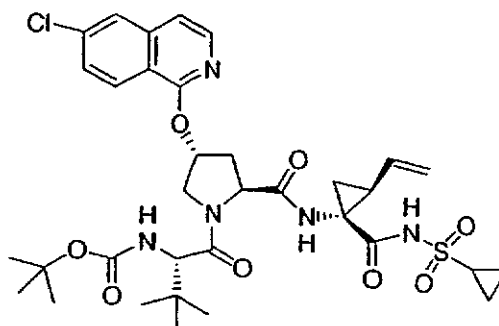


Compound 19

- Compound 19 was prepared by the same procedure as described in Example 16, Step 2, except using (S)-3-furanochloroformate (J. Campbell, A. Good, WO 20020808) instead.

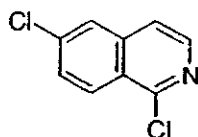
- ¹H NMR (CD₃OD) δ 1.03-1.08 (m, 11H), 1.23-1.26 (m, 2H), 1.38-1.46 (m, 1H), 1.64-1.71 (m, 1H), 1.85-1.90 (m, 2H), 2.20-2.30 (m, 2H), 2.55-2.61 (m, 1H), 2.91-2.97 (m, 1H), 3.66-3.72 (m, 4H), 3.93 (s, 3H), 4.05-4.09 (m, 1H), 4.27-4.29 (m, 1H),
 20 4.40-4.42 (m, 1H), 4.55-4.59 (m, 1H), 4.75-4.77 (m, 1H), 5.12 (d, *J*=10.5 Hz, 1H), 5.28 (d, *J*=18 Hz, 1H), 5.73-5.80 (m, 1H), 5.85 (b, 1H), 7.06 (d, *J*=10.0 Hz, 1H), 7.13 (d, *J*=9.0 Hz, 1H), 7.20 (s, 1H), 7.25 (d, *J*=6.0 Hz, 1H), 7.89 (d, *J*=6.0 Hz, 1H), 8.07 (d, *J*=9.0 Hz, 1H);

LC-MS (retention time: 1.52 min, method B), MS *m/z* 728 (M⁺+H).

Example 20: Preparation of Compound 20.

Compound 20

Step 1:

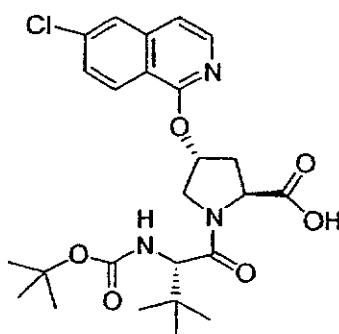


- 5 This product was prepared by the same procedure as described in Example 11, Step 2, except using 6-chloro-2H-isoquinolin-1-one ((Nicolas Briet *et al*, **Tetrahedron**, 2002, 5761-5766) instead.

LC-MS (retention time: 1.07 min, method B). MS m/z 180 ($M^+ + H$).

10

Step 2:



This product was prepared by the same procedure as described in Example 1, Step 5, except using the product of Example 20, Step 1 instead.

- 15 ^1H NMR (CD_3OD) δ 1.04 (s, 9H), 1.20 (s, 9H), 2.36-2.41 (m, 1H), 2.74-2.78 (m, 1H), 4.01-4.04 (m, 1H), 4.19-4.21 (m, 1H), 4.47-4.49 (m, 1H), 4.67-4.70 (m, 1H), 5.84 (b, 1H), 7.28 (d, $J=6.0$ Hz, 1H), 7.47 (d, $J=6.0$ Hz, 1H), 7.84 (s, 1H), 8.00 (d, $J=6.0$ Hz, 1H), 8.20 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.88 min, method B), MS m/z 506 ($M^+ + H$).

Step 3:

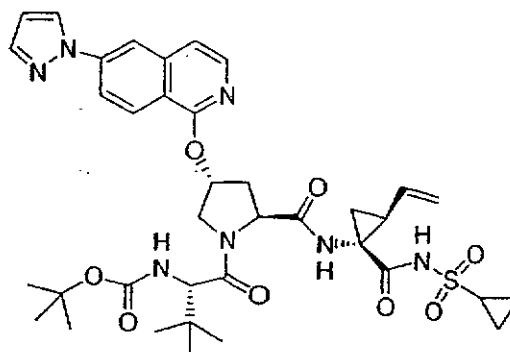
Compound 20 was prepared by the same procedure as described in Example

1, Step 9, except using the product of Example 20, Step 2 instead.

^1H NMR (CD_3OD) δ 0.99-1.11 (m, 12H), 1.20-1.26 (m, 10H), 1.43-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.22-2.31 (m, 2H), 2.60-2.64 (m, 1H), 2.92-2.97 (m, 1H), 4.06-4.08 (m, 1H), 4.21-4.23 (m, 1H), 4.45-4.47 (m, 1H), 4.53-4.56 (m, 1H), 5.13 (d, $J=10.5$ Hz, 1H), 5.29 (d, $J=18.0$ Hz, 1H), 5.72-5.80 (m, 1H), 5.88 (b, 1H), 6.58 (d, $J=10.0$ Hz, 1H), 7.29 (d, $J=6.0$ Hz, 1H), 7.47 (d, $J=9.0$ Hz, 1H), 7.86 (s, 1H), 8.01 (d, $J=6.0$ Hz, 1H), 8.18 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.94 min, method B), MS m/z 718 ($M^+ + H$).

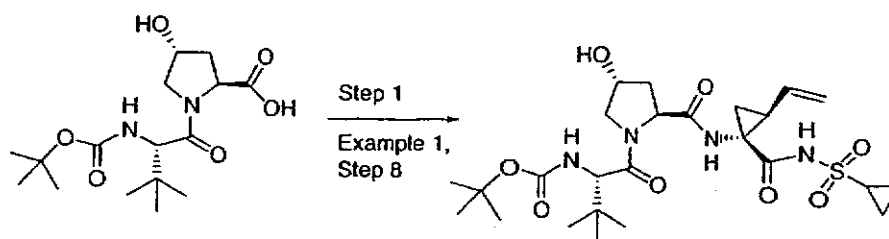
Example 21: Preparation of Compound 21.



Compound 21

15

Scheme 1



Step 1:

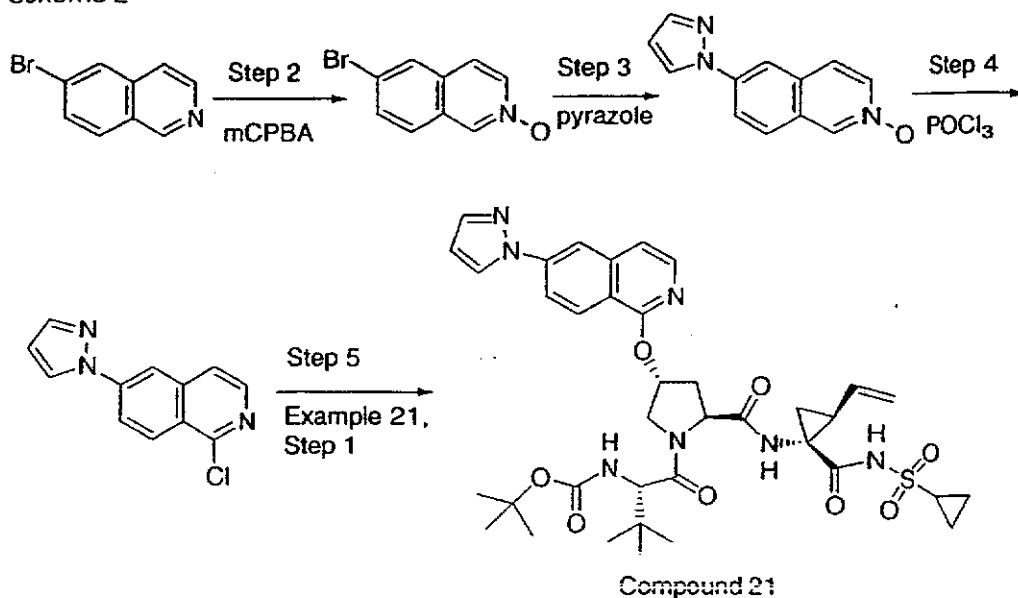
To a mixture of the product of Example 1, Step 4 (3.00 g, 8.72 mmol), HATU (4.97 g, 13.1 mmol), and product of Example 1, Step 8 (2.55 g, 9.59 mmol) in CH_2Cl_2 (100 mL) was added DIPEA (3.02 g, 27.0 mmol) at $0^\circ C$. After stirring at the

20

ambient temperature for 12 h, the formed solution was diluted with CH_2Cl_2 (100 mL), washed with iced 5% citric acid (aq). The organic layer was washed with 5% citric acid (aq) and brine respectively, dried over MgSO_4 , and filtered. The filtrate was evaporated in vacuo to dryness. The residue was purified by flash column (1:1
5 hexane:acetone) to yield 3.64 g (75%) of the desired product as a foam.

LC-MS (retention time: 1.41 min, method B), MS m/z 557 ($\text{M}^+ + \text{H}$).

Scheme 2



Step 2:

To an iced solution of 6-bromoisoquinoline (4.16 g, 20 mmol) in CH_2Cl_2 (100
10 mL) was added *m*CPBA (9.38 g, 77% pure, 42 mmol) as solid in one portion. After stirring at the ambient temperature for 12 h, diluted with CH_2Cl_2 (100 mL) and washed with 1M NaOH (100 mL, X2) and brine. The organic layer was dried over MgSO_4 , filtered, evaporated to dryness to yield 3.83 g (86%) of the desired product as a white solid. This material was used as crude without further purification.

15 LC-MS (retention time: 0.77min, method B), MS m/z 224, 226($\text{M}^+ + \text{H}$).

Step 3:

A mixture of 6-bromo-isoquinoline 2-oxide (88 mg, 0.2 mmol), pyrazole (68
20 mg, 1.0 mmol), CuBr (57 mg, 0.4 mmol) and cesium carbonate (130 mg, 0.4 mmol) in DMF (2 mL) was heated to 140°C for 4 h in a sealed tube. After filtration, the

filtrated was purified by prep-HPLC to yield 41 mg (98%) of the desired product as an off-white solid.

¹H NMR (CDCl₃) δ 6.58-6.59 (m, 1H), 7.82 (d, *J*=1.0 Hz, 1H), 7.89 (d, *J*=7.0 Hz, 1H), 8.02 (d, *J*=9.0 Hz, 1H), 8.11 (d, *J*=2.5 Hz, 1H), 8.18-8.22 (m, 2H), 8.29 (d, *J*=7.0 Hz, 1H), 9.07 (b, 1H);

LC-MS (retention time: 0.77 min, method B), MS *m/z* 212 (M⁺+H).

Step 4:

This product was prepared by the same procedure as described in Example 11, Step 2 as an off-white solid, except using 6-pyrazol-isoquinoline 2-oxide instead.

¹H NMR (CD₃OD) δ 7.82-7.83 (m, 2H), 8.23-8.32 (m, 4H), 8.44-8.49 (m, 2H);

LC-MS (retention time: 1.35 min, method B), MS *m/z* 230, (M⁺+H).

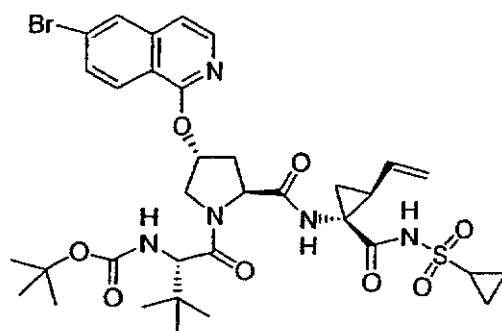
Step 5:

To a solution of product of Example 21, Step 1 (45 mg, 0.08 mmol) in DMSO (2 mL) was added potassium tert-butoxide (41 mg, 0.37 mmol). The formed solution was stirred at the ambient temperature for 30 min before addition of 1-chloro-6-pyrazol-1-yl-isoquinoline (17 mg, 0.07 mmol). The final solution was stirred for 12 h. Quenched with iced water, acidified with 1M HCl to pH 4, extracted with EtOAc (20 mL, X2). The organic layers were washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC to yield 10 mg (16%) of Compound 21 as a pink solid.

¹H NMR (CD₃OD) δ 1.04-1.10 (m, 12H), 1.23-1.27 (m, 10H), 1.43-1.47 (m, 1H), 1.87-1.91 (m, 1H), 2.22-2.29 (m, 2H), 2.61-2.68 (m, 1H), 2.92-2.98 (m, 1H), 4.07-4.11 (m, 1H), 4.24 (b, 1H), 4.46-4.60 (m, 2H), 5.13 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=18 Hz, 1H), 5.70-5.83 (m, 1H), 5.89 (b, 1H), 6.59-6.61 (m, 1H), 7.40 (d, *J*=10.0 Hz, 1H), 7.80 (d, *J*=2.5 Hz, 1H), 8.01 (d, *J*=10.0 Hz, 2H), 8.15 (s, 1H), 8.31 (d, *J*=15.0 Hz, 1H), 8.42 (d, *J*=4.5 Hz, 1H);

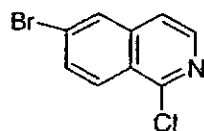
LC-MS (retention time: 1.77 min, method B), MS *m/z* 750 (M⁺+H).

Example 22: Preparation of Compound 22.



Compound 22

Step 1:



This product was prepared by the same procedure as described in Example 11, Step 2
 5 as an off- white solid, except using 6-bromo-isoquinoline 2-oxide instead.

^1H NMR (CD_3OD) δ 7.73 (d, $J=5.5$ Hz, 1H), 7.85-7.91 (m, 1H), 8.22-8.31 (m, 3H);

LC-MS (retention time: 1.53 min, method B), MS m/z 241, 243, 245 (M^++H).

Step 2:

Compound 22 was prepared by the same procedure as described in Example 21. Step
 10 5 as a white solid, except using 1-chloro-6-bromo-isoquinoline instead.

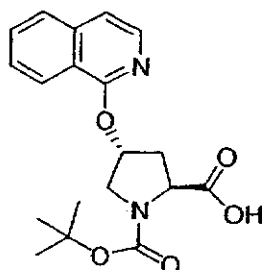
^1H NMR (CD_3OD) δ 0.99-1.09 (m, 12H), 1.22-1.27 (m, 10H), 1.40-1.47 (m, 1H),
 1.86-1.91 (m, 1H), 2.20-2.34 (m, 2H), 2.57-2.66 (m, 1H), 2.90-2.97 (m, 1H), 4.05-
 4.09 (m, 1H), 4.21 (b 1H), 4.44-4.57 (m, 2H), 5.13 (d, $J=10.5$ Hz, 1H), 5.29 (d,
 15 $J=18.0$ Hz, 1H), 5.70-5.82 (m, 1H), 5.88 (b, 1H), 7.29 (d, $J=9.5$ Hz, 1H), 7.60-7.63
 (m, 1H), 8.00-8.12 (m, 3H);

LC-MS (retention time: 1.90 min, method B), MS m/z 762, 764 (M^++H).

Example 23: Preparation of Compound 23.

Step 1:

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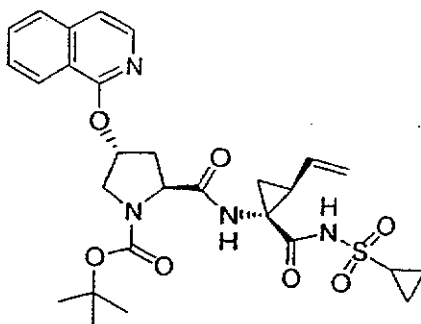


This product was prepared by the same procedure as described in Example 11, Step 3 as a white solid, except using 1-chloro-isoquinoline instead.

¹H NMR (CD₃OD) δ 1.42, 1.44 (rotamers, 9H), 2.39-2.44 (m, 1H), 2.68-2.72 (m, 1H), 3.80-3.87 (m, 2H), 4.44-4.52 (m, 1H), 5.78 (b, 1H), 7.32-7.33 (m, 1H), 7.58 (t, *J*=7.8 Hz, 1H), 7.71 (t, *J*=7.5 Hz, 1H), 7.81 (d, *J*=8.0 Hz, 1H), 7.95 (d, *J*=6.0 Hz, 1H), 8.19 (d, *J*=8.0 Hz, 1H);

LC-MS (retention time: 1.61 min, method B), MS *m/z* 359 (M⁺+H).

Step 2:



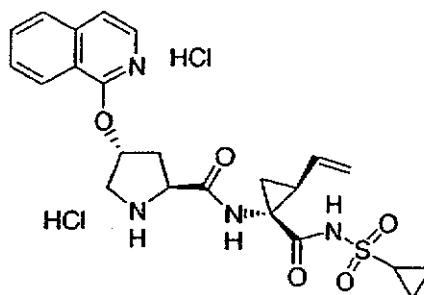
This product was prepared by the same procedure as described in Example 11, Step 4, except using the product of Example 23, Step 1 instead.

¹H NMR (DMSO-*d*₆) δ 1.00-1.09 (m, 4H), 1.35-1.38 (m, 10H), 1.69-1.84 (m, 1H), 2.11-2.66 (m, 3H), 2.89-2.93 (m, 1H), 3.62-3.89 (m, 2H), 4.31 (t, *J*=8.1 Hz, 1H), 5.12 (d, *J*=10.8 Hz, 1H), 5.27 (d, *J*=16.8 Hz, 1H), 5.58-5.70 (m, 1H), 5.76 (b, 1H), 7.43 (d, *J*=5.7 Hz, 1H), 7.66 (t, *J*=7.4 Hz, 1H), 7.79 (t, *J*=7.5 Hz, 1H), 7.92 (d, *J*=8.1 Hz, 1H), 8.02 (d, *J*=10.0 Hz, 1H), 8.13 (d, *J*=8.1 Hz, 1H), 9.02 (b, 1H);

LC-MS (retention time: 1.72 min, method B), MS *m/z* 571 (M⁺+H).

20

Step 3:



This product was prepared by the same procedure as described in Example 11, Step 5, except using the product of Example 23, Step 2 instead.

LC-MS (retention time: 1.16 min, method B), MS m/z 471 ($M^+ + H$).

5

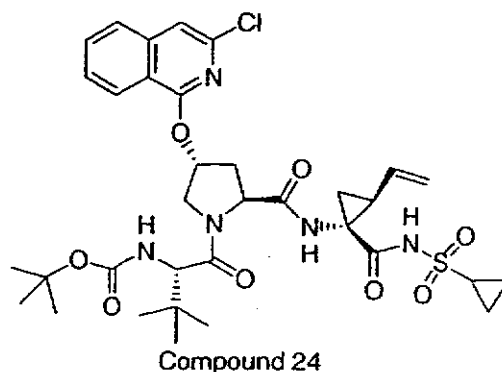
Step 4:

Compound 23 was prepared by the same procedure as described in Example 11, Step 6 as a white solid, except using the product of Example 23, Step 3 instead.

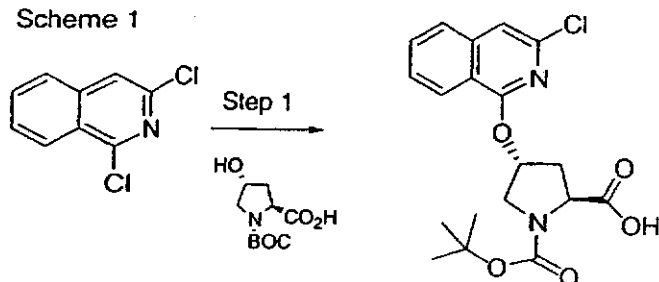
^1H NMR (CD_3OD) δ 1.00-1.09 (m, 12H), 1.25-1.27 (m, 10H), 1.42-1.46 (m, 1H),
 10 1.86-1.90 (m, 1H), 2.22-2.34 (m, 2H), 2.60-2.67 (m, 1H), 2.92-2.99 (m, 1H), 4.06-
 4.11 (m, 1H), 4.26 (b, 1H), 4.45-4.57 (m, 2H), 5.12 (d, $J=10.2$ Hz, 1H), 5.27 (d,
 $J=16.8$ Hz, 1H), 5.70-5.82 (m, 1H), 5.88 (b, 1H), 7.32 (d, $J=6.0$ Hz, 1H), 7.52 (t,
 $J=7.4$ Hz, 1H), 7.70 (t, $J=7.5$ Hz, 1H), 7.80 (d, $J=8.1$ Hz, 1H), 7.97 (d, $J=6$ Hz, 1H),
 8.20 (d, $J=8.4$ Hz, 1H), 9.18 (b, 1H);

15 LC-MS (retention time: 1.80 min, method B), MS m/z 684 ($M^+ + H$).

Example 24: Preparation of Compound 24.



Scheme 1

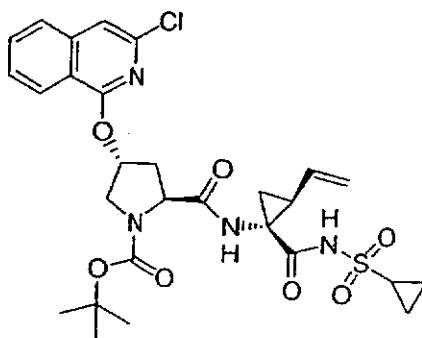


Step 1:

To a solution of N-BOC-3-(*R*)-hydroxy-L-proline (6.22 g, 26.9 mmol) in DMF (250 mL) at 0°C was added NaH (60%, 3.23 g, 80.8 mmol) by several portions.

- 5 The formed suspension was stirred at this temperature for 30 min. 1,3-dichloro-isoquinoline (5.33 g, 26.9 mmol) was added as solid in one portion and the final mixture was stirred at the ambient temperature for 12 h. Quenched with iced 5% citric acid (aq), extracted with EtOAc (300 mL). The aqueous phase was extracted with EtOAc again. The combined organic layers were washed with 5% citric acid
- 10 (aq) and brine respectively, dried over MgSO₄, filtered. The filtrate was evaporated in vacuo to dryness to yield 10.53 g (99.8%) of 4-(6-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester as an off-white foam. This material was used in the next step reaction as crude without further purification.
- ¹H NMR (CD₃OD) δ 1.43, 1.44 (rotamers, 9H), 2.39-2.44 (m, 1H), 2.68-2.72 (m, 1H), 3.80-3.90 (m, 2H), 4.44-4.52 (m, 1H), 5.77 (b, 1H), 7.39 (s, 1H), 7.58 (t, *J*=7.3 Hz, 1H), 7.71-7.78 (m, 2H), 8.16 (d, *J*=7.5 Hz, 1H);
- 15 LC-MS (retention time: 1.80 min, method B), MS *m/z* 392 (M⁺+H).

Step 2:

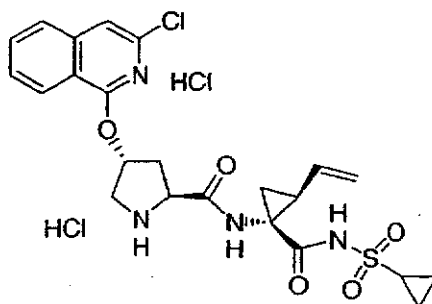


This product was prepared by the same procedure as described in Example 11, Step 4, except using the product of Example 24, Step 1 instead.

¹H NMR (CD₃OD) δ 1.02-1.08 (m, 2H), 1.18-1.26 (m, 2H), 1.44-1.48 (m, 10H), 1.84-1.91 (m, 1H), 2.22-2.36 (m, 2H), 2.57-2.60 (m, 1H), 2.95-2.99 (m, 1H), 3.81-3.93 (m, 2H), 4.38-4.41 (m, 1H), 5.13 (d, J=10.8 Hz, 1H), 5.31 (d, J=16.8 Hz, 1H), 5.75-5.82 (m, 2H), 7.41 (s, 1H), 7.59 (t, J=7.4 Hz, 1H), 7.74-7.79 (m, 2H), 8.16 (d, J=8.0 Hz, 1H);

LC-MS (retention time: 1.82 min, method B), MS *m/z* 605 (M⁺+H).

Step 3:



This product was prepared by the same procedure as described in Example 11, Step 5, except using the product of Example 24, Step 2 instead.

LC-MS (retention time: 1.30 min, method B), MS *m/z* 505 (M⁺+H).

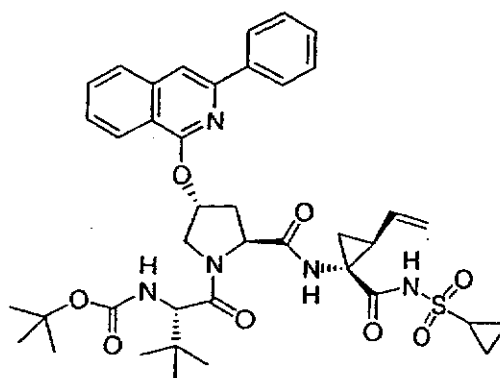
Step 4:

Compound 24 was prepared by the same procedure as described in Example 11, Step 6 as a white solid, except using the product of Example 24, Step 3 instead.

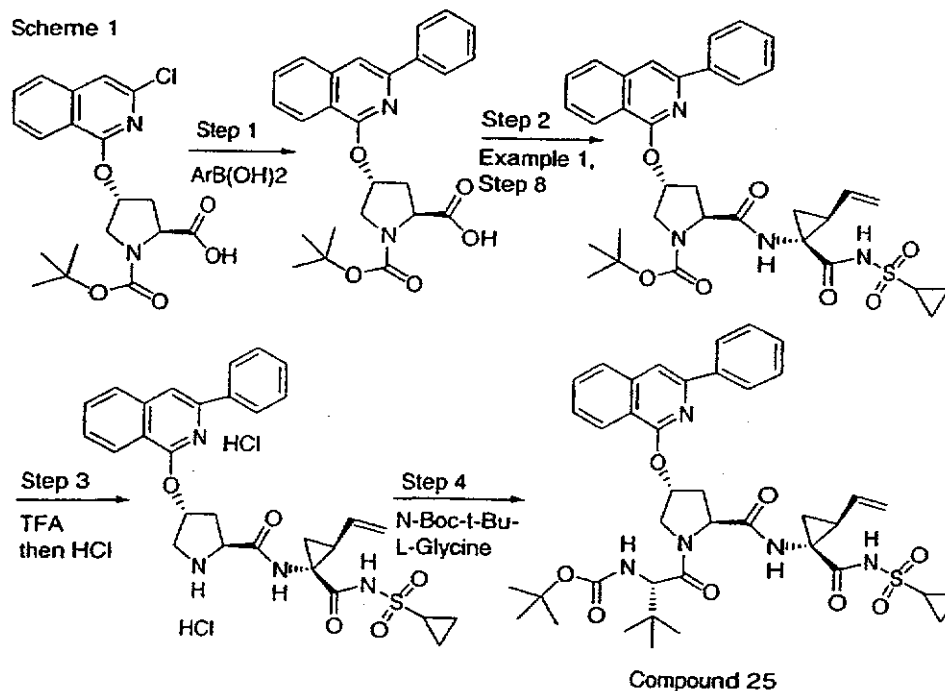
¹H NMR (CD₃OD) δ 0.99-1.09 (m, 12H), 1.22-1.29 (m, 10H), 1.42-1.46 (m, 1H), 1.86-1.90 (m, 1H), 2.21-2.34 (m, 2H), 2.62-2.66 (m, 1H), 2.92-2.99 (m, 1H), 4.06-4.11 (m, 1H), 4.26 (b, 1H), 4.46-4.56 (m, 2H), 5.13 (d, J=10.5 Hz, 1H), 5.29 (d, J=17.2 Hz, 1H), 5.72-5.79 (m, 1H), 5.89 (b, 1H), 7.40 (d, J=6.0 Hz, 1H), 7.52 (t, J=7.4 Hz, 1H), 7.72-7.76 (m, 2H), 8.18 (d, J=8.5 Hz, 1H);

LC-MS (retention time: 1.95 min, method B), MS *m/z* 718 (M⁺+H).

Example 25, Compound 25.



Compound 25



Step 1:

A mixture of Example 24, Step 1 (39 mg, 0.10 mmol), phenylboronic acid (14.6 mg, 0.12 mmol), sodium tert-butoxide (38 mg, 0.40 mmol) and ((t-Bu)₂POH)₂PdCl₂ (POPd) (5 mg, 0.01 mmol) in THF (2 mL) was heated to reflux for 4 h. After cooling down, the formed mixture was quenched with 5% citric acid (aq) and extracted with EtOAc (20 mL). The organic layer was washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC to yield 36 mg (83%) of the desired product as an off-white foam.

¹H NMR (CD₃OD) δ 1.43, 1.45 (rotamers, 9H), 2.51-2.56 (m, 1H), 2.74-2.82 (m, 1H), 3.88-3.92 (m, 1H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.95 (b, 1H), 7.36-

7.39 (m, 1H), 7.45-7.48 (m, 2H), 7.55 (t, $J=7.3$ Hz, 1H), 7.70 (t, $J=7.5$ Hz, 1H), 7.84-7.89 (m, 2H), 8.14-8.17 (m, 3H), 9.05 (b, 1H);

LC-MS (retention time: 1.97 min, method B), MS m/z 435 ($M^+ + H$).

5 Step 2:

This product was prepared by the same procedure as described in Example 11, Step 4, except using the product of Example 25, Step 1 instead.

^1H NMR (DMSO- d_6) δ 0.98-1.10 (m, 4H), 1.38-1.41 (m, 10H), 1.74-1.81 (m, 1H), 2.18-2.34 (m, 2H), 2.47-2.49 (m, 1H), 2.95-2.99 (m, 1H), 3.74-3.96 (m, 2H), 4.34-4.37 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.26 (d, $J=17.8$ Hz, 1H), 5.75-5.82 (m, 1H), 5.95 (b, 1H), 7.41-7.45 (m, 1H), 7.51-7.54 (m, 2H), 7.61-7.64 (m, 1H), 7.78-7.82 (m, 1H), 7.98 (d, $J=9.0$ Hz, 1H), 8.06 (s, 1H), 8.13-8.14 (m, 1H), 8.18-8.20 (m, 2H), 9.05 (b, 1H), 10.34 (b, 1H);

LC-MS (retention time: 1.99 min, method B), MS m/z 647 ($M^+ + H$).

15

Step 3:

This product, was prepared by the same procedure as described in Example 11, Step 5 as a white solid, except using the product of Example 25, Step 2 instead.

LC-MS (retention time: 1.55 min, method B), MS m/z 547 ($M^+ + H$).

20

Step 4:

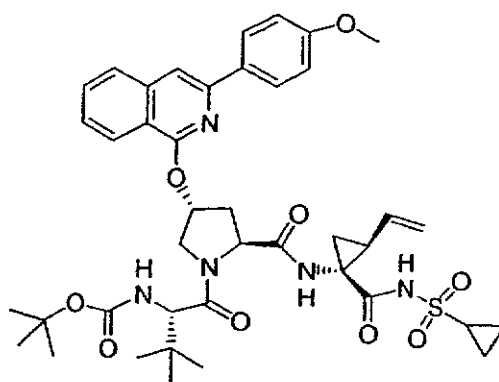
Compound 25 was prepared by the same procedure as described in Example 11, Step 6 as a white solid, except using the product of Example 25, Step 3 instead.

^1H NMR (CD_3OD) δ 0.92-1.09 (m, 12H), 1.26-1.30 (m, 10H), 1.43-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.21-2.26 (m, 1H), 2.36-2.41 (m, 1H), 2.70-2.75 (m, 1H), 2.93-2.97 (m, 1H), 4.18-4.30 (m, 2H), 4.46-4.48 (m, 1H), 4.55-4.58 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.29 (d, $J=18.0$ Hz, 1H), 5.72-5.79 (m, 1H), 6.10 (b, 1H), 7.37-7.40 (m, 1H), 7.46-7.49 (m, 3H), 7.70 (t, $J=7.5$ Hz, 1H), 7.85-7.89 (m, 2H), 8.16-8.20 (m, 3H);

30 LC-MS (retention time: 2.08 min, method B), MS m/z 760 ($M^+ + H$).

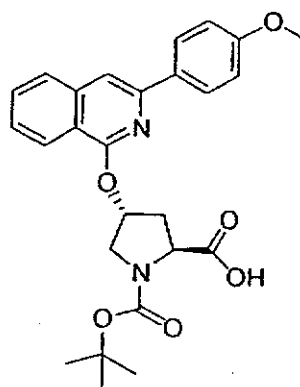
Example 26: Preparation of Compound 26.

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Compound 26

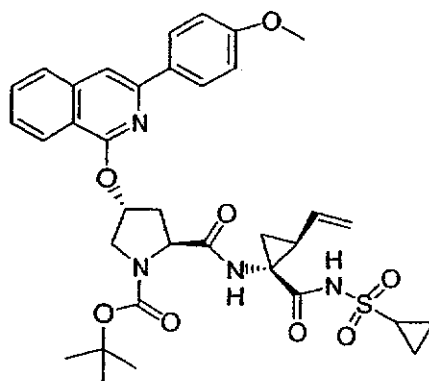
Step 1:



This product was prepared by the same procedure as described in Example 25, Step 1, except using 4-methoxyphenylboronic acid instead.

- ¹H NMR (CD₃OD) δ 1.40, 1.45 (rotamers, 9H), 2.50-2.55 (m, 1H), 2.73-2.81 (m, 1H), 3.81-3.89 (m, 4H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.93 (b, 1H), 7.02 (d, $J=9.0$ Hz, 2H), 7.50 (t, $J=7.3$ Hz, 1H), 7.67 (t, $J=7.5$ Hz, 1H), 7.73 (s, 1H), 7.83 (d, $J=8.5$ Hz, 1H), 8.09 (d, $J=8.5$ Hz, 2H), 8.15 (d, $J=8.0$ Hz, 1H);
- LC-MS (retention time: 2.00 min, method B), MS m/z 465 ($M^+ + H$).

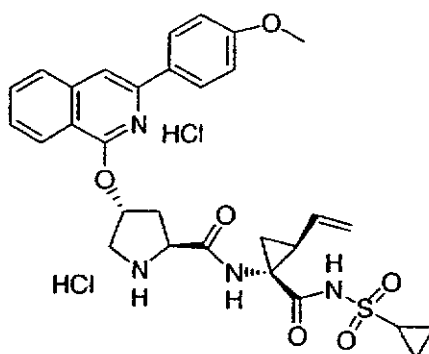
Step 2:



This product was prepared by the same procedure as described in Example 11, Step 4, except using the product of Example 26, Step 1 instead.

- ¹H NMR (CD₃OD) δ 1.06-1.09 (m, 2H), 1.17-1.27 (m, 2H), 1.42-1.47 (m, 10H),
 5 1.88-1.90 (m, 1H), 2.21-2.26 (m, 1H), 2.33-2.39 (m, 1H), 2.61-2.65 (m, 1H), 2.95-
 2.99 (m, 1H), 3.85 (s, 3H), 3.86-3.90 (m, 1H), 3.99-4.00 (m, 1H), 4.43-4.45 (m, 1H),
 5.13 (d, $J=10.8$ Hz, 1H), 5.31 (d, $J=18.0$ Hz, 1H), 5.77-5.80 (m, 1H), 5.99 (b, 1H),
 7.02 (d, $J=9.0$ Hz, 2H), 7.51 (t, $J=7.3$ Hz, 1H), 7.68 (t, $J=7.5$ Hz, 1H), 7.76 (s, 1H),
 7.84 (d, $J=8.5$ Hz, 1H), 8.09 (d, $J=8.5$ Hz, 2H), 8.15 (d, $J=8.0$ Hz, 1H);
 10 LC-MS (retention time: 2.02 min, method B), MS m/z 677 ($M^+ + H$).

Step 3:



- This product was prepared by the same method as described in Example 11, Step 5 as
 15 a white solid, except using the product of Example 26, Step 2 instead.
 LC-MS (retention time: 1.53 min, method B), MS m/z 577 ($M^+ + H$).

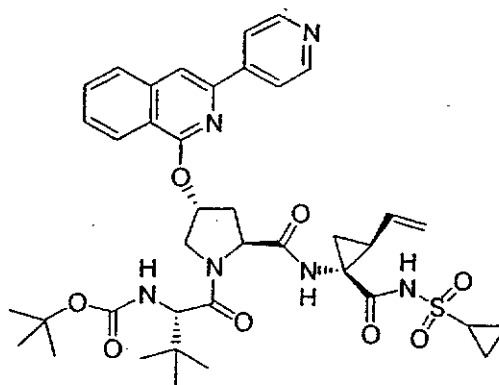
Step 4:

Compound 26 was prepared by the same method as described in Example 11, Step 6, except using the product of Example 26, Step 3 instead.

¹H NMR (CD₃OD) δ 0.93-1.09 (m, 12H), 1.26-1.30 (m, 10H), 1.44-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.21-2.26 (m, 1H), 2.36-2.41 (m, 1H), 2.70-2.75 (m, 1H), 2.93-2.97 (m, 1H), 3.86 (s, 3H), 4.18-4.25 (m, 1H), 4.30 (b, 1H), 4.46-4.48 (m, 1H), 4.55-4.58 (m, 1H), 5.12 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=18.0 Hz, 1H), 5.72-5.79 (m, 1H), 6.08 (b, 1H), 7.02 (d, *J*=9.0 Hz, 2H), 7.44 (t, *J*=7.3 Hz, 1H), 7.66 (t, *J*=7.5 Hz, 1H), 7.75 (s, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 8.09 (d, *J*=8.5 Hz, 2H), 8.15 (d, *J*=8.0 Hz, 1H); LC-MS (retention time: 2.03 min, method B), MS *m/z* 790 (M⁺+H).

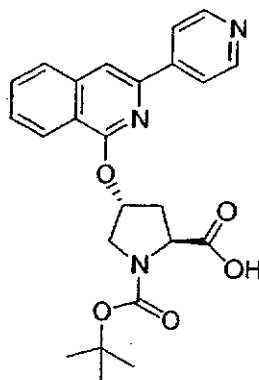
10

Example 27: Preparation of Compound 27.



Compound 27

Step 1:

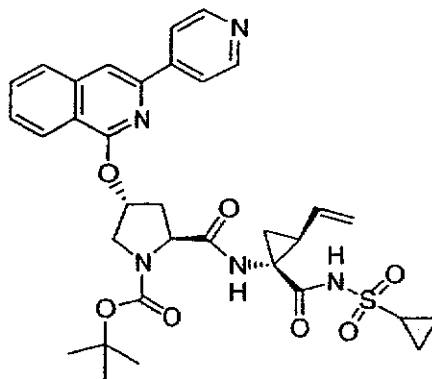


15 This product was prepared by the same method as described in Example 25, Step 1, except using 4-pyridylboronic acid instead.

¹H NMR (CD₃OD) δ 1.43, 1.46 (rotamers, 9H), 2.53-2.56 (m, 1H), 2.80-2.89 (m, 1H), 3.90-3.93 (m, 1H), 4.00-4.05 (m, 1H), 4.50-4.57 (m, 1H), 6.00, 6.05 (rotamers,

1H), 7.80 (t, $J=7.3$ Hz, 1H), 7.87 (t, $J=7.5$ Hz, 1H), 8.08 (d, $J=8.5$ Hz, 1H), 8.32 (d, $J=8.0$ Hz, 1H), 8.49 (s, 1H), 8.84 (d, $J=6.0$ Hz, 2H), 8.84 (d, $J=6.5$ Hz, 2H);
 LC-MS (retention time: 1.39 min, method B), MS m/z 436 ($M^+ + H$).

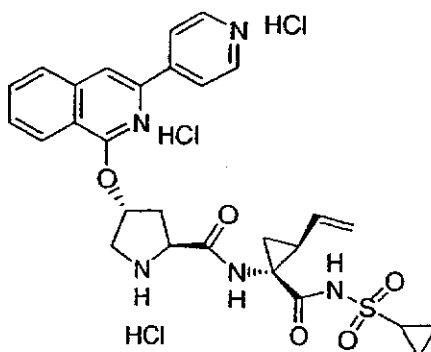
5 Step 2:



The product was prepared by the same method as described in Example 11, Step 4, except using the product of Example 27, Step 1 instead.

^1H NMR (CD_3OD) δ 1.06-1.09 (m, 2H), 1.17-1.27 (m, 2H), 1.42-1.46 (m, 10H),
 10 1.88-1.90 (m, 1H), 2.21-2.26 (m, 1H), 2.33-2.39 (m, 1H), 2.61-2.65 (m, 1H), 2.95-
 2.99 (m, 1H), 3.88-3.90 (m, 1H), 4.01-4.03 (m, 1H), 4.43-4.45 (m, 1H), 5.15 (d,
 $J=10.8$ Hz, 1H), 5.32 (d, $J=18.0$ Hz, 1H), 5.77-5.80 (m, 1H), 6.10 (b, 1H), 7.79 (t,
 $J=7.3$ Hz, 1H), 7.88 (t, $J=7.5$ Hz, 1H), 8.08 (d, $J=8.5$ Hz, 1H), 8.31 (d, $J=8.0$ Hz,
 1H), 8.47 (s, 1H), 8.79 (d, $J=7.0$ Hz, 2H), 8.86 (d, $J=6.5$ Hz, 2H);
 15 LC-MS (retention time: 1.49 min, method B), MS m/z 648 ($M^+ + H$).

Step 3:



This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 27, Step 2 instead.

LC-MS (retention time: 0.96 min, method B), MS m/z 548 ($M^+ + H$).

5 Step 4:

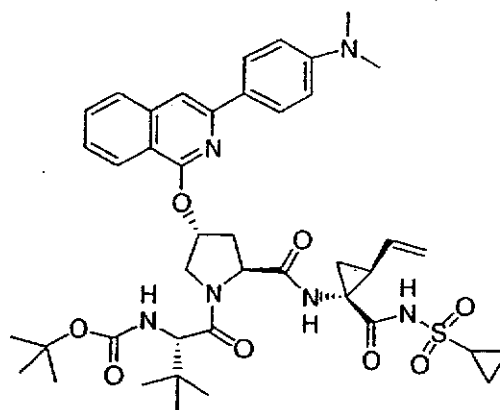
Compound 27 was prepared by the same method as described in Example 11, Step 6, except using the product of Example 27, Step 3 instead.

^1H NMR (CD_3OD) δ 0.94-1.09 (m, 12H), 1.22-1.26 (m, 10H), 1.44-1.49 (m, 1H), 1.88-1.92 (m, 1H), 2.22-2.25 (m, 1H), 2.41-2.44 (m, 1H), 2.70-2.75 (m, 1H), 2.93-2.98 (m, 1H), 4.18-4.21 (m, 1H), 4.25 (b, 1H), 4.53-4.62 (m, 2H), 5.12 (d, $J=10.0$ Hz, 1H), 5.29 (d, $J=20.0$ Hz, 1H), 5.72-5.77 (m, 1H), 6.12 (b, 1H), 7.67 (t, $J=7.3$ Hz, 1H), 7.82 (t, $J=7.5$ Hz, 1H), 8.02 (d, $J=8.5$ Hz, 1H), 8.29 (d, $J=8.0$ Hz, 1H), 8.31 (s, 1H), 8.55 (d, $J=7.0$ Hz, 2H), 8.76 (d, $J=6.5$ Hz, 2H);

LC-MS (retention time: 1.49 min, method B), MS m/z 761 ($M^+ + H$).

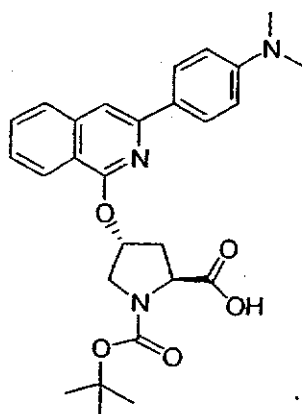
15

Example 28: Preparation of Compound 28.



Compound 28

Step 1:

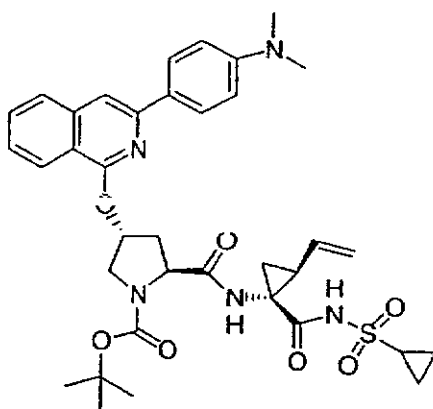


This product was prepared by the same method as described in Example 25, Step 1, except using 4-N,N-dimethylamino-phenylboronic acid instead.

LC-MS (retention time: 1.64 min, method B), MS m/z 478 ($M^+ + H$).

5

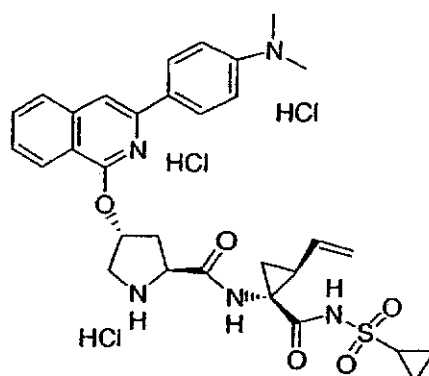
Step 2:



This product was prepared by the same method as described in Example 11, Step 4, except using the product of Example 28, Step 1 instead.

10 LC-MS (retention time: 1.70 min, method B), MS m/z 690 ($M^+ + H$).

Step 3:



This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 28, Step 2 instead.

LC-MS (retention time: 1.20 min, method B), MS m/z 590 ($M^+ + H$).

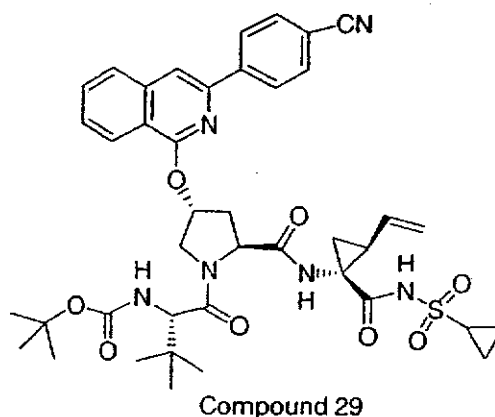
5

Step 4:

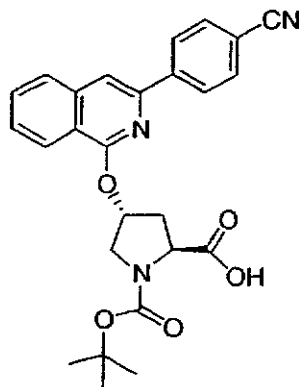
Compound 28 was prepared by the same method as described in Example 11, Step 6, except using the product of Example 28, Step 3 instead.

- ^1H NMR (d_6 -DMSO) δ 0.92-1.10 (m, 13H), 1.30 (s, 9H), 1.35-1.38 (m, 1H), 1.68-1.71 (m, 1H), 2.12-3.00 (m, 2H), 2.59-2.62 (m, 1H), 2.91-2.95 (m, 1H), 2.99 (s, 6H), 3.93-4.10 (m, 2H), 4.32-4.40 (m, 2H), 5.09 (d, $J=11.5$ Hz, 1H), 5.23 (d, $J=19.0$ Hz, 1H), 5.54-5.64 (m, 1H), 5.92 (b, 1H), 6.83 (d, $J=9.0$ Hz, 2H), 7.42 (t, $J=7.3$ Hz, 1H), 7.70 (t, $J=7.5$ Hz, 1H), 7.81 (s, 1H), 7.87 (d, $J=8.5$ Hz, 1H), 8.04 (d, $J=9.0$ Hz, 2H), 8.15 (d, $J=8.0$ Hz, 1H);
- LC-MS (retention time: 1.72min, method B), MS m/z 803 ($M^+ + H$).

Example 29: Preparation of Compound 29.



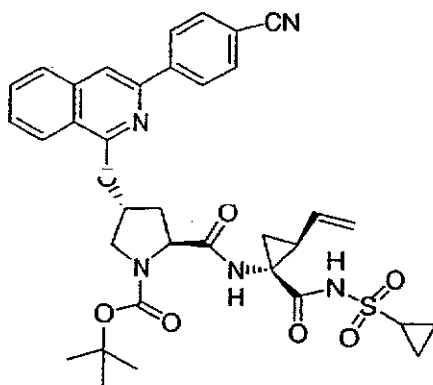
Step 1:



This product was prepared by the same method as described in Example 25, Step 1, except using 4-cyano-phenylboronic acid instead.

- 5 LC-MS (retention time: 1.87 min, method B), MS m/z 460 ($M^+ + H$).

Step2:

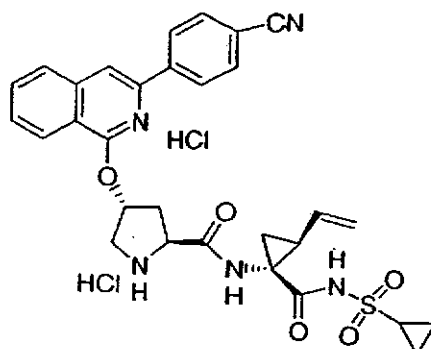


- 10 This product was prepared by the same method as described in Example 11, Step 4, except using the product of Example 29, Step 1 instead.

LC-MS (retention time: 1.88 min, method B), MS m/z 672 ($M^+ + H$).

Step 3:

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This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 29, Step 2 instead.

LC-MS (retention time: 1.41 min, method B), MS m/z 572 ($M^+ + H$).

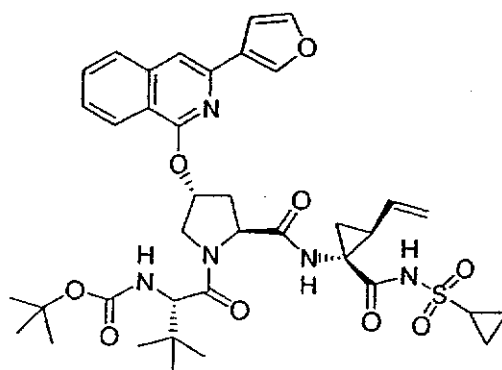
5

Step 4:

Compound 29 was prepared by the same method as described in Example 11, Step 6 as a white solid, except using the product of Example 29, Step 3 instead.

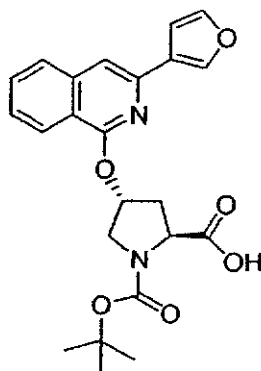
- ^1H NMR (CD_3OD) δ 0.92-1.09 (m, 12H), 1.25-1.26 (m, 10H), 1.42-1.46 (m, 1H),
 10 1.86-1.89 (m, 1H), 2.20-2.22 (m, 1H), 2.33-2.34 (m, 1H), 2.68-2.71 (m, 1H), 2.93-
 2.95 (m, 1H), 4.13-4.28 (m, 2H), 4.49-4.60 (m, 2H), 5.12 (d, $J=10.5$ Hz, 1H), 5.28 (d,
 $J=18.0$ Hz, 1H), 5.71-5.80 (m, 1H), 6.09 (b, 1H), 7.56 (t, $J=7.3$ Hz, 1H), 7.74 (t,
 $J=7.5$ Hz, 1H), 7.83 (d, $J=10.5$ Hz, 2H), 7.93 (d, $J=7.5$ Hz, 1H), 8.01 (s, 1H), 8.22 (d,
 $J=7.5$ Hz, 1H), 8.37 (d, $J=10.5$ Hz, 2H);
 15 LC-MS (retention time: 1.87 min, method B), MS m/z 785 ($M^+ + H$).

Example 30, Preparation of Compound 30.



Compound 30

Step 1:

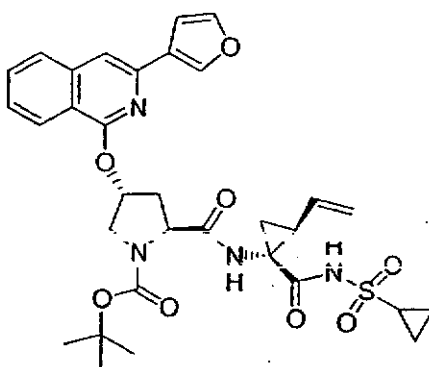


This product was prepared by the same method as described in Example 25, Step 1, except using 3-furanoboronic acid instead.

LC-MS (retention time: 1.85 min, method B), MS m/z 425 ($M^+ + H$).

5

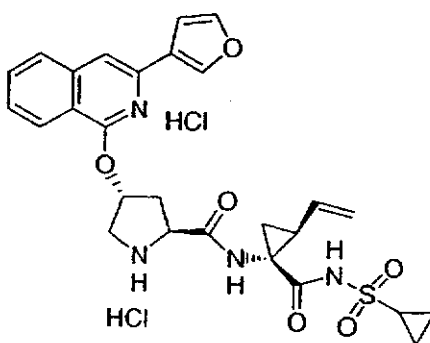
Step 2:



This product was prepared by the same method as described in Example 11, Step 4, except using the product of Example 30, Step 1 instead.

10 LC-MS (retention time: 1.88 min, method B), MS m/z 637 ($M^+ + H$).

Step 3:



This product was prepared by the same method as described in Example 11, Step 5, except using the product of Example 30, Step 2 instead.

LC-MS (retention time: 1.38 min, method B), MS m/z 537 ($M^+ + H$).

5 Step 4:

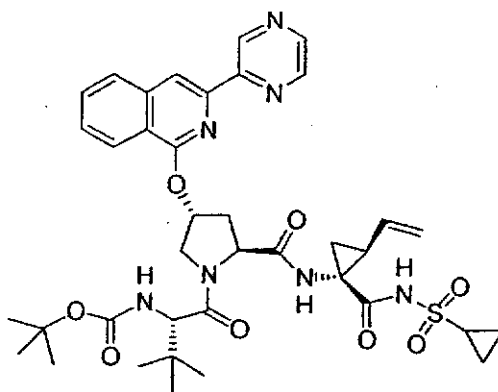
Compound 30 was prepared by the same method as described in Example 11, Step 6 as a white solid, except using the product of Example 30, Step 3 instead.

^1H NMR (CD_3OD) δ 0.95-1.09 (m, 12H), 1.23-1.30 (m, 10H), 1.43-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.21-2.23 (m, 1H), 2.30-2.34 (m, 1H), 2.64-2.70 (m, 1H), 2.93-
10 2.96 (m, 1H), 4.11-4.29 (m, 2H), 4.41-4.44 (m, 1H), 4.54-4.56 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.29 (d, $J=17.5$ Hz, 1H), 5.71-5.80 (m, 1H), 6.02 (b, 1H), 7.00 (s, 1H), 7.44 (t, $J=7.2$ Hz, 1H), 7.52 (s, 1H), 7.57 (s, 1H), 7.66 (t, $J=7.0$ Hz, 1H), 7.79 (d, $J=8.0$ Hz, 1H), 8.14-8.17 (m, 2H);

LC-MS (retention time: 1.93 min, method B), MS m/z 750 ($M^+ + H$).

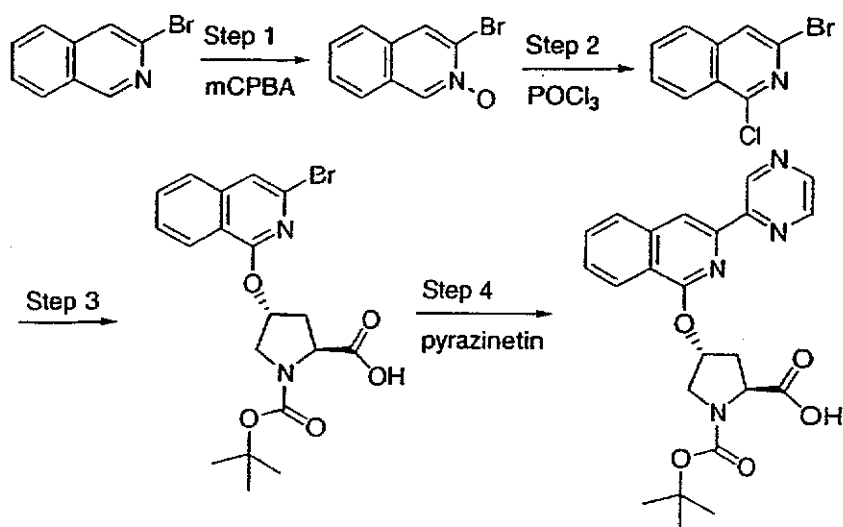
15

Example 31: Preparation of Compound 31.



Compound 31

Scheme 1



Step 1:

This product was prepared by the same method as described in making of Example 21, Step 2 as a white solid, except using 3-bromo-isoquinoline (Atkins et al, JOC, 1973, 400) instead.

¹H NMR (CDCl₃) δ 7.60-7.62 (m, 2H), 7.71-7.73 (m, 2H), 8.12 (s, 1H), 8.99 (s, 1H); LC-MS (retention time: 0.78 min, method B), MS *m/z* 224, 220 (*M*⁺+H).

Step 2:

This product was prepared by the same method as described in Example 11, Step 2 as white solid, except using 3-bromo-isoquinoline 2-oxide instead.

¹H NMR (CDCl₃) δ 7.66-7.71 (m, 1H), 7.74-7.76 (m, 2H), 7.83 (s, 1H), 8.29 (d, *J*=8.5 Hz, 1H); LC-MS (retention time: 1.55 min, method B), MS *m/z* 242, 244 (*M*⁺+H).

Step 3:

This product was prepared by the same method as described in Example 11, Step 3 as a foam, except using 3-bromo-1-chloro-isoquinoline instead.

¹H NMR (CD₃OD) δ 1.43, 1.44 (rotamers, 9H), 2.41-2.47 (m, 1H), 2.69-2.72 (m, 1H), 3.80-3.84 (m, 1H), 3.88-3.90 (m, 1H), 4.46-4.52 (m, 1H), 5.76 (b, 1H), 7.57-7.61 (m, 2H), 7.73-7.75 (m, 2H), 8.15 (d, *J*=8.0 Hz, 1H);

LC-MS (retention time: 1.79 min, method B), MS m/z 437, 439 ($M^+ + H$).

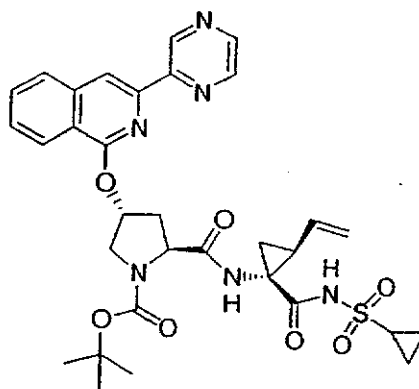
Step 4:

A mixture of 2-tributylstannanyl-pyrazine (44 mg, 0.12 mmol),
5 tetrakis(triphenylphosphine) palladium (0) (12 mg, 0.01 mmol) and the product of
Example 31, Step 3 (44 mg, 0.1 mmol) in toluene (1 mL) was heated to reflux for 3
h. After removing the volatiles in vacuo, the residue was purified by prep-HPLC to
yield 35 mg (80%) of the desired product as a yellow solid.

LC-MS (retention time: 1.77 min, method B), MS m/z 437 ($M^+ + H$).

10

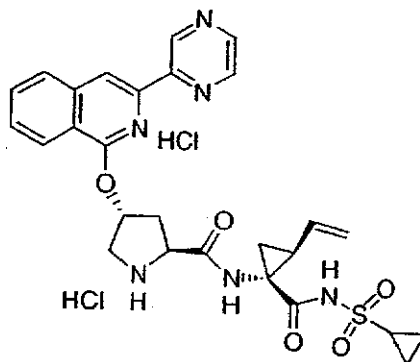
Step 5:



This product was prepared by the same method as described in Example 11, Step 4,
except using the product of Example 31, Step 4 instead.

15 LC-MS (retention time: 1.78 min, method B), MS m/z 649 ($M^+ + H$).

Step 6:



This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 31, Step 5 instead.

LC-MS (retention time: 1.26 min, method B), MS m/z 549 ($M^+ + H$).

5 Step 7:

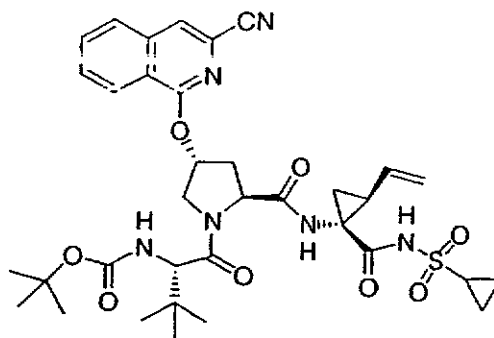
Compound 31 was prepared by the same method as described in Example 11, Step 6, except using the product of Example 31, Step 6 instead.

^1H NMR (CD_3OD) δ 0.95-1.10 (m, 12H), 1.24-1.27 (m, 10H), 1.44-1.47 (m, 1H), 1.87-1.90 (m, 1H), 2.19-2.22 (m, 1H), 2.38-2.44 (m, 1H), 2.71-2.76 (m, 1H), 2.93-2.96 (m, 1H), 4.18-4.28 (m, 2H), 4.50-4.61 (m, 2H), 5.12 (d, $J=10.5$ Hz, 1H), 5.29 (d, $J=17.5$ Hz, 1H), 5.71-5.80 (m, 1H), 6.12 (b, 1H), 7.60 (t, $J=7.2$ Hz, 1H), 7.77 (t, $J=7.0$ Hz, 1H), 7.97 (d, $J=8.5$ Hz, 1H), 8.26 (d, $J=8.5$ Hz, 1H), 8.44 (s, 1H), 8.59 (s, 1H), 8.70 (s, 1H), 9.61 (s, 1H);

LC-MS (retention time: 1.84 min, method B), MS m/z 762 ($M^+ + H$).

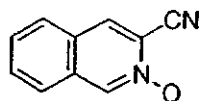
15

Example 32: Preparation of Compound 32.



Compound 32

Step 1:

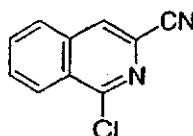


20 This product, 2-oxy-isoquinoline-3-carbonitrile, was prepared by the same method as described in Example 21, Step 2 as a white solid, except using 3-cyano-isoquinoline instead.

^1H NMR ($DMSO-d_6$) δ 7.74 (t, $J=8.0$ Hz, 1H), 7.84 (t, $J=8.2$ Hz, 1H), 7.97 (d, $J=8.5$ Hz, 1H), 8.03 (d, $J=8.5$ Hz, 1H), 8.85 (s, 1H), 9.17 (s, 1H);

LC-MS (retention time: 0.48 min, method B), MS m/z 171 ($M^+ + H$).

Step 2:

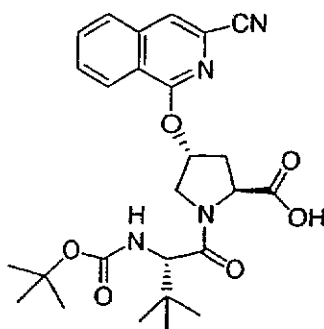


- 5 This product, 1-chloro-isoquinoline-3-carbonitrile was prepared by the same method as described in Example 11, Step 2 as white solid, except using 3-cyano-isoquinoline 2-oxide instead.

^1H NMR (CDCl_3) δ 7.87-7.91 (m, 2H), 7.92-7.94 (m, 1H), 8.09 (s, 1H), 8.42-8.44 (m, 1H);

- 10 LC-MS (retention time: 1.22 min, method B), MS m/z 189 ($M^+ + H$).

Step 3:



- 15 This product was prepared by the same method as described in Example 1, Step 5, except using 1-chloro-isoquinoline-3-carbonitrile instead.

^1H NMR (CD_3OD) δ 1.05 (s, 9H), 1.17 (s, 9H), 2.34-2.40 (m, 1H), 2.71-2.78 (m, 1H), 4.09-4.11 (m, 1H), 4.21 (b, 1H), 4.48-4.52 (m, 1H), 4.68-4.72 (m, 1H), 5.89 (b, 1H), 7.74 (t, $J=7.5$ Hz, 1H), 7.86 (t, $J=7.5$ Hz, 1H), 7.94-7.97 (m, 2H), 8.31 (d, $J=8.0$ Hz, 1H);

- 20 LC-MS (retention time: 1.66 min, method B), MS m/z 497 ($M^+ + H$).

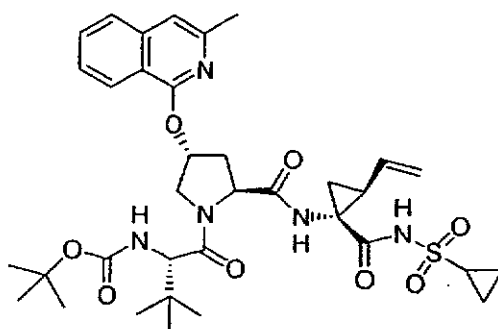
Step 4:

Compound 32 was prepared by the same method as described in Example 1, Step 9 as a white solid, except using the product of Example 32, Step 3 instead.

¹H NMR (CD₃OD) δ 1.04-1.09 (m, 12H), 1.20-1.27 (m, 10H), 1.39-1.45 (m, 1H), 1.85-1.88 (m, 1H), 2.20-2.30 (m, 2H), 2.63-2.71 (m, 1H), 2.91-2.97 (m, 1H), 4.09-4.13 (m, 1H), 4.23 (d, *J*=9.3 Hz, 1H), 4.49-4.58 (m, 2H), 5.13 (d, *J*=10.5 Hz, 1H), 5.28 (d, *J*=18.0 Hz, 1H), 5.69-5.81 (m, 1H), 5.92 (b, 1H), 6.60 (d, *J*=10.0 Hz, 1H), 7.72 (t, *J*=7.5 Hz, 1H), 7.86 (t, *J*=7.5 Hz, 1H), 7.96-7.99 (m, 2H), 8.29 (d, *J*=8.0 Hz, 1H);

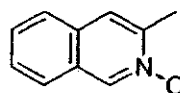
LC-MS (retention time: 1.75 min, method B), MS *m/z* 714 (M⁺+H).

Example 33: Preparation of Compound 33.



Compound 33

Step 1:

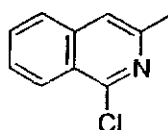


This product, 3-methyl-isoquinoline 2-oxide, was prepared by the same method as described in Example 21, Step 2 as a white solid, except using 3-methyl-isoquinoline instead.

¹H NMR (CD₃OD) δ 2.64 (s, 3H), 7.64-7.72 (m, 2H), 7.88-7.95 (m, 2H), 9.05 (s, 1H);

LC-MS (retention time: 0.61 min, method B), MS *m/z* 160 (M⁺+H).

Step 2:

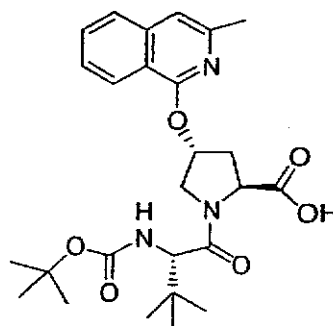


This product, 1-chloro-3-methyl-isoquinoline was prepared by the same method as described in Example 11, Step 2 as white solid, except using 3-methyl-isoquinoline 2-oxide instead.

¹H NMR (CDCl₃) δ 2.65 (s, 3H), 7.25 (s, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 7.69 (t, *J*=7.5 Hz, 1H), 7.74 (d, *J*=8.0 Hz, 1H), 8.27 (d, *J*=8.5 Hz, 1H);

LC-MS (retention time: 1.47 min, method B), MS *m/z* 178 (M⁺+H).

Step 3:



This product was prepared by the same method as described in Example 1, Step 5 as a white solid, except using 1-chloro-3-methyl-isoquinoline instead.

¹H NMR (CD₃OD) δ 1.05 (s, 9H), 1.23 (s, 9H), 2.51 (s, 3H), 2.34-2.40 (m, 1H), 2.72-2.78 (m, 1H), 4.05-4.12 (m, 1H), 4.26 (b, 1H), 4.41 (d, *J*=10 Hz, 1H), 4.62-4.67 (m, 1H), 5.90 (b, 1H), 7.14 (s, 1H), 7.38 (t, *J*=7.5 Hz, 1H), 7.62 (t, *J*=7.5 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 8.14 (d, *J*=8.0 Hz, 1H);

LC-MS (retention time: 1.84 min, method B), MS *m/z* 486 (M⁺+H).

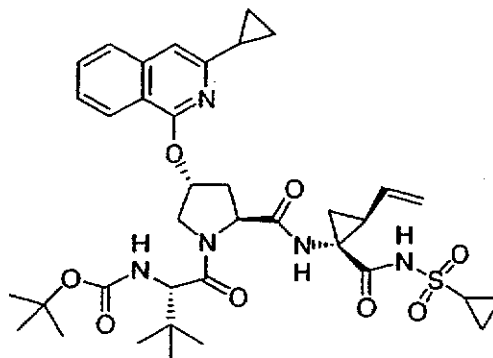
Step 4:

Compound 33 was prepared by the same method as described in Example 1, Step 9 as a white solid, except using the product of Example 33, Step 3 instead.

¹H NMR (CD₃OD) δ 0.99-1.09 (m, 12H), 1.23-1.25 (m, 10H), 1.41-1.45 (m, 1H), 1.86-1.90 (m, 1H), 2.21-2.31 (m, 2H), 2.52 (s, 3H), 2.58-2.61 (m, 1H), 2.91-2.97 (m, 1H), 4.08-4.12 (m, 1H), 4.28 (b, 1H), 4.40 (d, *J*=10.0 Hz, 1H), 4.50-4.55 (m, 1H), 5.12 (d, *J*=10.0 Hz, 1H), 5.30 (d, *J*=18.0 Hz, 1H), 5.71-5.81 (m, 1H), 5.93 (b, 1H), 7.13 (s, 1H), 7.38 (t, *J*=7.5 Hz, 1H), 7.62 (t, *J*=7.5 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 9.12 (b, 1H);

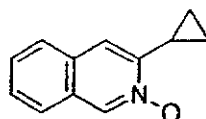
LC-MS (retention time: 1.85 min, method B), MS m/z 698 ($M^+ + H$).

Example 34: Preparation of Compound 34.



Compound 34

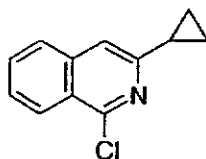
5 Step 1:



This product, 3-cyclopropyl-isoquinoline 2-oxide was prepared by the same method as described in Example 21, Step 2 as a white solid, except using 3-cyclopropyl-isoquinoline (L. Flippin, J. Muchowski, J. O. C, 1993, 2631-2632) instead.

10 LC-MS (retention time: 0.95 min, method B), MS m/z 186 ($M^+ + H$).

Step 2:

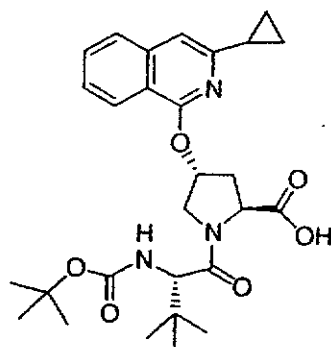


15 This product, 1-chloro-3-cyclopropyl-isoquinoline was prepared by the same method as described in Example 11, Step 2 as white solid, except using 3-cyclopropyl-isoquinoline 2-oxide instead.

^1H NMR (CD_3OD) δ 1.00-1.04 (m, 4H), 2.11-2.18 (m, 1H), 7.55 (s, 1H), 7.61 (t, $J=8.0$ Hz, 1H), 7.72 (t, $J=8.0$ Hz, 1H), 7.83 (d, $J=13.5$ Hz, 1H), 8.27 (d, $J=14.5$ Hz, 1H);

20 LC-MS (retention time: 1.70 min, method B), MS m/z 204 ($M^+ + H$).

Step 3:



This product was prepared by the same method as described in Example 1, Step 5 as a white solid, except using 1-chloro-3-cyclopropyl-isoquinoline instead.

¹HNMR (CD₃OD) δ 0.93-1.05 (m, 13H), 1.29 (s, 9H), 2.06-2.10 (m, 1H), 2.39-2.44 (m, 1H), 2.70-2.76 (m, 1H), 4.05-4.12 (m, 1H), 4.27 (b, 1H), 4.35 (d, *J*=10.0 Hz, 1H), 4.62-4.67 (m, 1H), 5.78 (b, 1H), 7.18 (s, 1H), 7.38 (t, *J*=7.5 Hz, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H);

LC-MS (retention time: 1.96 min, method B), MS *m/z* 512 (M⁺+H).

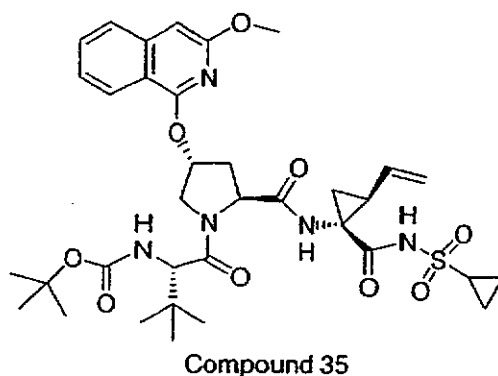
Step 4:

Compound 34 was prepared by the same method as described in Example 1, Step 9 as a white solid, except using the product of Example 34, Step 3 instead.

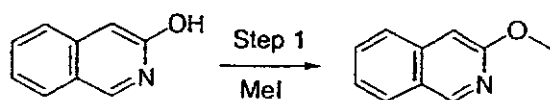
¹HNMR (CD₃OD) δ 0.93-1.09 (m, 16H), 1.24-1.30 (m, 10H), 1.42-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.06-2.11 (m, 1H), 2.21-2.32 (m, 2H), 2.56-2.61 (m, 1H), 2.92-2.97 (m, 1H), 4.08-4.12 (m, 1H), 4.28 (b, 1H), 4.32 (d, *J*=10.0 Hz, 1H), 4.48-4.53 (m, 1H), 5.12 (d, *J*=10.5 Hz, 1H), 5.30 (d, *J*=17.5 Hz, 1H), 5.72-5.77 (m, 1H), 5.82 (b, 1H), 7.18 (s, 1H), 7.36 (t, *J*=7.5 Hz, 1H), 7.60 (t, *J*=7.5 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 8.07 (d, *J*=8.0 Hz, 1H);

LC-MS (retention time: 2.00 min, method B), MS *m/z* 724 (M⁺+H).

Example 35: Preparation of Compound 35.



Scheme 1



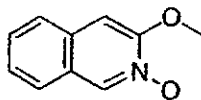
Step 1:

A mixture of 3-hydroxy-isoquinoline (725 mg, 5.0 mmol), cesium carbonate (4.89 g, 15.0 mmol), MeI (781 mg, 5.5 mmol) in DMF (50 mL) was stirred at the ambient temperature for 12 h. The mixture was diluted with EtOAc (200 mL), filtered, washed with water (200 mL, X2) and 1M NaOH (aq), brine respectively. The organic layer was dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC to yield 120 mg (15%) of the desired product as a white solid.

¹H NMR (CDCl₃) δ 4.03 (s, 3H), 6.99 (s, 1H), 7.36 (t, *J*=8.0 Hz, 1H), 7.56 (t, *J*=8.2 Hz, 1H), 7.68 (d, *J*=8.5 Hz, 1H), 7.87 (*J*=8.5 Hz, 1H);

LC-MS (retention time: 0.54 min, method B), MS *m/z* 160 (*M*⁺+H).

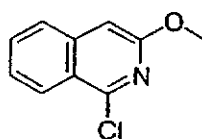
Step 2:



This product, 3-methoxy-isoquinoline 2-oxide, was prepared by the same method as described in Example 21, Step 2 as a white solid, except using 3-methoxy-isoquinoline instead.

LC-MS (retention time: 0.83 min, method B), MS *m/z* 176 (*M*⁺+H).

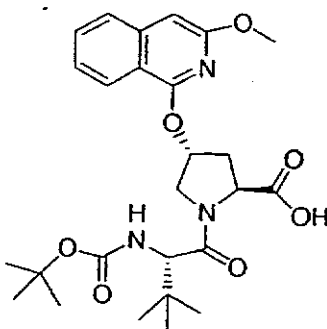
Step 3:



This product, 1-chloro-3-methoxyisoquinoline was prepared by the same method as described in Example 11, Step 2 as white solid, except using 3-methoxyisoquinoline 2-oxide instead.

- 5 LC-MS (retention time: 1.62 min, method B), MS m/z 194 ($M^+ + H$).

Step 4:



- 10 This product was prepared by the same method as described in Example 1, Step 5 as a white solid, except using 1-chloro-3-methoxyisoquinoline instead.

$^1\text{H NMR}$ (CD_3OD) δ 1.05 (s, 9H), 1.23 (s, 9H), 2.35-2.43 (m, 1H), 2.72-2.79 (m, 1H), 3.96 (s, 3H), 4.01-4.11 (m, 1H), 4.26 (b, 1H), 4.48 (d, $J=10.0$ Hz, 1H), 4.62-4.67 (m, 1H), 5.83 (b, 1H), 6.61 (s, 1H), 7.25 (t, $J=7.5$ Hz, 1H), 7.54 (t, $J=7.5$ Hz, 1H), 7.63 (d, $J=8.1$ Hz, 1H), 8.08 (d, $J=8.4$ Hz, 1H);

- 15 LC-MS (retention time: 1.82 min, method B), MS m/z 502 ($M^+ + H$).

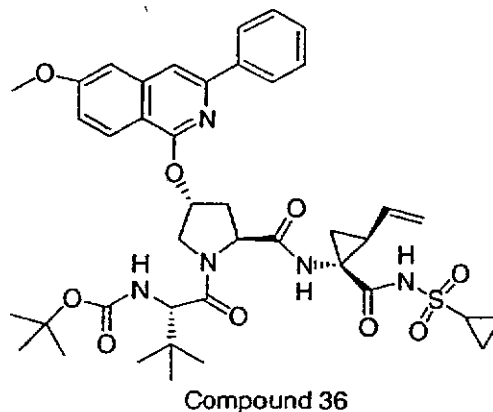
Step 5:

Compound 35 was prepared by the same method as described in Example 1, Step 9 as a white solid, except using the product of Example 35, Step 4 instead.

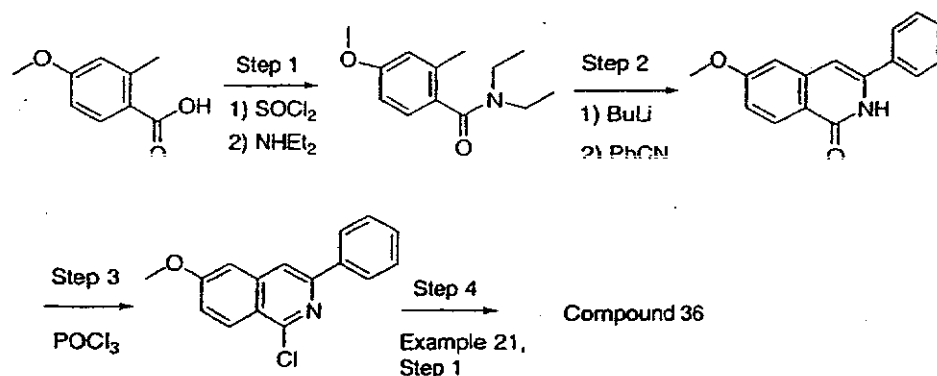
- 20 $^1\text{H NMR}$ (CD_3OD) δ 1.04-1.08 (m, 12H), 1.24-1.27 (m, 10H), 1.43-1.45 (m, 1H), 1.86-1.89 (m, 1H), 2.21-2.26 (m, 1H), 2.30-2.34 (m, 1H), 2.62-2.66 (m, 1H), 2.91-2.97 (m, 1H), 3.99 (s, 3H), 4.09-4.12 (m, 1H), 4.27-4.28 (m, 1H), 4.46 (d, $J=10.0$ Hz, 1H), 4.51-4.58 (m, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.30 (d, $J=18.0$ Hz, 1H), 5.72-5.76

(m, 1H), 5.88 (b, 1H), 6.62 (s, 1H), 7.26 (t, $J=7.5$ Hz, 1H), 7.55 (t, $J=7.5$ Hz, 1H), 7.65 (d, $J=8.0$ Hz, 1H), 8.06 (d, $J=8.5$ Hz, 1H);
 LC-MS (retention time: 1.85 min, method B), MS m/z 714 ($M^+ + H$).

5 Example 36: Preparation of Compound 36.



Scheme 1



Step 1:

A mixture of 4-methoxy-2-methyl-benzoic acid (5.00 g, 30.1 mmol) and thionyl chloride (20.0 g, 0.17 mol) was heated to reflux for 30 min. Removed the volatile in vacuo. After pumping overnight, the viscous oily acid chloride was used as crude for the next reaction without any purification.

To a solution of 4-methoxy-2-methyl-benzoyl chloride in CH_2Cl_2 (60 mL) at 0°C was added diethylamine dropwise. The formed mixture was allowed to warm up to the ambient temperature for 2 h with stirring. Removed the volatiles in vacuo. The residue was triturated with EtOAc (100 mL) and filtered. The filtrate was washed

with 1M HCl, 1M NaOH and brine, dried over MgSO_4 . Evaporation of the solvent yielded 6.51 g (98%) of the desired product as a viscous oil.

LC-MS (retention time: 1.20 min, method B), MS m/z 222 ($\text{M}^+ + \text{H}$).

5 Step 2:

To a solution of N,N-diethyl-4-methoxy-2-methyl-benzamide (221 mg, 1.0 mmol) in THF (2 mL) at -78°C was added n-BuLi (0.84 mL of 2.5 M in hexane, 2.10 mmol) dropwise. The formed orange solution was kept at this temperature for additional 30 min before dropwise addition of benzonitrile (103 mg, 1.0 mmol). The
10 final solution was allowed to warm up to the ambient temperature over night with stirring. Quenched with iced 5% citric acid. Filtered, washed with water, dried. Trituration with 2:1 hexane-EtOAc (5 mL) yielded 205 mg (82%) of the desired product as a white solid.

^1H NMR (d_6 -DMSO) δ 3.89 (s, 3H), 6.84 (s, 1H), 7.05-7.07 (m, 1H), 7.18 (d, $J=2.5$
15 Hz, 1H), 7.44-7.51 (m, 3H), 7.78 (d, $J=7.0$ Hz, 1H), 8.11 (d, $J=9.0$ Hz, 1H);
LC-MS (retention time: 1.20 min, method B), MS m/z 252 ($\text{M}^+ + \text{H}$).

Step 3:

This product, 1-chloro-6-methoxy-3-phenyl-isoquinoline, was prepared by the
20 same method as described in Example 11, Step 2 as a white solid, except using 6-methoxy-3-phenyl-2H-isoquinolin-1-one instead.

^1H NMR (CDCl_3) δ 3.97 (s, 3H), 7.12 (d, $J=2.5$ Hz, 1H), 7.23-7.26 (m, 1H), 7.40-7.42 (m, 1H), 7.46-7.50 (m, 2H), 7.89 (s, 1H), 8.08 (d, $J=7.0$ Hz, 2H), 8.21 (d, $J=9.0$ Hz, 1H);
25 LC-MS (retention time: 1.90 min, method B), MS m/z 270, 271 ($\text{M}^+ + \text{H}$).

Step 4:

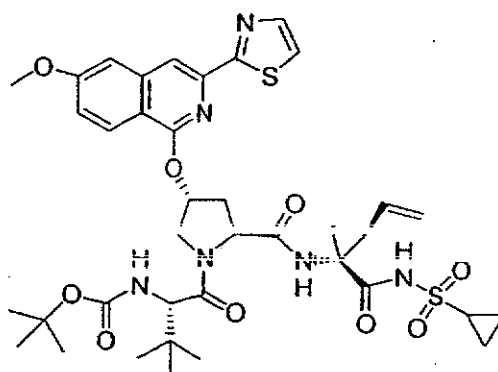
To a solution of the product of Example 21, Step 1 (320 mg, 0.57 mmol) in DMSO (5 mL) was added potassium tert-butoxide (321 mg, 2.87 mmol). The formed
30 solution was stirred at the ambient temperature for 30 min before addition of 1-chloro-6-methoxy-3-phenyl-isoquinoline (Example 36, Step 3) (155 mg, 0.57 mmol). The final solution was stirred for 12 h. Quenched with iced water, acidified with 1M

HCl to pH 4, extracted with EtOAc (20 mL, X2). The organic layers were washed with brine, dried over MgSO₄, filtered, evaporated. The residue was purified by prep-HPLC (40%B to 100%B, 15 min gradient) to yield 289 mg (64%) of Compound 36 as a white solid.

- 5 ¹H NMR (CD₃OD) δ 0.95-1.05 (m, 12H), 1.24-1.32 (m, 10H), 1.44-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m, 1H), 2.65-2.71 (m, 1H), 2.93-2.97 (m, 1H), 3.94 (s, 3H), 4.12-4.28 (m, 2H), 4.38-4.52 (m, 2H), 5.12 (d, *J*=10.0 Hz, 1H), 5.28 (d, *J*=17.0 Hz, 1H), 5.69-5.74 (m, 1H), 6.05 (b, 1H), 7.06-7.07 (m, 1H), 7.26 (s, 1H), 7.37-7.39 (m, 1H), 7.44-7.48 (m, 2H), 7.77 (s, 1H), 8.07 (d, *J*=9.0 Hz, 1H), 8.15 (d, *J*=8.5 Hz, 2H);

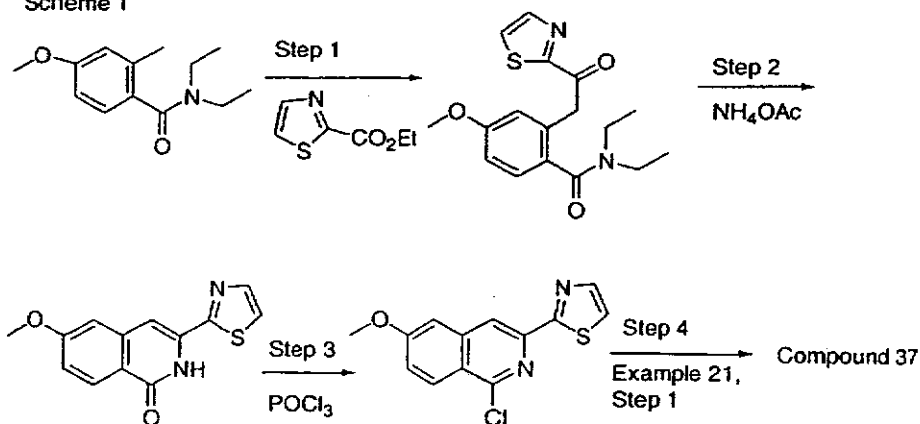
LC-MS (retention time: 2.02 min, method B), MS *m/z* 790 (M⁺+H).

Example 37: Preparation of Compound 37.



Compound 37

Scheme 1



15

Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methyl-benzamide (633 mg, 2.9 mmol) in THF (15 mL) at -78°C was added n-BuLi (2.3 mL of 2.5 M in hexane, 5.74 mmol) dropwise. The formed red solution was kept at this temperature for additional 30 min before being cannulated to a solution of thiazole-2-carboxylic acid ethyl ester
5 (A. Medici et al, *Tetrahedron Lett.* 1983, p2901) (450 mg, 2.9 mmol) in THF (5 mL) at -78°C . The final dark green solution was kept to this temperature for 2 h with stirring. Quenched with sat. NH_4Cl (aq) and extracted with EtOAc (50 mL). The organic layer was washed with sat. NH_4Cl (aq) and brine, dried, purified by flash column chromatography, eluting with 2:1 EtOAc:hexane to provide 405 mg (45%) of
10 the desired product as an off-white viscous oil.

^1H NMR (CDCl_3) δ 1.08 (t, $J=7.0$ Hz, 6H), 3.22 (b, 2H), 3.44 (b, 2H), 3.79 (s, 3H), 4.59 (s, 2H), 6.79-6.81 (m, 1H), 6.86 (d, $J=2.5$ Hz, 1H), 7.16 (d, $J=8.5$ Hz, 1H), 7.66 (d, $J=3.0$ Hz, 1H), 8.00 (d, $J=3.0$ Hz, 1H);

LC-MS (retention time: 1.30 min, method B), MS m/z 333 ($\text{M}^+ + \text{H}$).

15

Step 2:

A mixture of N,N-diethyl-4-methoxy-2-(2-oxo-2-thiazol-2-yl-ethyl)-benzamide (405 mg, 1.22 mmol) and NH_4OAc (3.0 g, 38.9 mmol) was heated to 140°C in a sealed tube for 1 h. The melted solution was poured into iced water,
20 filtered, washed the cake thoroughly with water. The dried brownish solid (240 mg, 76%) was used as crude for the next reaction without further purification.

LC-MS (retention time: 1.24 min, method B), MS m/z 259 ($\text{M}^+ + \text{H}$).

Step 3:

25 This product, 1-chloro-6-methoxy-3-thiazol-2-yl-isoquinoline, was prepared by the same method as described in Example 11, Step 2 as a white solid, except using 6-methoxy-3-thiazol-2-yl-2H-isoquinolin-1-one instead.

^1H NMR (CDCl_3) δ 3.97 (s, 3H), 7.16 (d, $J=4.0$ Hz, 1H), 7.27-7.31 (m, 1H), 7.46 (d, $J=5.0$ Hz, 1H), 7.93 (d, $J=5.5$ Hz, 1H), 8.22 (d, $J=15.5$ Hz, 1H), 8.39 (s, 1H);

30 LC-MS (retention time: 1.66 min, method B), MS m/z 277 ($\text{M}^+ + \text{H}$).

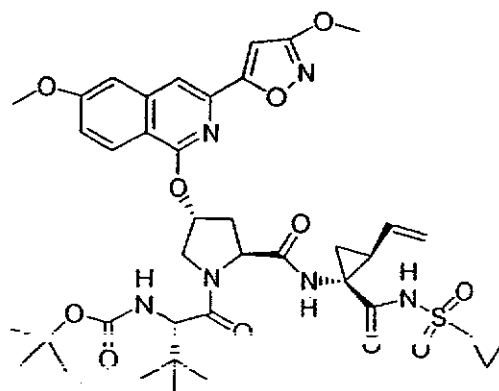
Step 4:

Compound 37 was prepared by the same method as described in Example 36, Step 4, except using 1-chloro-6-methoxy-3-thiazol-2-yl-isoquinoline instead.

¹H NMR (CD₃OD) δ 0.97-1.09 (m, 12H), 1.24-1.29 (m, 10H), 1.44-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m, 1H), 2.65-2.71 (m, 1H), 2.93-2.96 (m, 1H), 3.96 (s, 3H), 4.12-4.27 (m, 2H), 4.38-4.52 (m, 2H), 5.12 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=17.5 Hz, 1H), 5.69-5.74 (m, 1H), 5.99 (b, 1H), 7.14 (d, *J*=9.0 Hz, 1H), 7.33 (s, 1H), 7.66 (d, *J*=3.5 Hz, 1H), 7.93 (d, *J*=3.0 Hz, 1H), 8.05 (s, 1H), 8.11 (d, *J*=9.0 Hz, 1H), 9.14 (b, 1H);

LC-MS (retention time: 1.89 min, method B), MS *m/z* 797 (M⁺+H).

Example 38: Preparation of Compound 38.



Compound 38

Scheme 1



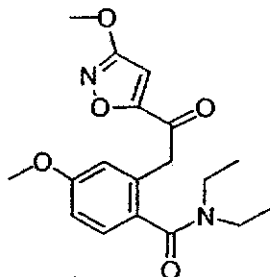
Step 1:

A mixture of 3-hydroxy-isoxazole-5-carboxylic acid methyl ester (5.72 g, 0.04 mol), methyl iodide (6.82 g, 0.044 mol) and cesium carbonate (39.1 g, 0.12 mol) in DMF (200 mL) was stirred at the ambient temperature over night. Diluted with EtOAc (1L), filtered. The filtrate was washed with water (1L, X2), 1M NaOH and brine respectively, dried over MgSO₄, evaporated in vacuo to afford 4.80 g (76%) of the desired product as a white solid. The product obtained here was used as crude without further purification.

^1H NMR (CDCl_3) δ 3.92 (s, 3H), 4.00 (s, 3H), 6.51 (s, 1H);

LC-MS (retention time: 0.69 min, method B), MS m/z 158 ($\text{M}^+ + \text{H}$).

Step 2:



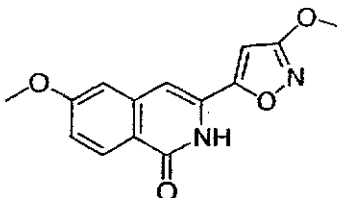
5

This product, N,N-diethyl-4-methoxy-2-[2-(3-methoxy-isoxazol-5-yl)-2-oxo-ethyl]-benzamide, was prepared by the same method as described in Example 37, Step 1, except using 3-methoxy-isoxazole-5-carboxylic acid methyl ester instead.

LC-MS (retention time: 1.28 min, method B), MS m/z 347 ($\text{M}^+ + \text{H}$).

10

Step 3:



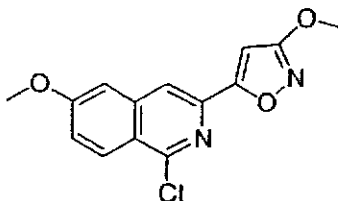
This product, 6-methoxy-3-(3-methoxy-isoxazol-5-yl)-2H-isoquinolin-1-one, was prepared by the same method as described in Example 37, Step 2, except using N,N-diethyl-4-methoxy-2-[2-(3-methoxy-isoxazol-5-yl)-2-oxo-ethyl]-benzamide instead.

15

^1H NMR ($\text{DMSO}-d_6$) δ 3.89 (s, 3H), 3.97 (s, 3H), 7.01 (s, 1H), 7.14-7.16 (m, 2H), 7.43 (s, 1H), 8.13 (d, $J=8.5$ Hz, 1H);

LC-MS (retention time: 1.31 min, method B), MS m/z 273 ($\text{M}^+ + \text{H}$).

20 Step 4:



This product, 1-chloro-6-methoxy-3-(3-methoxy-isoxazol-5-yl)-isoquinoline, was prepared by the same method as described in Example 11, Step 2 as a white solid, except using 6-methoxy-3-(3-methoxy-isoxazole-5-yl)-2H-isoquinolin-1-one instead.

¹H NMR (CDCl₃) δ 3.97 (s, 3H), 4.04 (s, 3H), 6.60 (s, 1H), 7.17 (d, *J*=2.5 Hz, 1H),
5 7.31-7.33 (m, 1H), 8.02 (s, 1H), 8.23 (d, *J*=9.0 Hz, 1H);
LC-MS (retention time: 1.73 min, method B), MS *m/z* 291, 293 (M⁺+H).

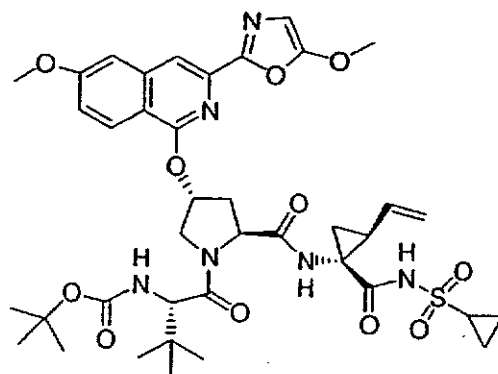
Step 5:

Compound 38 was prepared by the same method as described in Example 36,
10 Step 4, except using 1-chloro-6-methoxy-3-(3-methoxy-isoxazole-5-yl)-isoquinoline instead.

¹H NMR (CD₃OD) δ 0.99-1.09 (m, 12H), 1.23-1.28 (m, 10H), 1.44-1.46 (m, 1H),
1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m, 1H), 2.65-2.71 (m, 1H), 2.93-
2.96 (m, 1H), 3.95 (s, 3H), 4.02 (s, 3H), 4.13-4.14 (m, 1H), 4.24-4.26 (m, 1H), 4.41-
15 4.42 (m, 1H), 4.52-4.55 (m, 1H), 5.12 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=17.0 Hz, 1H),
5.72-5.79 (m, 1H), 5.96 (b, 1H), 6.60 (s, 1H), 7.15-7.17 (m, 1H), 7.32 (s, 1H), 7.80
(s, 1H), 8.10 (d, *J*=9.0 Hz, 1H);

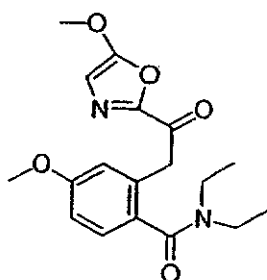
LC-MS (retention time: 1.95 min, method B), MS *m/z* 811 (M⁺+H).

20 Example 39: Preparation of Compound 39.



Compound 39

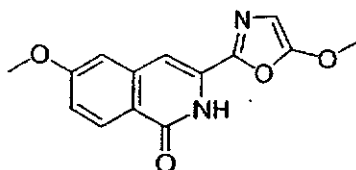
Step 1:



This product, N,N-diethyl-4-methoxy-2-[2-(5-methoxy-oxazol-2-yl)-2-oxo-ethyl]-benzamide, was prepared by the same method as described in Example 37, Step 1, except using 5-methoxy-oxazole-2-carboxylic acid ethyl ester instead.

- 5 LC-MS (retention time: 1.24 min, method B), MS m/z 347 ($M^+ + H$).

Step 2:



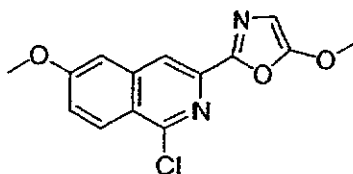
- 10 This product, 6-methoxy-3-(5-methoxy-oxazol-2-yl)-2H-isoquinolin-1-one, was prepared by the same method as described in Example 37, Step 2, except using N,N-diethyl-4-methoxy-2-[2-(5-methoxy-oxazol-2-yl)-2-oxo-ethyl]-benzamide instead.

^1H NMR (DMSO- d_6) δ 3.94 (s, 3H), 4.01 (s, 3H), 6.34 (s, 1H), 6.99 (d, $J=2.0$ Hz, 1H), 7.12-7.14 (m, 1H), 7.25 (s, 1H), 8.32 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.22 min, method B), MS m/z 274 ($M^+ + H$).

15

Step 3:



- 20 This product, 1-chloro-6-methoxy-3-(5-methoxy-oxazol-2-yl)-isoquinoline, was prepared by the same method as described in Example 11, Step 2 as a white solid, except using 6-methoxy-3-(5-methoxy-oxazole-2-yl)-2H-isoquinolin-1-one instead.

^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.00 (s, 3H), 6.34 (s, 1H), 7.12 (d, $J=2.5$ Hz, 1H), 7.28-7.31 (m, 1H), 8.13 (s, 1H), 8.23 (d, $J=9.0$ Hz, 1H);

LC-MS (retention time: 1.58 min, method B), MS m/z 291, 293 ($M^+ + H$).

Step 4:

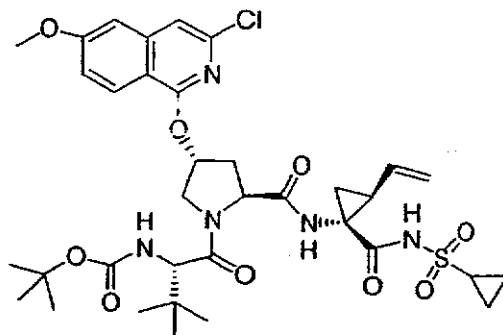
Compound 39 was prepared by the same method as described in Example 36,

- 5 Step 4, except using 1-chloro-6-methoxy-3-(3-methoxy-isoxazole-5-yl)-isoquinoline instead.

^1H NMR (CD_3OD) δ 0.99-1.09 (m, 12H), 1.23-1.28 (m, 10H), 1.44-1.46 (m, 1H),
1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m, 1H), 2.65-2.71 (m, 1H), 2.93-
2.96 (m, 1H), 3.95 (s, 3H), 4.02 (s, 3H), 4.13-4.14 (m, 1H), 4.25 (b, 1H), 4.41-4.42
10 (m, 1H), 4.52-4.55 (m, 1H), 5.12 (d, $J=10.0$ Hz, 1H), 5.29 (d, $J=17.0$ Hz, 1H), 5.72-
5.79 (m, 1H), 6.07 (b, 1H), 6.45 (s, 1H), 7.15-7.16 (m, 1H), 7.29 (s, 1H), 7.85 (s,
1H), 8.10 (d, $J=9.0$ Hz, 1H), 9.11 (b, 1H);

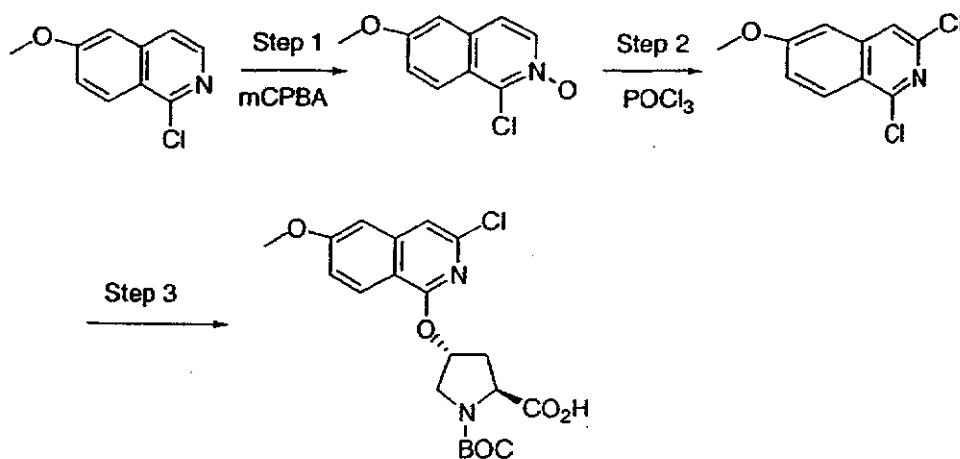
LC-MS (retention time: 1.75 min, method B), MS m/z 811 ($M^+ + H$).

15 **Example 40: Preparation of Compound 40.**



Compound 40

Scheme 1



Step 1:

This product, 1-chloro-6-methoxyisoquinoline 2-oxide was prepared by the same method as described in Example 21, Step 2, except using 1-chloro-6-methoxyisoquinoline (the product of Example 11, Step 2) instead.

¹H NMR (CDCl₃) δ 4.00 (s, 3H), 7.14 (d, *J*=2.5 Hz, 1H), 7.41-7.43 (m, 1H), 7.62 (d, *J*=7.0 Hz, 1H), 8.15 (d, *J*=9.5 Hz, 1H), 8.36 (d, *J*=7.0 Hz, 1H);

LC-MS (retention time: 0.85 min, method B), MS *m/z* 210 (M⁺+H).

Step 2:

This product, 1,3-dichloro-6-methoxyisoquinoline was prepared by the same method as described in Example 11, Step 2, except using 1-chloro-6-methoxyisoquinoline 2-oxide instead.

¹H NMR (CDCl₃) δ 3.94 (s, 3H), 6.98 (s, 1H), 7.25-7.26 (m, 1H), 7.52 9s, 1H), 8.16 (d, *J*=9.5 Hz, 1H);

LC-MS (retention time: 1.54 min, method B), MS *m/z* 228, 230 (M⁺+H).

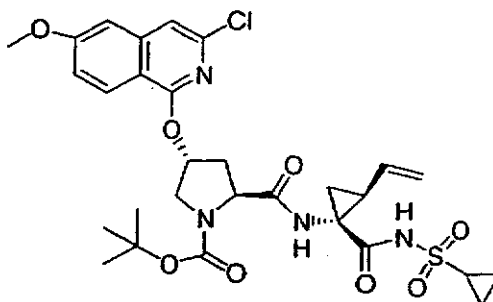
Step 3:

This product was prepared by the same method as described in Example 24, Step 1 as a foam, except using 1,3-dichloro-6-methoxyisoquinoline instead.

¹H NMR (CD₃OD) δ 1.43, 1.44 (rotamers, 9H), 2.39-2.44 (m, 1H), 2.68-2.72 (m, 1H), 3.80-3.90 (m, 2H), 3.91 (s, 3H), 4.79-4.82 (m, 1H), 5.71 (b, 1H), 7.10-7.14 (m, 2H), 7.26 (s, 1H), 7.99-8.01 (m, 1H);

LC-MS (retention time: 1.79 min method B), MS m/z 422 ($M^+ + H$).

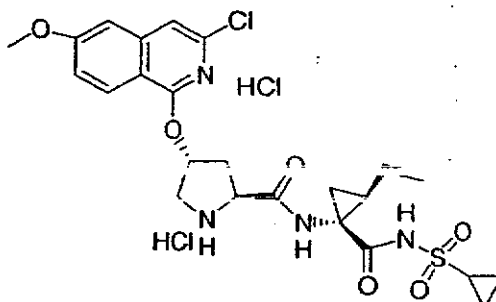
Step 4:



- 5 This product was prepared by the same method as described in Example 11, Step 4, except using the product of Example 40, Step 3 instead.

LC-MS (retention time: 1.83 min, method B), MS m/z 635 ($M^+ + H$).

Step 5:



10

This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 40, Step 4 instead.

LC-MS (retention time: 1.36 min, method B), MS m/z 535 ($M^+ + H$).

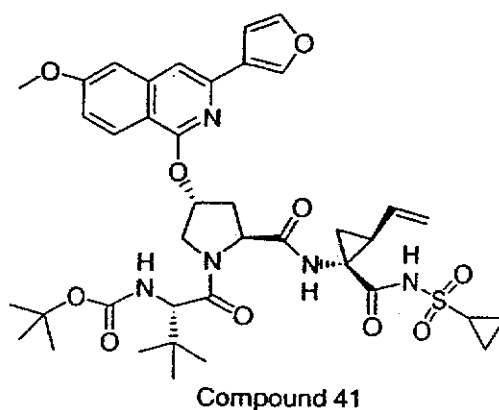
15 Step 6:

Compound 40 was prepared by the same method as described in Example 11, Step 6 as a white solid, except using the product of Example 40, Step 5 instead.

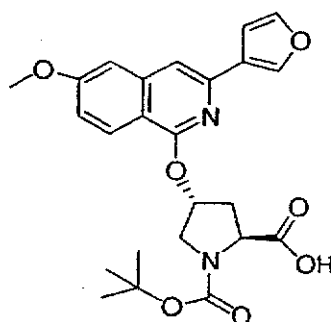
- ^1H NMR (CD_3OD) δ 1.07-1.11 (m, 12H), 1.26-1.30 (m, 10H), 1.46-1.48 (m, 1H), 1.87-1.91 (m, 1H), 2.21-2.34 (m, 2H), 2.62-2.66 (m, 1H), 2.94-2.99 (m, 1H), 3.95 (s, 3H), 4.06-4.11 (m, 1H), 4.26-4.28 (m, 1H), 4.46-4.56 (m, 2H), 5.15 (d, $J=10.0$ Hz, 1H), 5.29 (d, $J=17.0$ Hz, 1H), 5.72-5.79 (m, 1H), 5.89 (b, 1H), 6.63 (d, $J=9.0$ Hz, 1H), 7.08-7.09 (m, 1H), 7.18 (s, 1H), 7.34 (s, 1H), 8.08 (d, $J=9.5$ Hz, 1H);
- 20

LC-MS (retention time: 1.99 min, method B), MS m/z 748 ($M^+ + H$).

Example 41: Preparation of Compound 41.



5 Step 1:

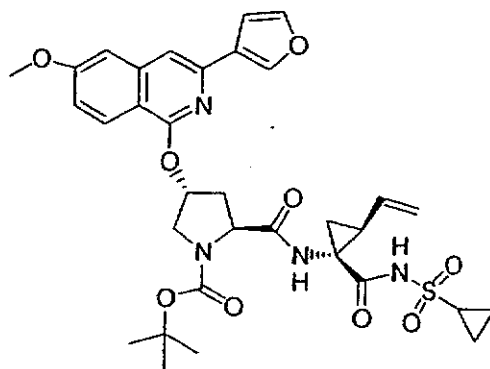


This product was prepared by the same method as described in Example 30, Step 1, except using the product of Example 40, Step 3 instead.

LC-MS (retention time: 1.85 min, method B), MS m/z 455 ($M^+ + H$).

10

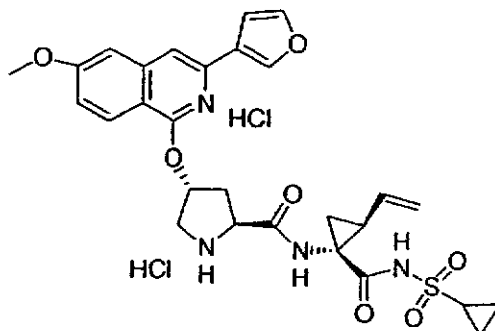
Step 2:



This product was prepared by the same method as described in Example 11, Step 4 as a foam, except using the product of Example 41, Step 1 instead.

LC-MS (retention time: 1.88 min, method B), MS m/z 667 ($M^+ + H$).

5 Step 3:



This product was prepared by the same method as described in Example 11, Step 5 as a white solid, except using the product of Example 41, Step 2 instead.

LC-MS (retention time: 1.38 min, method B), MS m/z 567 ($M^+ + H$).

10

Step 4:

Compound 41 was prepared by the same method as described in Example 11, Step 6 as a white solid, except using the product of Example 41, Step 3 instead.

^1H NMR (CD_3OD) δ 0.99-1.04 (m, 12H), 1.22-1.31 (m, 10H), 1.43-1.45 (m, 1H),
 15 1.87-1.89 (m, 1H), 2.22-2.24 (m, 1H), 2.30-2.34 (m, 1H), 2.65-2.68 (m, 1H), 2.93-
 2.96 (m, 1H), 3.92 (s, 3H), 4.11-4.14 (m, 1H), 4.28-4.30 (m, 1H), 4.38-4.42 (m, 1H),
 4.53-4.55 (m, 1H), 5.12 (d, $J=10.0$ Hz, 1H), 5.29 (d, $J=18.0$ Hz, 1H), 5.72-5.77 (m,
 1H), 5.99 (b, 1H), 6.61 (d, $J=5.0$ Hz, 1H), 6.98 (s, 1H), 6.99-7.02 (m, 1H), 7.17 (s,
 1H), 7.44 (s, 1H), 7.57 (d, $J=5.0$ Hz, 1H), 8.03 (d, $J=10.0$ Hz, 1H), 8.14 (s, 1H);

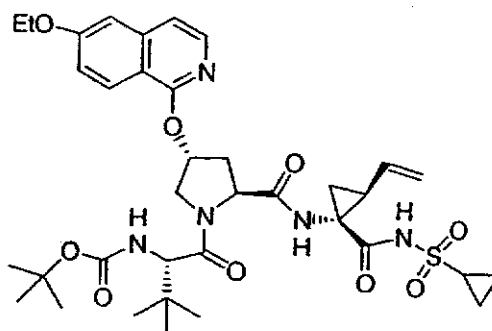
20 LC-MS (retention time: 1.92 min, method B), MS m/z 780 ($M^+ + H$).

Example 42: Preparation of Compound 42.

Prepared following the procedures used in the preparation of Example 11.

Compound 11, except that 6-ethoxy cinnamic acid was used in place of 6-methoxy
 25 cinnamic acid as starting material for the P2 element.

149



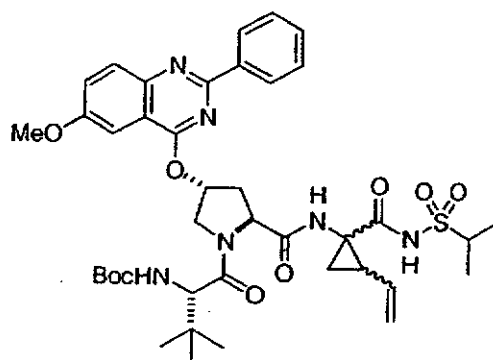
Compound 42

¹H NMR (500 MHz, CD₃OD) δ ppm 0.98-1.09 (m, 15H), 1.24-1.31 (m, 10H), 1.42-1.46 (m, 1H), 1.85-1.90 (m, 1H), 2.19-2.32 (m, 2H), 2.57-2.63 (m, 1H), 2.91-2.97 (m, 1H), 4.03-4.09 (m, 1H), 4.17 (q, *J*=7.0 Hz, 2H), 4.42 (d, *J*=11.3 Hz, 1H), 4.49-4.54 (m, 1H), 5.12 (d, *J*=17.4 Hz, 1H), 5.72-5.78 (m, 1H), 5.83 (s, 1H), 7.07-7.10 (m, 1H), 7.15 (s, 1H), 7.22 (d, *J*=5.8 Hz, 1H), 7.87 (d, *J*=5.8 Hz, 1H), 8.08 (d, *J*=8.8 Hz, 1H); MS: (M+H)⁺ 728.

Section C:

10

Example 45: Preparation of Compound 45

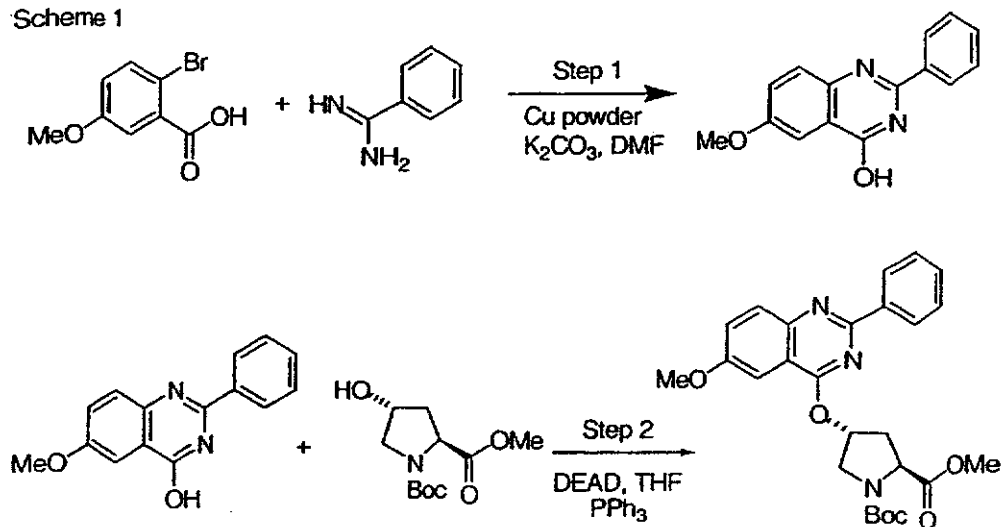


(1R,2S) and (1S,2R), 1:1 Mixture at P1

Compound 45

15

Scheme 1



Step 1:

To a solution of 2-bromo-5-methoxybenzoic acid (1.68g, 7.27mmol) in DMF (50mL) in a medium pressure flask (Chemglass) was added benzamidine (1.25g, 8.00mmol), K₂CO₃ (6.0g, 43.6mmol), and copper powder (336mg, 1.45mmol). The reaction mixture was heated to 180°C for 1h. Copper and excess K₂CO₃ were removed by vacuum filtration and washed with MeOH. The filtrate was concentrated and the resulting crude was purified by flash column chromatography (SiO₂, 5% MeOH in DCM) to give a light green solid (1.55g, 84% yield): ¹H NMR (DMSO-d₆) δ 3.84 (s, 3H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.46 (br s, 5H), 7.57 (s, 1H), 8.38 (br s, 1 H); MS *m/z* (MH⁺) 253.

Step 2:

To a 0 °C slurry of Boc-*cis*-Hydroxyproline-OMe (2.0g, 8.15mmol) and the product from Example 45, Step 1 (2.26g, 8.97mmol) in THF (82mL) was added Ph₃P and diisopropyl azocarboxylate (1.98 g, 8.97mmol). After stirring at rt for 17h, the reaction mixture was diluted with EtOAc (100mL) and washed with H₂O (50mL). The aqueous layer was separated and back-extracted with EtOAc (2 x 50mL). The combined organic layer was washed with brine, dried over MgSO₄ and concentrated to give a viscous oil which was redissolved in minimal amount of EtOAc and

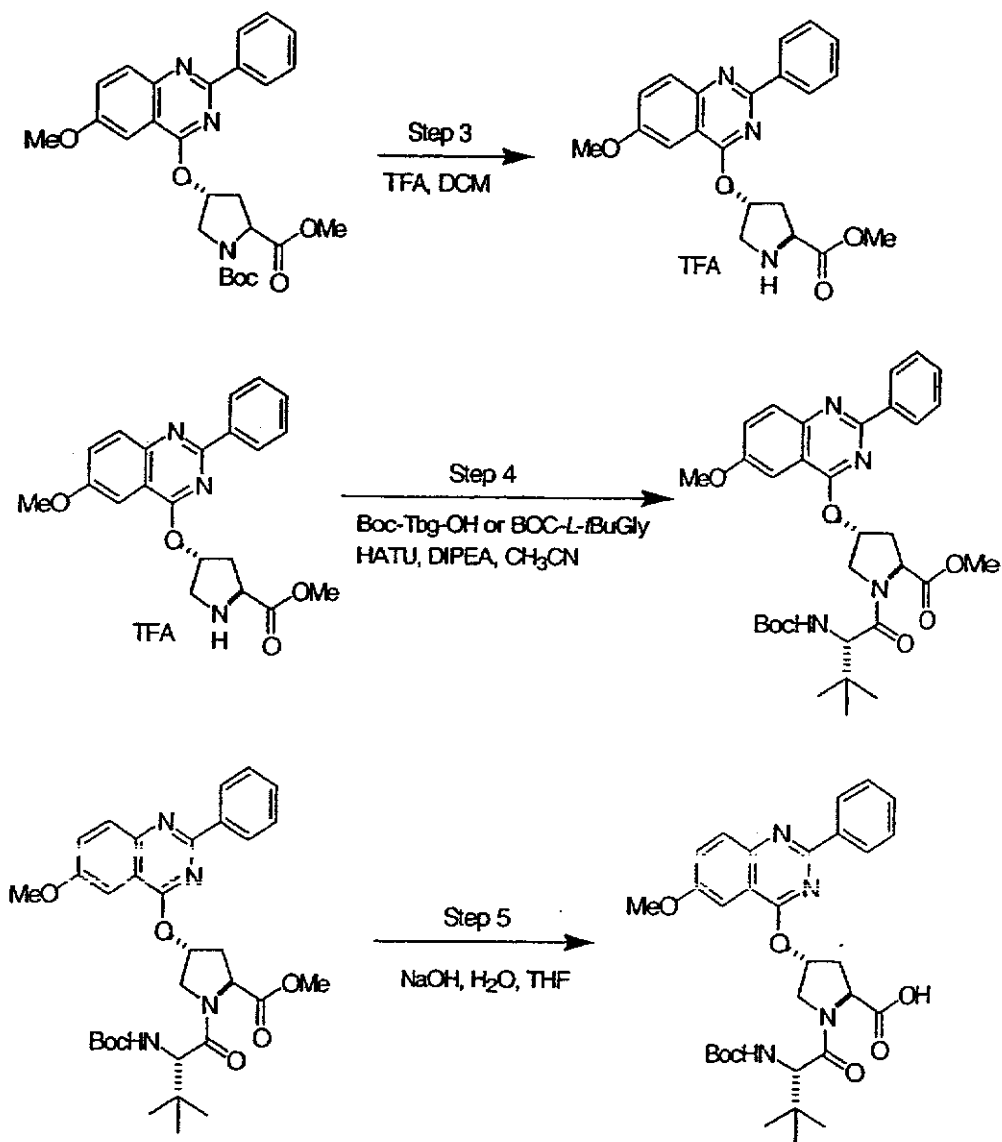
hexanes was added to effect the precipitation of most of the Ph_3PO by-product.

Ph_3PO was removed by vacuum filtration and the liquid filtrate was concentrated.

The resulting viscous oil was purified by a flash column chromatography (SiO_2 , 4:1 hex:EtOAc) to give a white solid product (1.76g, 45% yield): ^1H NMR (60/40

- 5 rotomers, CDCl_3) δ 1.47 (s, 9H), 2.49-2.55 (m, 1H), 2.73-2.83 (m, 1H), 3.80 (s, 1.8H), 3.81 (s, 1.2H), 3.96 (s, 3H), 4.03-4.09 (m, 1H), 4.54 (t, $J = 8.0$ Hz, 0.6H), 4.66 (t, $J = 7.8$ Hz), 4.96-5.06 (m, 1H), 5.97 (br s, 0.6H), 6.04 (br s, 0.4H), 7.33 (dd, $J = 6.1, 2.7$ Hz, 1H), 7.46-7.51 (m, 4H), 7.91 (d, $J = 9.2$ Hz, 1H), 8.49 (t, $J = 8.5$ Hz, 2H); ^{13}C NMR (rotomers, CDCl_3) δ 21.7, 22.0, 28.3, 28.4, 35.8, 36.8, 52.3, 52.4, 52.6, 10
55.8, 55.9, 57.9, 58.3, 74.5, 74.9, 80.6, 101.2, 101.3, 115.7, 125.8, 126.0, 128.1, 128.5, 129.7, 130.2, 137.9, 147.8, 153.8, 157.7, 158.0, 158.0, 164.8, 173.1, 173.3; MS m/z (MH^+) 480.

Scheme 2



Step 3:

The product from **Example 45**, Step 2 (760.0mg, 1.59mmol) was dissolved in 50% TFA in DCM and stirred at rt for 2h. The solvent was concentrated and the resulting brown viscous oil was dried *in vacuo* overnight. The product was used directly for the next reaction.

Step 4:

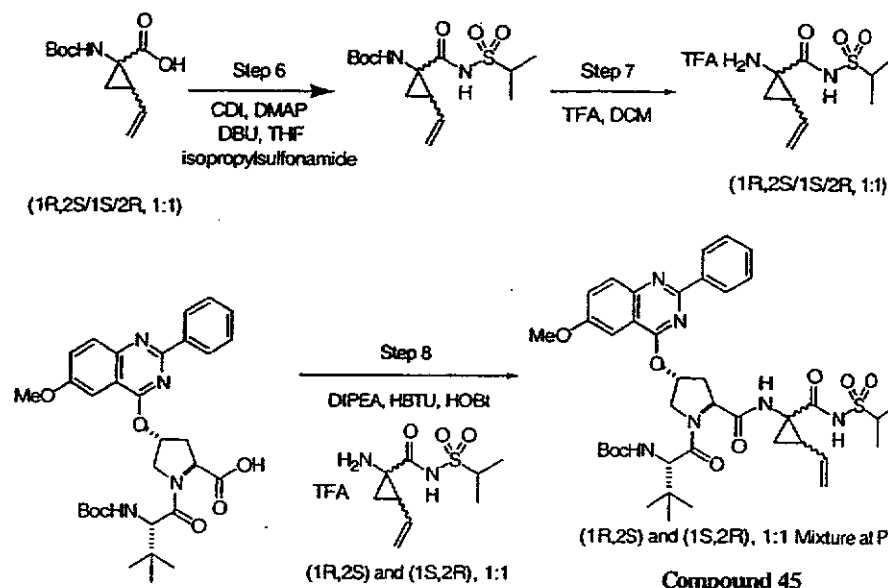
To a solution of the brown viscous oil product from **Example 45**, Step 3 (963mg, 1.59 mmol) and DIPEA (1.23g, 9.54mmol) in DCM (11mL) were added *N*-

BOC *L*-*t*BuGly (440mg, 1.90mmole), HBTU (902mg, 2.38mmole) and HOBt (364mg, 2.38mmole). After stirring at rt for 14h, the solvent and excess DIPEA was concentrated and the resulting brown viscous oil was purified by flash column (SiO₂, 4:1 hex:EtOAc) to give a white solid (0.922mg, 98% yield for the two steps): ¹H NMR (CDCl₃/MeOD) δ 0.94 (s, 9H), 1.15 (s, 9H), 2.38-2.42 (m, 1H), 2.60-2.73 (m, 1H), 3.61 (s, 3H), 3.83 (s, 3H), 4.08-4.17 (m, 2H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.69 (t, *J* = 8.0 Hz, 1H), 5.99 (br s, 1H), 7.13 (s, 1H), 7.38 (s, 5H), 7.80 (d, *J* = 9.0 Hz, 1H), 8.32 (d, *J* = 5.5 Hz, 1H); ¹³C NMR (CDCl₃/MeOD) δ 29.6, 31.4, 31.6, 33.04, 38.2, 39.0, 55.8, 56.9, 59.2, 61.5, 62.1, 78.3, 83.1, 105.0, 119.0, 129.4, 131.5, 131.9, 132.6, 133.8, 141.2, 151.0, 161.4, 161.6, 168.2, 175.2, 175.7; MS *m/z* (MH⁺) 593.

Step 5:

To a solution of the product from Example 45, Step 4 (409mg, 0.69mmol) in THF (10mL) was added 1N NaOH (2mL). After stirring at rt for 19h, the reaction was acidified with concentrated HCl to about pH 5 and extracted with DCM (3 x 50mL). The combined organic layer was dried over MgSO₄ and concentrated to give a yellow solid product (370mg, 92% yield) which was used directly in the next reaction after drying *in vacuo*: ¹H NMR (CDCl₃) δ 1.05 (s, 9H), 1.25 (s, 9H), 2.76-2.83 (m, 2H), 3.94 (s, 3H), 4.23-4.27 (m, 2H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.92 (t, *J* = 7.6 Hz, 1H), 5.20 (d, *J* = 8.9 Hz, 1H), 6.08 (br s, 1H), 7.31 (s, 1H), 7.46-7.50 (m, 5H), 7.93 (d, *J* = 9.15 Hz, 1H), 8.51 (d, *J* = 7.3 Hz, 2H); MS *m/z* (MH⁺) 579.

Scheme 3



Step 6:

To a solution *N*-Boc-vinylcyclopropanecarboxylic acid (1R, 2S/1S, 2R 1:1 mixture) (1.01g, 4.46mmol) in THF (20 mL) and DMSO (2mL) was added CDI (1.08g, 6.69mmol) and DMAP (817mg, 6.69mmol). After stirring at 70 °C for 1h, the reaction mixture was allowed to cool to rt and was treated with isopropylsulfonamide (1.1g, 8.92mmol) and DBU (1.36g, 8.92mmol). The reaction mixture was stirred at rt for 16h and it was concentrated and purified by flash column chromatography (SiO₂, 5% MeOH in DCM) to give a brown viscous oil (1.4g, 98% yield): ¹H NMR (Methanol-d₄) δ 1.25 (m, 1H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.45 (s, 9H), 1.84 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.16 (d, *J* = 7.6 Hz, 1H), 3.58 (br s, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 5.27 (d, *J* = 15.6 Hz, 1H), 5.58-5.66 (m, 1H); MS *m/z* (MH⁺) 332.

Step 7:

The product from Example 45, Step 6 (113mg, 0.34mmol) was treated with a 50% solution of trifluoroacetic acid in DCM (10mL) and stirred at rt for 1.4h. Solvent and excess trifluoroacetic acid were removed *in vacuo*. The resulting brown viscous oil was dried *in vacuo* (1.3g, 99% yield) and used without further purification: ¹H NMR (DMSO-d₆) δ 1.24 (d, *J* = 6.7 Hz, 3H), 1.26 (d, *J* = 6.7 Hz,

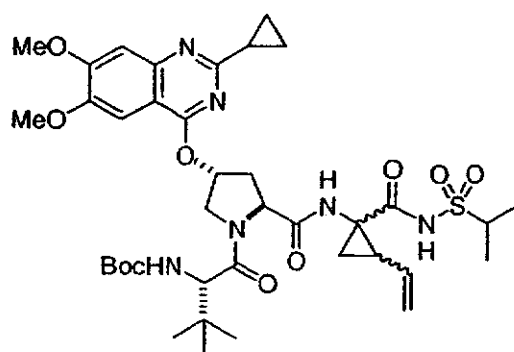
3H), 1.54 (dd, $J = 9.6, 6.6$ Hz, 1H), 1.99 (t, $J = 6.9$ Hz, 1H), 2.24 (d, $J = 8.5$ Hz, 1H), 3.58-3.63 (m, 1H), 5.18 (d, $J = 10.4$ Hz, 1H), 5.33 (d, $J = 17.1$ Hz, 1H), 5.61-5.69 (m, 1H), 8.83 (br s, 3H); ^{13}C NMR (DMSO- d_6) δ 15.2, 15.9, 16.5, 29.9, 41.6, 52.1, 116.0, 118.9, 132.0, 158.2, 167.3; MS m/z (MH^+) 233.

5

Step 8:

To a mixture of the product from Example 45, Step 5 (117mg, 0.338mmol) and DIPEA (174mg, 1.35mmol) in DCM (5mL) was added HBTU (128mg, 0.338mmole), HOBt (52mg, 0.338mmole) and the product from Example 45, Step 7
10 (130mg, 0.225mmol) After stirring at rt for 16h, the mixture was concentrated and the resulting brown viscous oil was purified by flash column chromatography (SiO_2 , 1:3 hex:EtOAc then 95:5 DCM:MeOH) to give an off white solid product (150mg, 84% yield) The final product, **Compound 45**, is a mixture of isomers; the variation occurring at the P1 vinylcyclopropyl portion of the molecule (1*R*, 2*S*/1*S*, 2*R* 1:1
15 mixture): ^1H NMR (Methanol- d_4) δ 0.92 (br s, 2H), 1.03 (s, 9H), 1.17 (s, 9H), 1.27-1.38 (m, 9H), 1.42-1.46 (m, 1H), 1.83 (dd, $J = 8.1, 5.3$ Hz, 0.4H), 1.90 (dd, $J = 7.9, 5.5$ Hz, 0.6H), 2.24-2.31 (m, 1H), 2.37-2.45 (m, 1H), 2.67-2.75 (m, 1H), 3.73-3.79 (m, 1H), 3.90 (s, 3H), 4.21 (dd, $J = 9.3, 6.0$ Hz, 2H), 4.48 (d, $J = 11.3$ Hz, 1H), 4.61 (q, $J = 8.9$ Hz, 1H), 5.14 (t, $J = 9.0$ Hz, 1H), 5.33 (t, $J = 17.9$ Hz, 1H), 5.70-5.76 (m,
20 1H), 6.06 (d, $J = 11.9$ Hz, 1H), 6.61 (d, $J = 8.9$ Hz, 1H), 7.34 (d, $J = 2.8$ Hz, 1H), 7.49 (br s, 5H), 7.87 (d, $J = 8.9$ Hz, 1H), 8.46 (d, $J = 4.3$ Hz, 2H); ^{13}C NMR (Methanol- d_4) δ 15.7, 16.1, 16.5, 16.8, 23.9, 27.1, 28.6, 35.8, 36.0, 36.2, 36.3, 36.4, 42.6, 42.8, 54.7, 54.8, 55.5, 56.4, 61.1, 61.2, 80.5, 102.9, 117.0, 118.8, 118.9, 126.8, 129.4, 129.6, 130.2, 131.5, 134.4, 139.2, 148.8, 158.0, 159.3, 159.8, 166.3, 171.1,
25 175.1, 184.3; MS m/z (MH^+) 793.

Example 46: Preparation of Compound 46



(1R,2S) and (1S,2R), 1:1 Mixture at P1
Compound 46

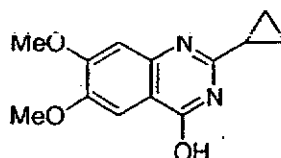
Compound 46 was prepared by following Steps 1 through 5 and Step 8 of Example 45 except that the following modifications were made:

5

Step 1:

Modifications: 2-bromo-4,5-dimethoxybenzoic acid and cyclopropylcarbamidine hydrochloride were utilized as starting materials.

Product:



10

Data: ¹H NMR (DMSO-d₆) δ 0.97-1.01 (m, 2H), 1.03-1.06 (m, 2H), 1.90-1.94 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.93 (s, 1H), 7.37 (s, 3H), 12.28 (s, 1H); ¹³C NMR (DMSO-d₆) δ 9.03, 13.17, 55.47, 55.73, 104.81, 107.27, 113.26, 145.16, 147.48,

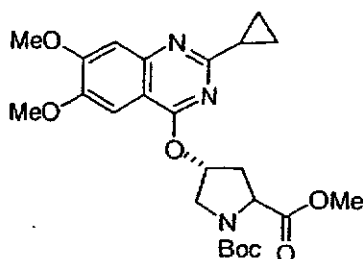
15 154.44, 157.21, 160.89 ; MS m/z (MH^+) 247.

Step 2:

Modifications: The product from **Example 46**, Step 1 was used as starting material in place of the product from **Example 45**, Step 1.

20 Product:

157



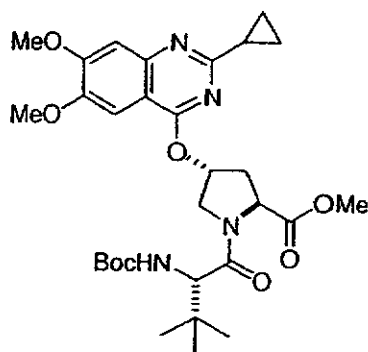
Data: ^1H NMR (CDCl_3) δ 1.00-1.04 (m, 2H), 1.07-1.11 (m, 2H), 1.43 (s, 5.4H), 1.46 (s, 3.6H), 2.17-2.21 (m, 1H), 2.37-2.43 (m, 1H), 2.62-2.69 (m, 1H), 3.75 (s, 1.8H),
 5 3.78 (s, 1.2H), 3.92 (d, $J = 2.8$ Hz, 1H), 4.00 (s, 3.6H), 4.01 (s, 2.4H), 4.48 (t, $J = 8.0$ Hz, 0.6H), 4.59 (t, $J = 7.6$ Hz, 0.4H), 5.7 (br s, 0.6H), 5.74 (br s, 0.4H), 7.18 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (CDCl_3) δ 9.6, 9.7, 18.1, 28.3, 28.4, 35.8, 36.7, 52.2, 52.4, 56.3, 57.8, 58.2, 74.0, 74.5, 80.5, 80.6, 101.0, 101.1, 106.3, 108.6, 148.8, 149.1, 153.8, 155.4, 164.4, 165.9, 172.9, 173.2; LC-MS m/z (MH^+) 474.

10

Steps 3 and 4:

The product from Example 46, Step 2 was used as starting material in place of the product from Example 45, Step 2.

Product:



15

Data: ^1H NMR (Methanol- d_4) δ 1.04 (s, 9H), 1.08-1.21 (m, 4H), 1.14 (s, 9H), 2.17-2.21 (m, 1H), 2.39-2.41 (m, 1H), 2.74-2.77 (m, 1H), 3.77 (s, 3H), 3.92 (s, 3H), 3.98 (m, 3H), 4.09 (dd, $J = 11.4, 3.8$ Hz, 1H), 4.17 (d, $J = 8.9$ Hz, 1H), 4.42 (d, $J = 11.3$ Hz, 1H), 4.76 (t, $J = 8.2$ Hz, 1H), 5.81 (br s, 1H), 6.43 (d, $J = 8.6$ Hz, 1H), 7.14 (d, $J = 6.1$ Hz, 1H), 7.27 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR (Methanol- d_4) δ 10.0, 10.3, 18.6,

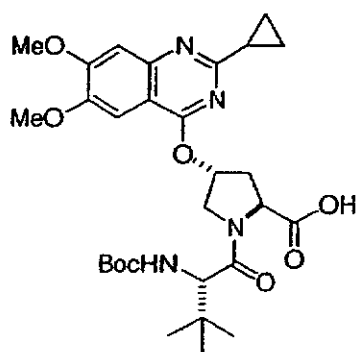
20

26.9, 28.5, 28.8, 35.8, 36.1, 38.9, 52.8, 54.9, 56.7, 59.6, 60.5, 76.6, 80.4, 102.7, 106.2, 109.9, 149.8, 150.7, 157.6, 166.0, 167.3, 173.5, 173.6; MS m/z (MH^+) 587.

Step 5:

- 5 The product from **Example 46**, Step 4 was used as starting material in place of the product from **Example 45**, Step 4.

Product:

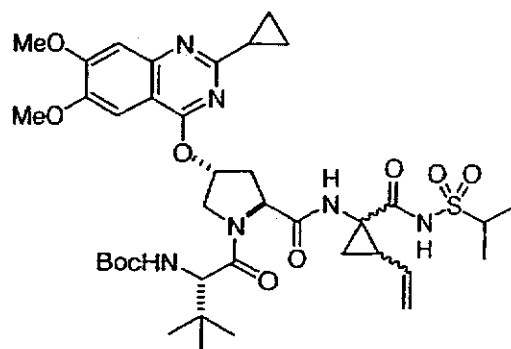


- 10 Data: ^1H NMR (Methanol- d_4) δ 1.03 (s, 9H), 1.13 (s, 9H), 1.20-1.23 (m, 4H), 2.15-2.19 (m, 1H), 2.40-2.45 (m, 1H), 2.70-2.76 (m, 1H), 3.90 (s, 3H), 3.96 (s, 3H), 4.08 (dd, $J = 11.4, 3.8$ Hz, 1H), 4.17 (d, $J = 5.8$ Hz, 1H), 4.37 (d, $J = 11.3$ Hz, 1H), 4.71 (t, $J = 8.1$ Hz, 1H), 5.77 (br s, 1H), 7.09 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (Methanol- d_4) δ 10.2, 10.5, 18.6, 26.9, 28.5, 28.8, 36.0, 36.3, 54.9, 56.8, 59.7, 60.4, 76.8, 80.4,
15 102.6, 105.9, 109.9, 126.9, 127.9, 149.3, 150.8, 157.65, 157.8, 166.1, 167.3, 173.3, 175.1; MS m/z (MH^+) 573.

Step 8:

- 20 The product from **Example 46**, Step 5 was used as starting material in place of the product from **Example 45**, Step 5. The final product, **Compound 46**, is a mixture of isomers; the variation occurring at the P1 vinylcyclopropyl portion of the molecule (1R, 2S/1S, 2R 1:1 mixture).

Product:



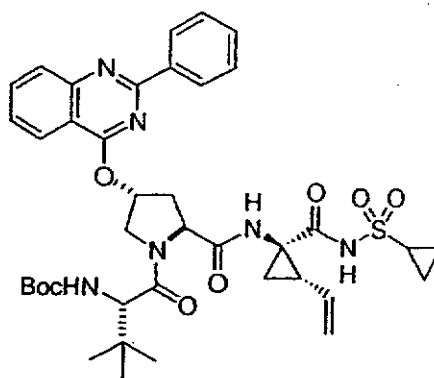
(1R,2S) and (1S,2R), 1:1 Mixture at P1

Compound 46

Data: ^1H NMR (Methanol- d_4) δ 1.03 (s, 9H), 1.05-1.09 (m, 4H), 1.16 (s, 4.5H), 1.17 (s, 4.5H), 1.19-1.22 (m, 1H), 1.31 (d, $J = 6.7$ Hz, 2H), 1.33-1.38 (m, 7H), 1.18-1.89 (m, 1H), 2.15-2.20 (m, 2H), 2.35-2.44 (m, 1H), 3.23 (q, $J = 7.4$ Hz, 1H), 3.70-3.75 (m, 1H), 3.91 (s, 3H), 3.98 (s, 3H), 4.08-4.13 (m, 2H), 4.16 (dd, $J = 8.9, 3.1$ Hz, 1H), 4.38 (t, $J = 13.1$ Hz, 1H), 4.58-4.62 (m, 1H), 4.06 (m, 1H), 5.29 (t, $J = 15.2$ Hz, 1H), 5.83 (br s, 1H), 7.15 (s, 1H), 7.27 (d, $J = 4.3$ Hz, 1H); MS m/z (MH^+) 787.

Example 47: Preparation of Compound 47

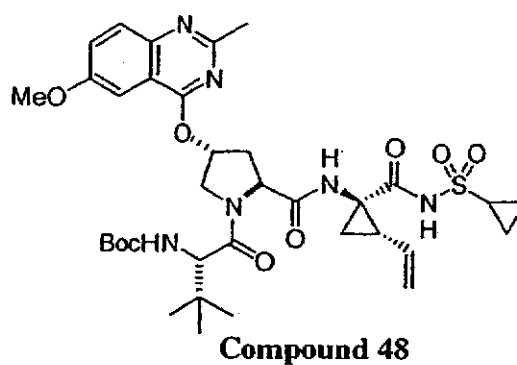
10



Compound 47

Compound 47 was prepared by following analogous steps used to procure **Compound 45** of Example 45 .ortho-bromobenzoic acid used as starting material as was cyclopropanesulfonic acid (1R-amino-2S-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt . **Compound 47**: $\text{MH}^+ = 761$

15

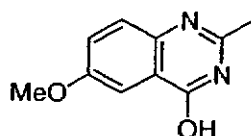
Example 48: Preparation of Compound 48

- 5 **Compound 48** was prepared by following Steps 1 through 5 and Step 8 of **Example 45** except that the following modifications were made:

Step1:

Modifications: Acetamidine hydrochloride and 2-bromo-5-methoxybenzoic acid were utilized as starting materials.

Product:



5

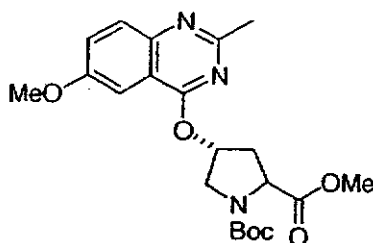
Data: ^1H NMR (DMSO) δ 2.31 (s, 3H), 3.85 (s, 3H), 7.36 (d, J = 6.2 Hz, 1H), 7.37 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 12.15 (s, 1H); ^{13}C NMR (DMSO) δ 21.11, 55.41, 105.57, 121.22, 123.59, 128.12, 143.34, 151.68, 157.00, 161.45; LC-MS m/e (MH^+) 191.

10

Step 2:

Modifications: The product from **Example 48**, Step 1 was used as starting material in place of the product from **Example 45**, Step 1.

Product:



15

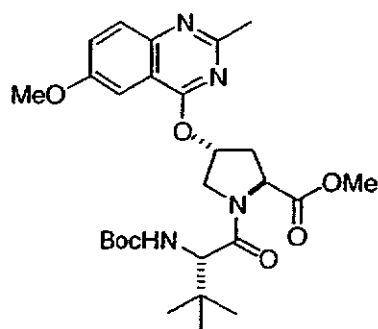
Data: ^1H NMR (CDCl_3) δ 1.43 (s, 5.4H), 1.45 (s, 3.6H), 2.38-2.45 (m, 1H), 2.62-2.71 (m, 1H), 2.66 (s, 1.8H), 2.68 (s, 1.2H), 3.77 (1.8H), 3.79 (s, 1.2H), 3.92 (s, 3H), 3.93-3.98 (m, 2H), 4.49 (t, J = 8.0 Hz, 0.6H), 4.61 (t, J = 7.8 Hz, 0.4H), 5.82 (t, J = 2.1 Hz, 0.6H), 5.89 (t, J = 2.3 Hz, 0.4H), 7.26 (dd, J = 4.7, 3.2 Hz, 1H), 7.42 (dd, J = 6.3, 2.8 Hz, 1H), 7.75 (d, J = 9.15 Hz, 1H); ^{13}C NMR (CDCl_3) δ 26.1, 28.3, 28.4, 35.8, 36.7, 52.2, 52.2, 52.4, 52.5, 55.755.8, 57.9, 58.2, 74.1, 74.7, 80.6, 101.0, 101.2, 114.9, 125.6, 125.9, 128.6, 147.3, 153.8, 154.5, 157.6, 157.6, 161.2, 164.6, 173.0, 173.3; LC-MS m/e (MH^+) 418.

25

Steps 3 and 4:

Modifications: The product from **Example 48**, Step 2 was used as starting material in place of the product from **Example 45**, Step 2.

Product:



5

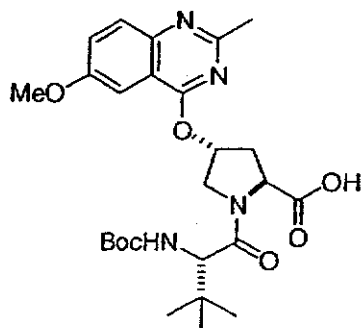
Data: ^1H NMR (MeOD) δ 1.03 (s, 9H), 1.07 (s, 9H), 2.38-2.42 (m, 1H), 2.68 (s, 3H), 2.80 (q, $J = 7.8$ Hz, 1H), 3.76 (s, 3H), 3.89 (s, 3H), 4.07 (dd, $J = 11.9, 3.4$ Hz, 1H), 4.13 (br s, 1H), 4.55 (d, $J = 12.2$ Hz, 1H), 4.78 (t, $J = 8.7$ Hz, 1H), 5.93 (s, 1H), 7.37 (d, $J = 2.75$ Hz, 1H), 7.48-7.51 (m, 2H), 7.70 (d, $J = 5.7$ Hz, 1H); ^{13}C NMR (MeOD) δ 25.6, 26.9, 28.4, 28.8, 35.9, 52.8, 55.0, 56.4, 59.7, 60.6, 77.2, 80.4, 102.9, 111.6, 116.5, 127.0, 128.4, 147.5, 162.7, 166.4, 173.6, LC-MS m/z (MHT $^+$) 531.

10

Step 5:

15 Modifications: The product from **Example 48**, Step 4 was used as starting material in place of the product from **Example 45**, Step 4.

Product:



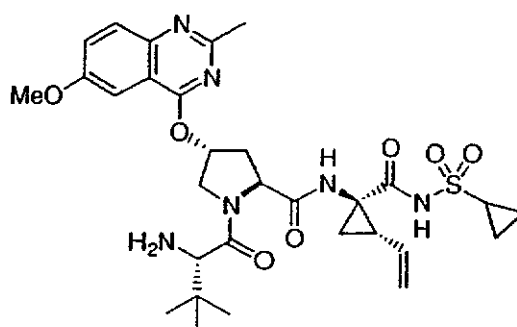
Data: ^1H NMR (MeOD) δ 1.03 (s, 9H), 1.08 (s, 9H), 2.41-2.46 (m, 1H), 2.68 (s, 3H), 2.81 (q, $J = 8.1$ Hz, 1H), 3.89 (s, 3H), 4.07 (dd, $J = 11.8, 3.2$ Hz, 1H), 4.18 (d, $J = 5.5$ Hz, 1H), 4.52 (d, $J = 11.9$ Hz, 1H), 4.74 (t, $J = 8.7$ Hz, 1H), 5.93 (br s, 1H), 7.37 (d, J

20

= 2.81 Hz, 1H), 7.49 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (MeOD) δ 25.7, 26.9, 28.5, 36.1, 55.0, 56.4, 59.7, 60.5, 77.1, 80.4, 103.0, 116.5, 127.0, 128.5, 147.7, 157.8, 159.6, 162.7, 166.4, 173.5, 174.9; LC- MS m/e (MH^+) 517.

5

Example 48: Preparation of Compound 48



Compound 48

10 Step 8:

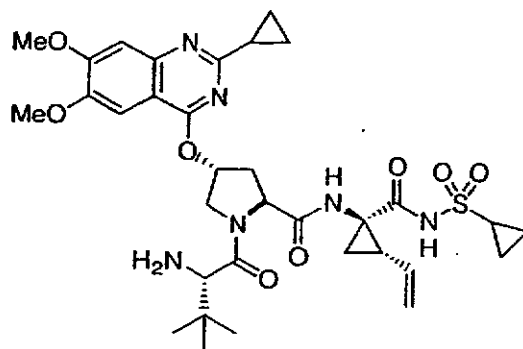
To a solution of the product from **Example 48**, Step 5 (45.8 mg, 0.089 mmol), cyclopropanesulfonic acid (1R-amino-2S-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (21.0 mg, 0.089 mmol) and DIEA (34.5 mg, 0.267 mmol) in DCM (1 mL) was added HATU (44.0 mg, 0.116 mmol). After stirring at rt overnight, the reaction mixture was washed with 5% aqueous NaHCO_3 (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The organic layer was washed with 5% aqueous citric acid (1 mL), brine, dried over MgSO_4 , concentrated and purified by reversed prep-HPLC. This purification step resulted in the loss of the N-BOC protecting group at the P3 *tert*-leucine portion of the molecule: ^1H NMR (MeOD) δ 1.07-1.12 (m, 2 H) 1.14 (s, 2 H) 1.14-1.16 (m, 2 H) 1.17 (s, 9 H) 1.20-1.30 (m, 3 H) 1.45 (dd, $J=9.46, 5.49$ Hz, 1 H) 1.56 (s, 1 H) 1.92 (dd, $J=8.20, 5.60$ Hz, 1 H) 2.25-2.31 (m, 1 H) 2.39-2.45 (m, 1 H) 2.73 (m, 1 H) 2.76 (s, 3 H) 2.93-2.97 (m, 1 H) 3.94 (s, 1 H) 3.96 (s, 3 H) 4.07 (s, 1 H) 4.21 (d, $J=3.97$ Hz, 0.4 H) 4.23 (d, $J=3.97$ Hz, 0.6 H) 4.31 (m, 1 H) 4.73 (dd, $J=10.38, 7.02$ Hz, 1 H) 5.15 (dd, $J=10.38, 1.52$ Hz, 1 H) 5.32 (dd, $J=17.1, 1.52$ Hz, 1 H), 5.71-5.78 (m, 1H) 6.11 (t, $J=3.51$ Hz, 1 H) 7.46 (d, $J=2.75$ Hz,

25

1 H) 7.67 (d, $J=3.06$ Hz, 0.4 H) 7.69 (d, $J=3.05$ Hz, 0.6 H) 7.82 (s, 0.6 H) 7.84 (s, 0.4 H).

Example 49: Preparation of Compound 49

5



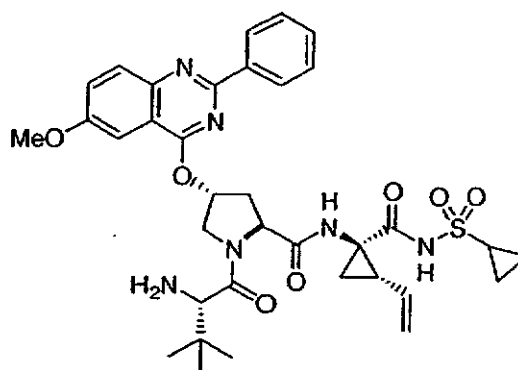
Compound 49

Compound 49 was prepared by the same method as described for the preparation of **Compound 48**, except the product from Example 46, Step 5 and

10 cyclopropanesulfonic acid (1R-amino-2S-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt were used as starting material. The preparative HPLC purification step resulted in the loss of the N-BOC protecting group at the P3 *tert*-leucine portion of the molecule: ^1H NMR (MeOD) δ 1.09 (m, 2 H) 1.14 (d, $J=3.97$ Hz, 2 H) 1.17 (s, 9 H) 1.25 (m, 3 H) 1.37 (m, 3 H) 1.44 (dd, $J=9.31, 5.65$ Hz, 2 H) 1.57 (s, 1 H) 1.92
15 (dd, $J=8.09, 5.65$ Hz, 1 H) 2.28 (dd, $J=17.70, 8.55$ Hz, 1 H) 2.32 (m, 1 H) 2.68 (dd, $J=14.19, 7.78$ Hz, 1 H) 2.95 (m, 1 H) 3.98 (s, 3 H) 4.06 (s, 3 H) 4.08 (s, 1 H) 4.22 (d, $J=2.75$ Hz, 1 H) 4.70 (dd, $J=9.77, 7.32$ Hz, 1 H) 5.15 (dd, $J=10.38, 1.53$ Hz, 1 H) 5.32 (dd, $J=17.40, 1.22$ Hz, 1 H) 5.74 (m, 1 H) 6.04 (m, 1 H) 7.24 (s, 1 H) 7.37 (s, 1 H)

20

Example 50: Preparation of Compound 50

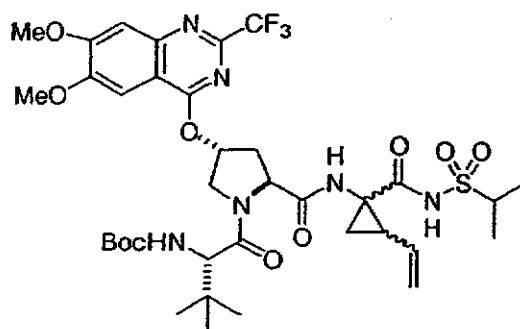


Compound 50

Compound 50 was prepared by the same method as described for the preparation of **Compound 48**, except the product from Example 45, Step 5 and cyclopropanesulfonic acid (1R-amino-2S-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt were used as starting material. The preparative HPLC purification step resulted in the loss of the N-BOC protecting group at the P3 *tert*-leucine portion of the molecule: ¹H NMR (MeOD) δ 1.10 (m, 2 H) 1.14 (s, 1 H) 1.15 (d, *J*=3.36 Hz, 1 H) 1.17 (d, *J*=3.05 Hz, 9 H) 1.22 (m, 1 H) 1.27 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.56 (s, 1 H) 1.93 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.29 (q, *J*=8.55 Hz, 1 H) 2.48 (m, 1 H) 2.78 (dd, *J*=13.89, 8.09 Hz, 1 H) 2.97 (m, 1 H) 3.96 (s, 2 H) 4.07 (s, 1 H) 4.32 (d, *J*=2.14 Hz, 2 H) 4.76 (d, *J*=7.02 Hz, 1 H) 4.78 (m, 1 H) 4.86 (d, *J*=3.05 Hz, 1 H) 5.32 (dd, *J*=17.09, 1.22 Hz, 1 H) 5.75 (m, 1 H) 6.24 (d, *J*=2.44 Hz, 1 H) 7.45 (d, *J*=2.75 Hz, 1 H) 7.52 (m, 3 H) 7.61 (dd, *J*=9.16, 2.75 Hz, 1 H) 7.96 (d, *J*=9.16 Hz, 1 H).

Example 51: Preparation of Compound 51

166



(1R,2S) and (1S,2R), 1:1 Mixture at P1

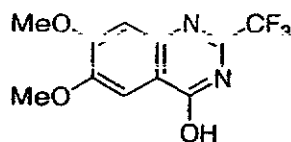
Compound 51

Compound 51 was prepared by following Steps 1 through 5 and Step 8 of Example 45 except that the following modifications were made:

5

Step 1:

Modifications: 2-bromo-4,5-dimethoxybenzoic acid and trifluoroamidine were utilized as starting materials.

Product:

10

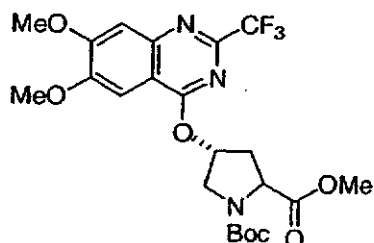
Data: ^1H NMR (DMSO) δ 3.92 (s, 3H), 3.94 (s, 3H), 7.33 (s, 1H), 7.50 (s, 1H), 13.40 (br s, 1H); ^{13}C NMR (DMSO) δ 55.8, 56.1, 104.9, 108.7, 150.2, 155.0; LC-MS m/e (MH^+) 275.

15

Step 2:

Modifications: The product from **Example 51**, Step 1 was used as starting material in place of the product from **Example 45**, Step 1.

Product:

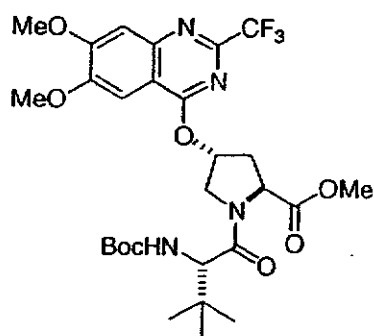


Data: ^1H NMR (CDCl_3) δ 1.42 (s, 3.6H), 1.44 (s, 5.4H), 2.42-2.49 (m, 1H), 2.67-
5 2.73 (m, 1H), 3.37 (s, 1.2H), 3.78 (s, 1.8H), 3.97 (t, $J = 6.5$ Hz, 1H), 4.02 (s, 2.4H),
4.04 (s, 3.6H), 4.48 (t, $J = 7.9$ Hz, 0.6H), 4.60 (t, $J = 7.7$ Hz, 0.4H), 5.86 (br s, 0.6H),
5.90 (br s, 0.4H), 7.27-7.29 (m, 1H), 7.38-7.44 (m, 1H); ^{13}C NMR (CDCl_3) δ 8.2,
28.3, 35.7, 36.7, 52.1, 52.2, 52.4, 56.5, 57.8, 58.2, 75.5, 76.0, 80.7, 100.8, 107.6,
111.0, 119.7, 148.2, 150.2, 151.4, 153.8, 154.5, 156.4, 165.1, 172.7, 173.0; LC-MS
10 m/e (MH^+) 502.

Steps 3 and 4:

Modifications: The product from **Example 51**, Step 2 was used as starting material in place of the product from **Example 45**, Step 2.

15 Product:

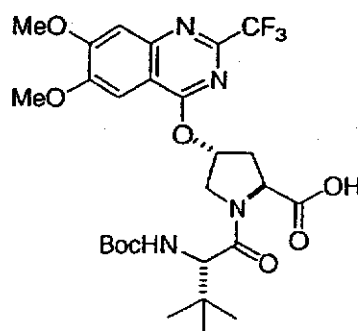


Data: ^1H NMR (MeOD) δ 1.03 (s, 9H), 1.08 (s, 9H), 2.41-2.45 (m, 1H), 2.80-2.84 (m, 1H), 3.76 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 4.10-4.14 (m, 2H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.80 (t, $J = 8.7$ Hz, 1H), 5.92 (br s, 1H), 7.35 (br s, 2H); ^{13}C NMR (MeOD) δ 26.9, 28.4, 28.8, 35.7, 36.0, 52.8, 54.8, 56.9, 59.6, 60.7, 77.9, 80.3, 102.2, 107.9, 112.4, 120.3, 149.3, 153.2, 157.8, 158.3, 173.5; LC-MS m/e (MH^+) 615.

Step 5:

Modifications: The product from **Example 51**, Step 4 was used as starting material in place of the product from **Example 45**, Step 4.

10 Product:

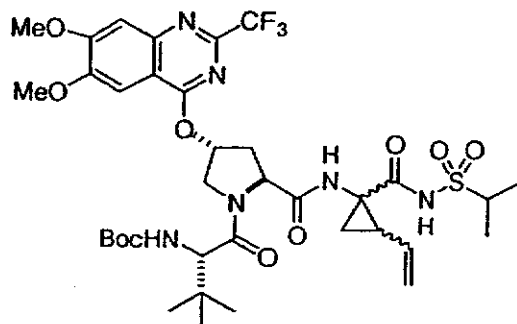


Data: ^1H NMR (MeOD) δ 1.03 (s, 9H), 1.09 (s, 9H), 2.44-2.49 (m, 1H), 2.80-2.84 (m, 1H), 3.97 (s, 3H), 4.01 (s, 3H), 4.10-4.24 (m, 3H), 4.50 (d, $J = 11.9$ Hz, 1H), 4.76 (t, $J = 7.9$ Hz, 1H), 5.93 (br s, 1H), 7.36 (br s, 2H); ^{13}C NMR (MeOD) δ 26.9, 28.4, 28.8, 36.0, 36.1, 54.8, 56.9, 57.0, 60.6, 77.9, 80.3, 102.3, 108.0, 112.5, 120.3, 149.3, 151.3, 153.2, 158.2, 158.3, 166.7, 173.5; LC-MS m/e (MH^+) 601.

Step 8:

20 Modifications: The product from **Example 51**, Step 5 was used as starting material in place of the product from **Example 45**, Step 5. The final product, **Compound 51**, is a mixture of isomers; the variation occurring at the P1 vinylcyclopropyl portion of the molecule (1*R*, 2*S*/1*S*, 2*R* 1:1 mixture).

Product:



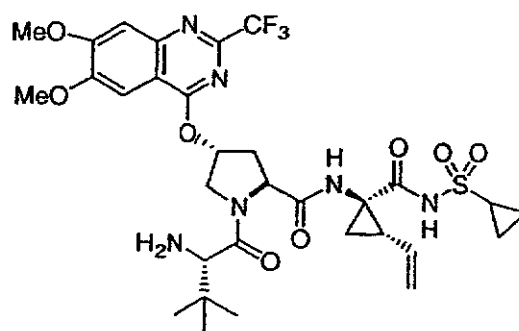
(1R,2S) and (1S,2R), 1:1 Mixture at P1

Compound 51

Data: ^1H NMR (DMSO) δ 0.23 (s, 4.5H), 0.23 (s, 4.5H), 0.35 (s, 4.5H), 0.36 (s, 4.5H), 0.45-0.59 (m, 8H), 0.63-0.66 (m, 1H), 1.04 (dd, $J = 8.2, 5.2$ Hz, 1H), 1.10 (dd, $J = 8.2, 5.5$ Hz, 1H), 1.47-1.53 (m, 1H), 1.58-1.61 (m, 1H), 1.87-1.90 (m, 1H), 2.95-3.01 (m, 1H), 3.17 (s, 1.5H), 3.18 (s, 1.5H), 3.22 (s, 3H), 3.37 (br s, 2H), 3.68 (q, $J = 5.9$ Hz, 1H), 3.82 (q, $J = 8.6$ Hz, 1H), 4.33-4.37 (m, 1H), 4.54 (t, $J = 16.5$ Hz, 1H), 4.93 (q, $J = 8.9$ Hz, 1H), 5.17 (d, $J = 15.9$ Hz, 1H), 6.53 (s, 1H), 6.58 (s, 1H); ^{13}C NMR (DMSO) δ 12.8, 13.2, 13.7, 13.9, 19.5, 20.6, 21.1, 24.3, 25.6, 32.9, 33.1, 33.4, 33.6, 36.1, 39.7, 39.9, 51.8, 51.9, 52.4, 54.0, 54.2, 57.7, 57.7, 58.1, 58.3, 75.1, 75.3, 77.5, 84.1, 99.2, 105.2, 107.9, 109.5, 116.0, 116.1, 118.7, 123.9, 127.4, 131.5, 146.5, 148.6, 150.3, 155.1, 155.5, 163.7, 164.7, 168.2, 168.3, 170.7, 172.2; LC-MS m/e (MH^+) 815.

15

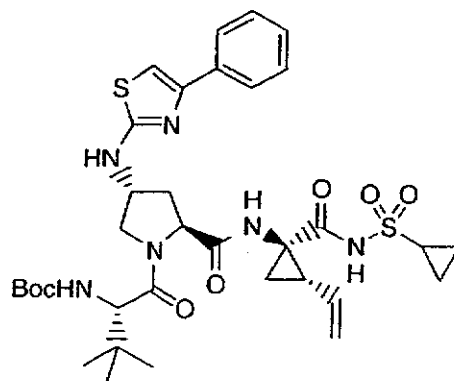
Example 52: Preparation of Compound 52

**Compound 52**

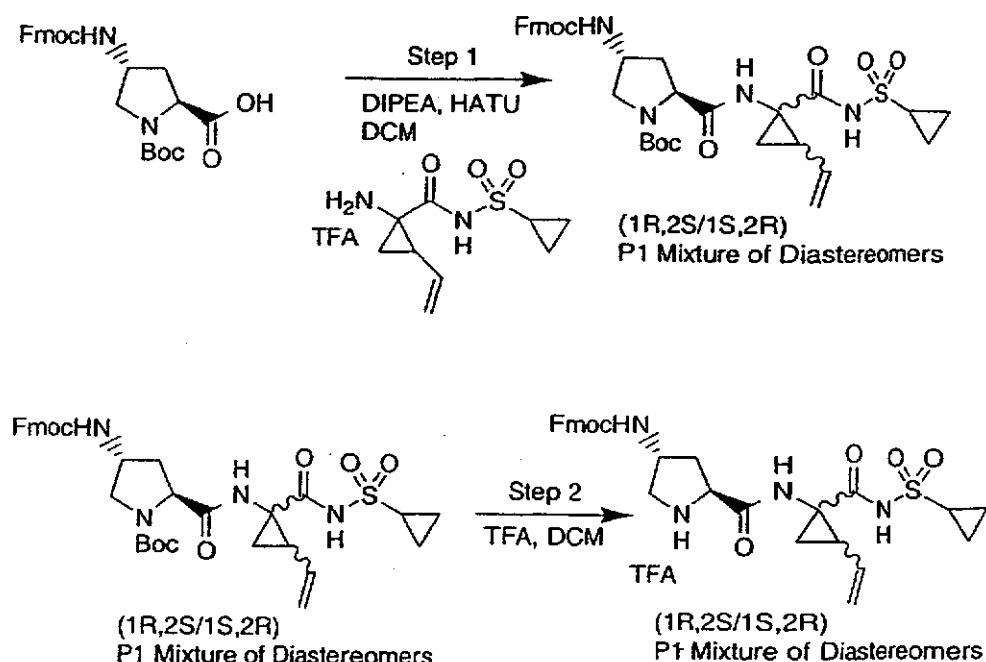
Compound 52 was prepared by the same method as described for the preparation of Compound 48, except the product from Example 51, Step 5 and cyclopropanesulfonic acid (1R-amino-2S-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt were used as starting material. The preparative HPLC purification step resulted in the loss of the N-BOC protecting group at the P3 *tert*-leucine portion of the molecule: ^1H NMR (MeOD) δ 1.11 (m, 3 H) 1.17 (s, 9 H) 1.25 (m, 3 H) 1.46 (dd, $J=9.46, 5.49$ Hz, 1 H) 1.92 (dd, $J=8.24, 5.49$ Hz, 1 H) 2.28 (q, $J=8.95$ Hz, 1 H) 2.42 (m, 1 H) 2.72 (dd, $J=14.19, 7.17$ Hz, 1 H) 2.96 (m, 1 H) 4.01 (s, 3 H) 4.04 (m, 5 H) 4.24 (m, 2 H) 4.73 (dd, $J=10.22, 7.17$ Hz, 1 H) 5.15 (dd, $J=10.53, 1.37$ Hz, 1 H) 5.32 (d, $J=17.09$ Hz, 1 H) 5.75 (m, 1 H) 6.07 (s, 1 H) 7.41 (s, 1 H) 7.47 (s, 1 H).

Example 53: Preparation of Compound 53

15

**Compound 53**

Scheme 1



Step 1:

To a solution of (1R, 2S/1S, 2R 1:1 mixture) cyclopropanesulfonic acid (1-amino-2-vinyl-cyclopropanecarbonyl)-amide trifluoroacetic acid salt (626mg, 1.82mmol) in DCM (17mL) was added and DIEA (555mg, 4.29mmol) in DCM (17mL), HATU (754mg, 1.98mmole), and (2S, 4R)-Fmoc-4-amino-1-boc-pyrrolidine-2-carboxylic acid (747mg, 1.65mmol). After stirring at rt for 24h, the mixture was washed with 1N HCl (10mL), 5% aqueous NaHCO₃ (4mL). Each aqueous layer was extracted with DCM (25 mL). The combined DCM was dried over MgSO₄ and concentrated. The resulting brown viscous oil was purified by flash column chromatography (SiO₂, 95:5 DCM:MeOH) to give a yellow solid 822mg, 75% yield):

¹H NMR (DMSO-d₆) δ 1.04-1.09 (m, 3H), 1.15-1.27 (m, 4H), 1.38-1.44 (m, 7H), 1.47 (s, 9H), 1.84 (dd, *J*=8.2, 5.2 Hz, 1H), 2.01-2.30 (m, 4H), 2.90-2.98 (m, 1H), 3.64-3.71 (m, 1H), 4.16-4.22 (m, 4H), 4.39 (bs, 2H), 5.13 (dd, *J*=10.7, 0.9 Hz, 1H), 3.31 (d, *J*=17.1 Hz, 1H), 5.72-5.79 (m, 1H), 7.31 (t, *J*=7.3 Hz, 3H), 7.38 (t, *J*=7.5 Hz, 3H), 7.64 (d, *J*=7.02 Hz, 3H), 7.79 (d, *J*=7.63 Hz, 3H); LC-MS *m/e* (Na+MH⁺) 687.

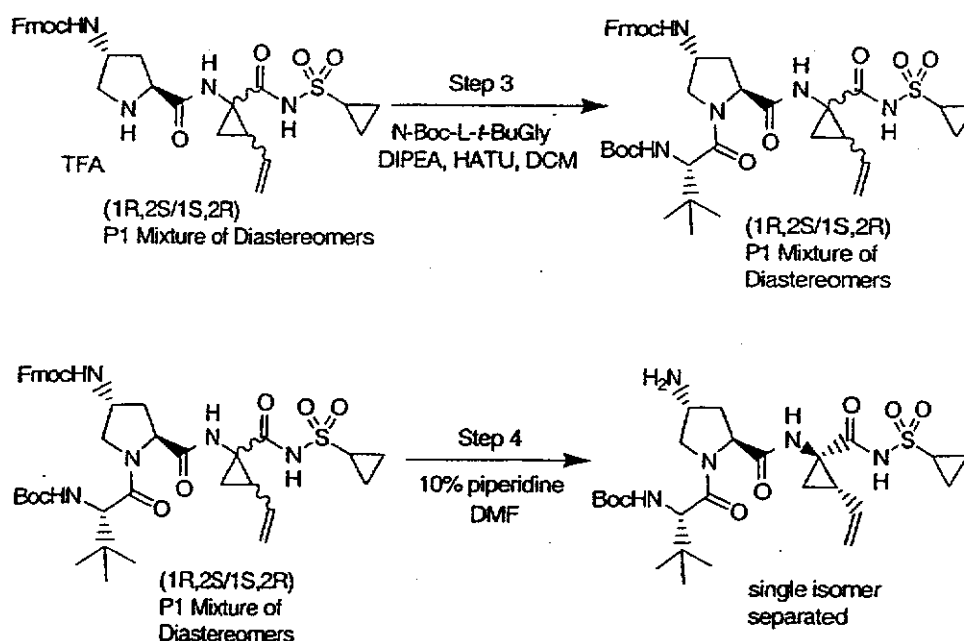
Step 2:

The product from Example 53, Step 1 (500mg, 0.752mmol) was treated with 50% TFA in DCM (10mL). After stirring at rt for 0.5h, the resulting brown reaction mixture was concentrated to give a brown solid (489mg, 84%yield): ¹H NMR

- 5 (DMSO-d₆) δ 1.03-1.19 (m, 4H), 1.24-1.26 (m, 1H), 1.35 (dd, *J*=9.5, 5.5 Hz, 1H), 1.91-1.96 (m, 1H), 2.22-2.30 (m, 1H), 2.40 (bs, 1H), 2.93-2.98 (m, 1H), 3.60 (bs, 1H), 4.21 (t, *J*=5.6 Hz, 2H), 4.47 (bs, 3H), 5.17 (d, *J*=9.2 Hz, 1H), 5.32 (d, *J*=17.1 Hz, 1H), 5.64-5.67 (m, 1H), 7.31 (t, *J*=7.3 Hz, 3H), 7.39 (t, *J*=7.5 Hz, 3H), 7.63 (d, *J*=7.3 Hz, 2H), 7.80 (d, *J*=7.3 Hz, 2H); (LC-MS *m/e* (MH⁺) 565.

10

Scheme 2



Step 3:

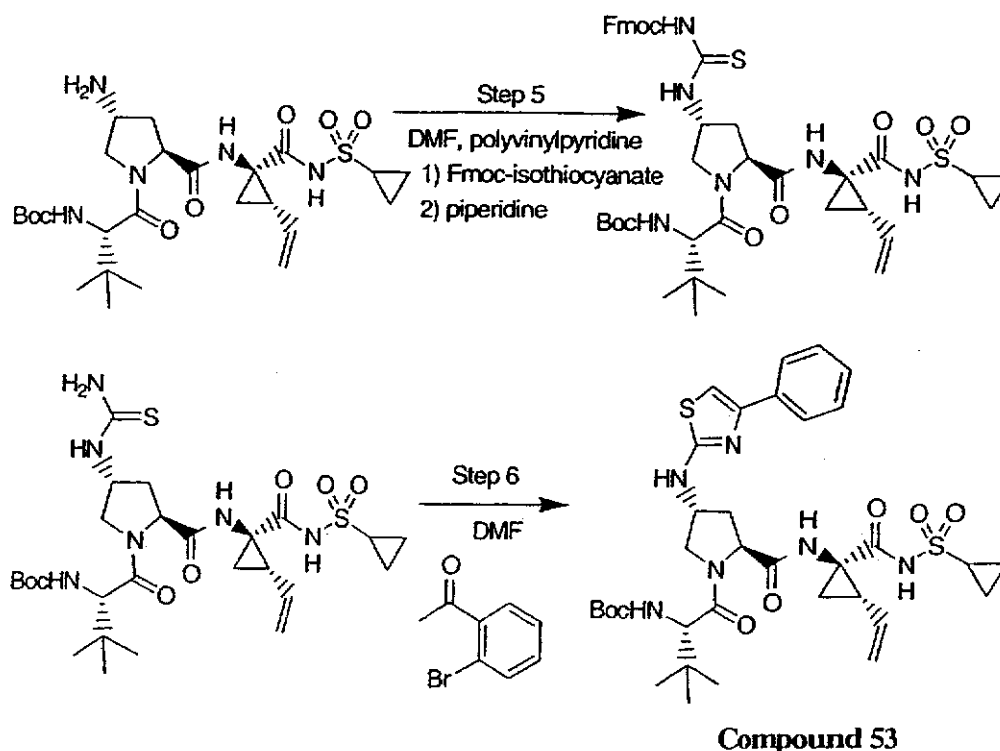
- To a solution of the product from Example 53, Step 2 (260mg, 0.383mmol) in DCM (4 mL) was added DIPEA (218mg, 1.69mmol), HATU (165mg, 0.422mmol), and N-BOC L-tBuGly (100mg, 0.422mmol). After stirring at rt for 16h, the reaction mixture was diluted with H₂O (3mL), acidified with 1N HCl to pH=1. The aqueous layer was extracted with DCM (2x15mL). The combined organic layer was washed with 5% NaHCO₃ (3mL), brine (5mL), dried over MgSO₄ and concentrated. The resulting brown viscous oil was purified by flashed column
- 15

chromatography (SiO_2 , 95:5 DCM:MeOH) to give a brown foamy solid (281mg, 94% yield): ^1H NMR ($\text{DMSO}-d_6$) δ 0.96-1.08 (m, 4H), 1.05 (s, 9H), 1.15-1.26 (m, 2H), 1.35-1.38 (m, 5H), 1.42 (s, 9H), 1.85 (dd, $J=9.5, 5.5$ Hz, 1H), 2.07 (bs, 1H), 2.22 (q, $J=8.7$ Hz, 1H), 2.92-2.95 (m, 1H), 3.90 (bs, 1H), 4.20 (d, $J=6.4$ Hz, 3H), 4.29-4.39 (m, 5H), 5.13 (d, $J=10.7$, 1H), 5.31 (dd, $J=18.0, 5.8$ Hz, 1H), 5.70-5.77 (m, 1H), 7.30 (t, $J=7.3$ Hz, 3H), 7.39 (t, $J=7.3$ Hz, 4H), 7.63 (dd, $J=6.7, 2.8$ Hz, 3H), 8.80 (d, $J=7.63$ Hz, 3H); LC-MS m/z (MH^+) 678.

Step 4:

The product from Example 53, Step 3 was treated with 10% piperidine in DMF (3.3mL). After stirring at rt for 14hr, solvent was removed and the resulting brown viscous oil was purified by flash column chromatography (SiO_2 , 95:5 DCM:MeOH) to isolate the pure highest R_f 1R,2S P1 diastereomer as a pale yellow solid (31mg). The other isomer was isolated in a mixture and was not used: LC-MS m/z (MH^+) 556.

Scheme 3



Steps 5 and 6:

To a solution of the product from **Example 53**, Step 4 in DMF (2mL) was added polyvinylpyridine (13mg) and Fmoc-isothiocyanate. After stirring at rt for 14h, the reaction mixture was treated with piperidine (172mg, 2.02mmol). The reaction was stirred at rt for an additional 6h after which it was concentrated and dried under vacuo overnight. The crude residue was re-dissolved in DMF (2mL) and treated with 2-bromoacetophenone and stirred at rt for another 14h. The reaction mixture was concentrated and the resulting residue was purified by flash column chromatography (SiO₂, 95:5 DCM:MeOH) to give **Compound 53** as a light yellow solid (21.9mg, 50% yield): ¹H NMR (DMSO-d₆) δ 0.87-0.92 (m, 1H), 1.05 (bs, 13H), 1.16-1.25 (m, 4H), 1.34-1.38 (m, 2H), 1.42 (s, 9H), 1.87 (t, *J*=6.6 Hz, 1H), 2.22-2.25 (m, 2H), 2.48 (t, *J*=10.7 Hz, 1H), 2.93 (bs, 1H), 3.04 (q, *J*=7.3 Hz, 1H), 3.30-3.31 (m, 2H), 3.43-3.49 (m, 1H), 4.01 (d, *J*=10.4 Hz, 1H), 4.07-4.12 (m, 1H), 4.27 (t, *J*=9.5 Hz, 1H), 4.44 (t, *J*=7.0 Hz, 1H), 4.58 (bs, 1H), 5.11 (d, *J*=10.1 Hz, 1H), 5.30 (dd, *J*=16.8, 9.6 Hz, 1H), 5.73-5.78 (m, 1H), 6.69 (d, *J*=8.2 Hz, 1H), 6.86 (s, 1H), 7.25 (t, *J*=7.3 Hz, 1H), 7.35 (t, *J*=7.63 Hz, 2H), 7.82 (d, *J*=8.2 Hz, 2H); LC-MS *m/z* (MH⁺) 715.

Reversed Phase Prep-HPLC conditions for Compound 55 through 155 as indicated:

Waters Xterra Prep MS C18 column, 5 mm (this means 5 micron particle size), 30mm x 100mm

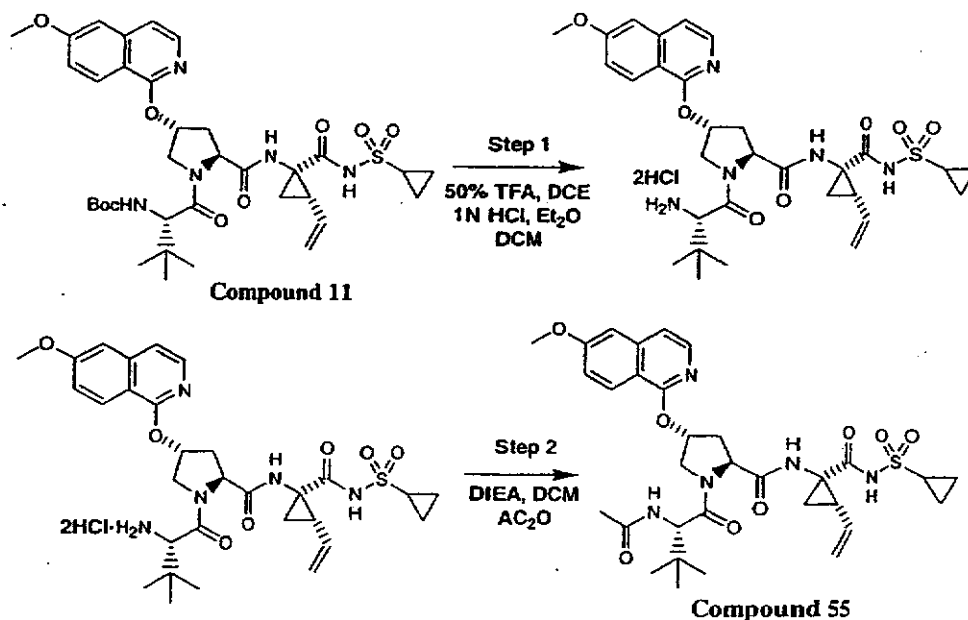
Solvent A: 10% MeOH, 90% H₂O, 10 mM NH₄OAc

Solvent B: 90% MeOH, 10% H₂O, 10 mM NH₄OAc
50mL/min flow rate

Gradient: 0%B to 100%B for 10 min, hold at 100%B for 4 min

Example 55: Preparation of Compound 55

Scheme 1

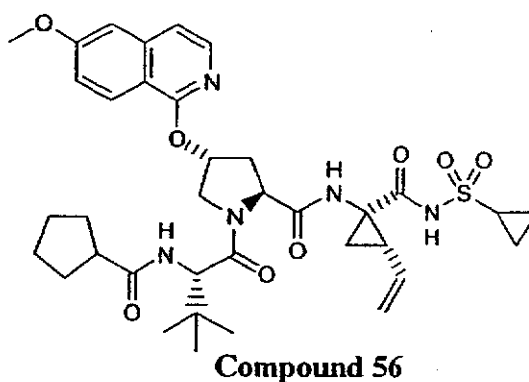


Step 1:

- To a solution of **Compound 11** (1.5 g, 2.10 mmol) in DCE (25 mL) was added TFA (25 mL). After stirring at rt for 15 min, the reaction mixture was concentrated. The resulting red viscous oil was re-dissolved in DCE (50 mL) and re-concentrated. It was then redissolved in DCM (15 mL) and treated with a solution of 1N HCl in Et₂O (25 mL). The resulting suspension was chilled at 0 °C, vacuum filtrated, washed with Et₂O and dried in vacuum oven to give product of step 1 as a white solid (1.4 g, 97% yield): ¹HNMR(CD₃OD, 500 MHz) δ 1.07-11.2 (m, 3 H) 1.14 (t, *J*=4.12 Hz, 1 H) 1.17 (s, 9 H) 1.22 (dd, *J*=10.53, 4.43 Hz, 1 H) 1.21-1.27 (m, 2 H) 1.42 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.91 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.27 (q, *J*=8.85 Hz, 1 H) 2.32-2.38 (m, 1 H) 2.70 (dd, *J*=13.43, 6.71 Hz, 1 H), 2.93-2.98 (m, 1 H) 3.96 (s, 3 H) 4.09 (s, 1 H) 4.14 (dd, *J*=12.21, 3.66 Hz, 1 H) 4.32-4.35 (m, 1 H) 4.69 (dd, *J*=10.53, 6.87 Hz, 1 H) 5.14 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.31 (dd, *J*=17.40, 1.22 Hz, 1 H) 5.70-5.77 (m, 1 H) 5.90 (t, *J*=3.51 Hz, 1 H) 7.24-7.27 (m, 1 H) 7.29 (d, *J*=4.27 Hz, 1 H) 7.39 (t, *J*=4.88 Hz, 1 H) 7.90 (d, *J*=6.10 Hz, 1 H) 8.19 (m, 1 H) 9.22 (s, 1 H).

Step 2:

To a solution mixture of product from step 1 of Example 55 (70.0 mg, 0.108 mmol) and DIEA (41.8 mg, 0.323 mmol) in DCM (2 mL) was added acetic anhydride (33.0 mg, 0.323 mmol). After stirring at rt for 14 h, solvent was removed and product was purified by reversed phase prep-HPLC to give **Compound 55** (39.1 mg, 14% yield): ¹HNMR(CD₃OD, 500 MHz) δ 1.00-1.03 (m, 1 H), 1.06 (s, 9 H), 1.07-1.10 (m, 1 H), 1.21-1.28 (m, 2 H), 1.43 (dd, *J*=9.46, 5.19 Hz, 1 H), 1.88 (dd, *J*=8.55, 5.49 Hz, 1 H), 2.23 (q, *J*=8.85 Hz, 1 H), 2.27-2.32 (m, 1 H), 2.59 (dd, *J*=13.73, 7.02 Hz, 1 H), 2.92-2.97 (m, 1 H), 3.93 (s, 3 H), 4.12 (dd, *J*=11.90, 3.97 Hz, 1 H), 4.35 (d, *J*=11.60 Hz, 1 H), 4.51 (dd, *J*=10.38, 7.02 Hz, 1 H), 4.61 (dd, *J*=5.80, 3.05 Hz, 1 H), 4.80 (d, *J*=4.27 Hz, 1 H), 4.88 (d, *J*=3.96 Hz, 1 H), 5.12 (dd, *J*=10.38, 1.83 Hz, 1 H), 5.29 (dd, *J*=17.24, 1.37 Hz, 1 H), 5.73-5.78 (m, 1 H), 5.84 (t, *J*=3.66 Hz, 1 H), 7.15 (dd, *J*=8.85, 2.44 Hz, 1 H), 7.19 (d, *J*=2.44 Hz, 1 H), 7.25 (d, *J*=6.10 Hz, 1 H), 7.88 (d, *J*=6.10 Hz, 1 H), 8.06 (d, *J*=9.16 Hz, 1 H); LC-MS (retention time: 1.49 min.), MS *m/z* 656 (MH⁺).

Example 56: Preparation of Compound 56

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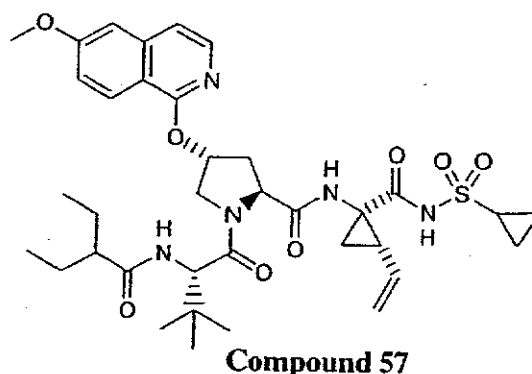
Compound 56 was prepared by the same method as **Compound 55** with the following modifications:

Modifications: Cyclopentanecarbonyl chloride was used as a starting material to give **Compound 56** (18.0 mg, 24% yield): ¹H NMR(CD₃OD, 500 MHz) δ 1.00-1.03 (m,

25

1 H), 1.05 (s, 9 H), 1.06-1.10 (m, 2 H), 1.24-1.27 (m, 2 H), 1.25-1.61 (m, 9 H), 1.80-1.83 (m, 1 H), 1.88 (dd, $J=8.24, 5.49$ Hz, 1 H), 2.22-2.31 (m, 2 H), 2.58-2.65 (m, 2 H), 2.93-2.98 (m, 1 H), 3.92 (s, 3 H), 4.10 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.35 (d, $J=11.91$ Hz, 1 H), 4.52 (dd, $J=10.38, 7.02$ Hz, 1 H), 4.65 (d, $J=9.46$ Hz, 1 H), 4.80 (d, $J=5.49$ Hz, 1 H), 4.88 (d, $J=5.19$ Hz, 1 H), 5.13 (dd, $J=10.37, 1.83$ Hz, 1 H), 5.30 (dd, $J=16.80, 1.22$ Hz, 1 H), 5.73-5.78 (m, 1 H), 5.84 (t, $J=4.27$ Hz, 1 H), 7.11 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.05 (d, $J=9.16$ Hz, 1 H)); LC-MS (retention time: 1.71 min.), MS m/z 710 (MH^+).

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Example 57: Preparation of Compound 57

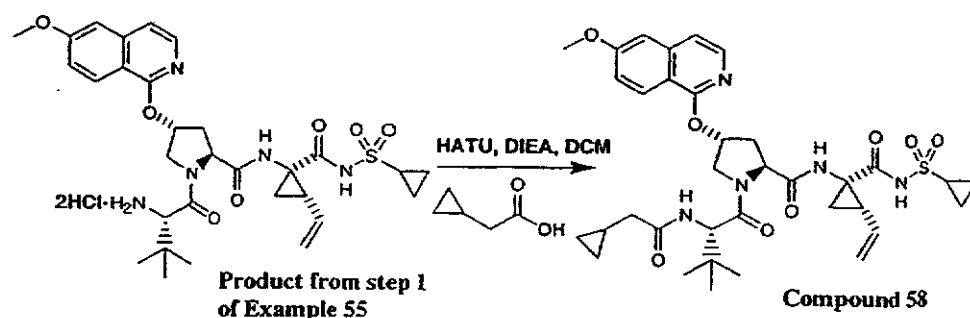
15 **Compound 57** was prepared by the same method as Compound 55 with the following modifications:

Modifications: 2-Ethylbutyryl chloride was used as a starting material to give **Compound 57** (20.7 mg, 27% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.66 (t, $J=7.32$ Hz, 3 H), 0.85 (t, $J=7.32$ Hz, 3 H), 1.02-1.05 (m, 1 H), 1.07 (s, 9 H), 1.10-1.12 (m, 1 H), 1.24-1.33 (m, 4 H), 1.36-1.39 (m, 1 H), 1.43 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.48-1.51 (m, 1 H), 1.88 (dd, $J=8.24, 5.19$ Hz, 1 H), 2.12-2.14 (m, 1 H), 2.22 (q, $J=8.85$ Hz, 1 H), 2.26-2.30 (m, 1 H), 2.59 (dd, $J=13.73, 6.71$ Hz, 1 H), 2.94-2.97 (m, 1 H), 3.92 (s, 3H), 4.11 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.40 (d, $J=11.90$ Hz, 1 H), 4.50 (dd, $J=10.68, 7.02$ Hz, 1 H), 4.75 (d, $J=9.46$ Hz, 1 H), 4.81 (d, $J=9.16$ Hz, 1 H), 4.89 (d, $J=9.16$ Hz, 1 H), 5.12 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.29 (dd, $J=17.09, 1.22$ Hz, 1 H),

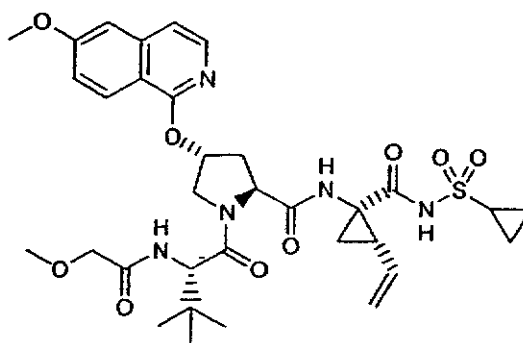
5.72-5.79 (m, 1 H), 5.85 (t, $J=3.66$ Hz, 1 H), 7.08 (dd, $J=9.16$, 2.44 Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1H), 7.98 (d, $J=9.16$ Hz, 1 H), 8.02 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.73 min.), MS m/z 712 (MH^+).

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Example 58: Preparation of Compound 58



To a solution mixture of product from step 1 of example 55 (70.0 mg, 0.108 mmol),
 10 DIEA (41.8 mg, 0.323 mmol) and cyclopropaneacetic acid (16.2 mg, 0.162 mmol) in DCM (2 mL) was added HATU (61.6 mg, 0.162 mmol). After stirring the reaction mixture at rt overnight, it was washed with 5% aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The combined organic layer was washed with 5% aqueous citric acid (2 mL), brine, dried over $MgSO_4$ and
 15 concentrated. Product was purified by reversed phase prep-HPLC to give **Compound 58** (21.9 mg, 29% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.11-0.14 (m, 2 H), 0.43-0.47 (m, 2 H), 0.87-0.09 (m, 1 H), 1.01-1.04 (m, 1 H), 1.07 (s, 9 H), 1.09-1.12 (m, 1 H), 1.23-1.27 (m, 2 H), 1.45 (dd, $J=9.46$, 5.49 Hz, 1 H), 1.88 (dd, $J=8.24$, 5.49 Hz, 1 H), 2.03 (d, $J=7.32$ Hz, 2 H), 2.23 (q, $J=8.75$ Hz, 1 H), 2.27-2.31 (m, 1 H),
 20 2.59 (dd, $J=13.73$, 7.02 Hz, 1 H), 2.92-2.96 (m, 1 H), 3.93 (m, 3 H), 4.13 (dd, $J=11.90$, 3.97 Hz, 1 H), 4.34 (d, $J=11.90$ Hz, 1 H), 4.53 (dd, $J=10.38$, 7.02 Hz, 1 H), 4.66 (d, $J=9.46$ Hz, 1 H), 4.81 (d, $J=6.10$ Hz, 1 H), 4.89 (d, $J=6.10$ Hz, 1 H), 5.12 (dd, $J=10.37$, 1.52 Hz, 1 H), 5.30 (dd, $J=17.09$, 1.22 Hz, 1 H), 5.75-5.81 (m, 1 H), 5.86 (s, 1 H), 7.12 (dd, $J=9.16$, 2.44 Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.81 (d, $J=9.46$ Hz, 1H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.06 (d, $J=9.16$ Hz, 1 H); LC-MS
 25 (retention time: 1.63 min.), MS m/z 696 (MH^+).

Example 59: Preparation of Compound 59**Compound 59**

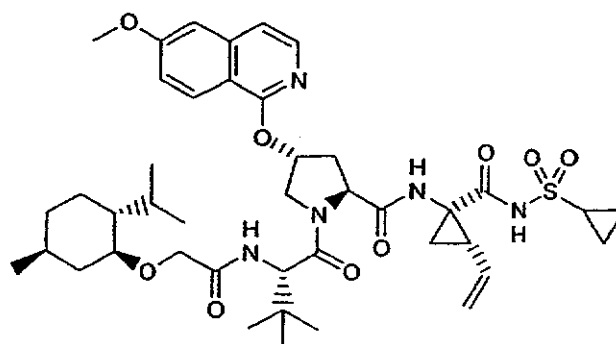
- 5 **Compound 59** was prepared by the same method as Compound 58 with the following modifications:

Modifications: Methoxyacetic acid was used as a starting material to give

- Compound 59** (23.5 mg, 32% yield): ¹HNMR(CD₃OD, 500 MHz) δ 10.99-1.04 (m, 2 H), 1.06 (s, 9 H), 1.09-1.12 (m, 1 H), 1.22-1.27 (m, 2 H), 1.45 (dd, *J*=9.46, 5.49 Hz, 1 H), 1.88 (dd, *J*=8.24, 5.49 Hz, 1 H), 2.22 (q, *J*=8.85 Hz, 1 H), 2.29-2.32 (m, 1 H), 2.60 (dd, *J*=13.89, 6.87 Hz, 1 H), 2.92-2.97 (m, 1 H), 3.35 (s, 3 H), 3.70 (d, *J*=15.26 Hz, 1 H), 3.84 (d, *J*=15.26 Hz, 1 H), 3.93 (s, 3 H), 4.13 (dd, *J*=11.90, 3.97 Hz, 1 H), 4.32 (d, *J*=11.60 Hz, 1 H), 4.54 (dd, *J*=10.38, 7.02 Hz, 1 H), 4.65 (s, 1 H), 4.81 (d, *J*=7.32 Hz, 1 H), 4.89 (d, *J*=7.32 Hz, 1 H), 5.12 (d, *J*=10.38 Hz, 1 H), 5.30 (d, *J*=16.79 Hz, 1 H), 5.74-5.81 (m, 1 H), 5.86 (t, *J*=3.36 Hz, 1 H), 7.14 (dd, *J*=9.00, 2.59 Hz, 1 H), 7.19 (d, *J*=2.44 Hz, 1 H), 7.26 (d, *J*=6.10 Hz, 1 H), 7.89 (d, *J*=6.10 Hz, 1 H), 8.04 (d, *J*=9.16 Hz, 1 H); LC-MS (retention time: 1.54 min.), MS *m/z* 686 (MH⁺).

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Example 60: Preparation of Compound 60

**Compound 60**

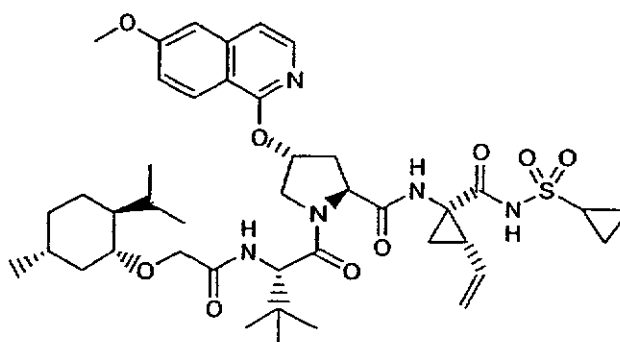
Compound 60 was prepared by the same method as **Compound 58** with the following modifications:

5

Modifications: (+)-Methoxyacetic acid was used as a starting material to give **Compound 60** (23.8 mg, 27% yield): ^1H NMR (CD_3OD , 500 MHz) δ 0.78 (d, $J=7.02$ Hz, 3 H), 0.83-0.88 (m, 2 H), 0.92 (t, $J=7.17$ Hz, 6 H), 0.94-0.98 (m, 1 H), 1.00-1.03 (m, 2 H), 1.06 (s, 9 H), 1.07-1.11 (m, 1 H), 1.22-1.26 (m, 2 H), 1.31-1.36 (m, 2 H), 1.45 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.63-1.68 (m, 2 H), 1.89 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.01-2.04 (m, 1 H), 2.17-2.21 (m, 1 H), 2.24 (q, $J=9.00$ Hz, 2 H), 2.28-2.33 (m, 1 H), 2.60 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.93-2.98 (m, 1 H), 3.15-3.20 (m, 1 H), 3.77 (d, $J=15.26$ Hz, 1 H), 3.87 (d, $J=15.26$ Hz, 1 H), 3.93 (s, 3 H), 4.12 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.32 (d, $J=11.90$ Hz, 1 H), 4.56 (dd, $J=10.38, 7.02$ Hz, 1 H), 4.65 (d, $J=9.77$ Hz, 1 H), 4.81 (d, $J=5.80$ Hz, 1 H), 4.89 (d, $J=5.80$ Hz, 1 H), 5.13 (dd, $J=10.22, 1.68$ Hz, 1 H), 5.30 (dd, $J=17.09, 1.53$ Hz, 1 H), 5.75-5.79 (m, 1 H), 5.85 (t, $J=3.66$ Hz, 1 H), 7.14 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.26 (d, $J=5.80$ Hz, 1 H), 7.52 (d, $J=9.77$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.03 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 2.043 min.), MS m/z 810 (MH^+).

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Example 61: Preparation of Compound 61

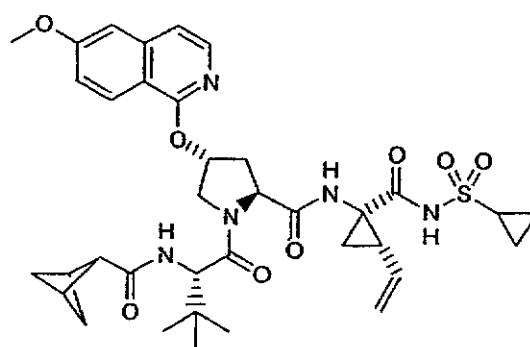
**Compound 61**

Compound 61 was prepared by the same method as Compound 58 with the following modifications:

- 5 Modifications: (-)-Methoxyacetic acid was used as a starting material to give
Compound 61 (26.4mg, 30% yield): ¹HNMR(CD₃OD, 500 MHz) δ 0.78 (d, $J=7.02$ Hz, 3 H), 0.82-0.84 (m, 1 H), 0.88 (dd, $J=8.39, 3.81$ Hz, 1 H), 0.91 (d, $J=7.01$ Hz, 3 H), 0.92 (d, $J=6.41$ Hz, 3 H), 0.94-0.99 (m, 2 H), 1.00-1.03 (m, 2 H), 1.06 (s, 9 H), 1.08-1.10 (m, 1 H), 1.23-1.26 (m, 2 H), 1.30-1.37 (m, 2 H), 1.44 (dd, $J=9.61, 5.34$ Hz, 1 H), 1.62-1.68 (m, 2 H), 1.89 (dd, $J=8.24, 5.49$ Hz, 1 H), 1.98-2.02 (m, 1 H),
 10 2.13-2.16 (m, 1 H), 2.24 (q, $J=8.85$ Hz, 1 H), 2.28-2.32 (m, 1 H), 2.60 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.94-2.98 (m, 1 H), 3.08-3.13 (m, 1 H), 3.63 (d, $J=15.56$ Hz, 1 H), 3.93 (s, 3H), 4.11 (dd, $J=12.05, 3.81$ Hz, 1 H), 4.32 (d, $J=11.90$ Hz, 1 H), 4.56 (dd, $J=10.38, 7.02$ Hz, 1 H), 4.62 (d, $J=9.46$ Hz, 1 H), 4.81 (d, $J=6.41$ Hz, 1 H), 4.89 (d,
 15 $J=6.72$ Hz, 1 H), 5.13 (dd, $J=10.38, 1.83$ Hz, 1 H), 5.30 (dd, $J=17.09, 1.23$ Hz, 1 H), 5.76-5.80 (m, 1 H), 5.85 (t, $J=3.51$ Hz, 1 H), 7.14 (dd, $J=9.00, 2.59$ Hz, 1 H), 7.20 (d, $J=2.44$ Hz, 1 H), 7.26 (d, $J=5.80$ Hz, 1 H), 7.52 (d, $J=9.77$ Hz, 1 H), 7.89 (d, $J=6.10$ Hz, 1 H), 8.04 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 2.05 min.), MS m/z 810 (MH⁺).

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Example 62: Preparation of Compound 62

**Compound 62**

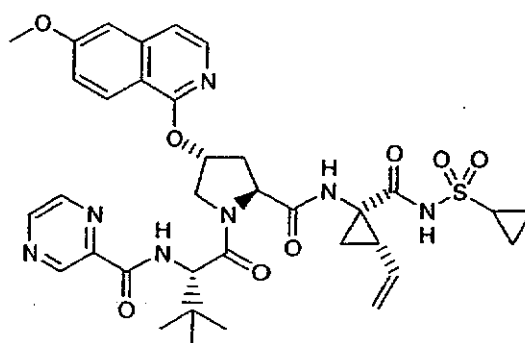
Compound 62 was prepared by the same method as **Compound 58** with the following modifications:

5

Modifications: Bicyclo[1.1.1]pentane-2-carboxylic acid was used as a starting material to give **Compound 62** (35.1, 45% yield): $^1\text{H NMR}$ (CD_3OD , 500 MHz) δ 1.03 (d, $J=5.49$ Hz, 1 H), 1.06 (s, 9 H), 1.08-1.11 (m, 3 H), 1.23-1.29 (m, 3 H), 1.37 (dd, $J=7.02, 3.36$ Hz, 13 H), 1.46 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.65 (dd, $J=9.77, 2.14$ Hz, 1 H), 1.69 (d, $J=2.14$ Hz, 1 H), 1.72 (dd, $J=7.32, 3.05$ Hz, 1 H), 1.88 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.12 (dd, $J=9.11, 3.05$ Hz, 1 H), 2.23 (d, $J=8.85$ Hz, 1 H), 2.21-2.51 (m, 1 H), 2.60 (t, $J=6.87$ Hz, 1 H), 2.63 (d, $J=1.83$ Hz, 2 H), 2.68 (d, $J=7.63$ Hz, 1 H), 2.93-2.96 (m, 1 H), 3.23 (q, $J=7.43$ Hz, 2 H), 3.70-3.75 (m, 2 H), 3.93 (s, 3 H), 4.11 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.35 (d, $J=11.90$ Hz, 1 H), 4.53 (dd, $J=10.53, 6.87$ Hz, 1 H), 4.71 (d, $J=9.46$ Hz, 1 H), 4.79 (d, $J=5.80$ Hz, 2 H), 4.87 (d, $J=5.49$ Hz, 2 H), 5.13 (dd, $J=10.38, 1.83$ Hz, 1 H), 5.30 (dd, $J=17.24, 1.37$ Hz, 1 H), 5.74-5.79 (m, 1 H), 5.86 (t, $J=3.20$ Hz, 1 H), 7.12 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.72 (d, $J=9.46$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.05 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.16 min.), MS m/z 708 (MH^+).

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Example 63: Preparation of Compound 63

**Compound 63**

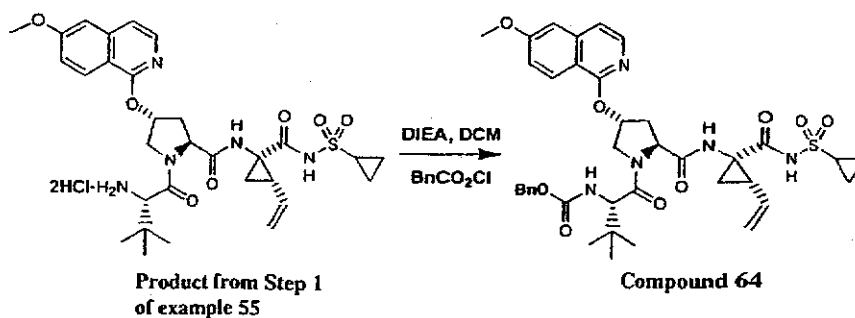
Compound 63 was prepared by the same method as **Compound 58** with the following modifications:

5

Modifications: pyrazine-2-carboxylic acid was used as a starting material to give **Compound 63** (42.3, 54% yield): ¹HNMR (CD₃OD, 500 MHz) δ 1.00-1.04 (m, 3 H), 1.05-1.09 (m, 1 H), 1.10 (s, 9 H), 1.15 (s, 1 H), 1.18-1.22 (m, 2 H), 1.43 (dd, *J*=9.46, 5.49 Hz, 1 H), 1.88 (dd, *J*=7.93, 5.49 Hz, 1 H), 2.17 (q, *J*=8.65 Hz, 1 H), 2.37-2.42 (m, 1 H), 2.64 (dd, *J*=13.73, 7.32 Hz, 1 H), 2.91-2.95 (m, 1 H), 3.88 (s, 3 H), 3.93 (d, *J*=3.35 Hz, 1 H), 4.13 (dd, *J*=11.90, 3.36 Hz, 1 H), 4.46 (d, *J*=11.90 Hz, 1 H), 4.61 (dd, *J*=10.07, 7.32 Hz, 1 H), 4.76 (s, 1 H), 4.80 (d, *J*=7.63 Hz, 1 H), 4.88 (d, *J*=7.93 Hz, 1 H), 5.09 (d, *J*=10.38 Hz, 1 H), 5.27 (d, *J*=17.09 Hz, 1 H), 5.77-5.83 (m, 1 H), 5.85 (s, 1 H), 6.85 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.08 (d, *J*=2.14 Hz, 1 H), 7.23 (d, *J*=5.80 Hz, 1 H), 7.87 (d, *J*=8.85 Hz, 1 H), 7.90 (d, *J*=6.10 Hz, 1 H), 8.57 (d, *J*=1.53 Hz, 1 H), 8.73 (d, *J*=2.44 Hz, 1 H), 8.81 (s, 1 H).

10

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Example 64: Preparation of Compound 64

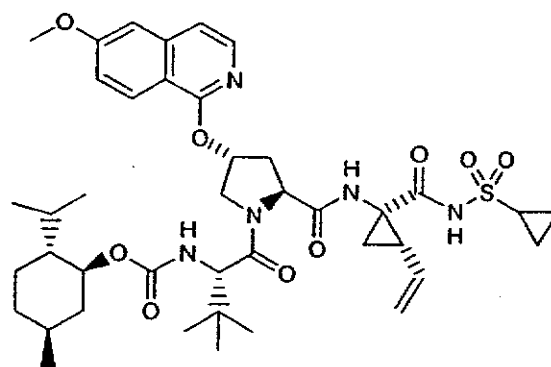
To a solution mixture of product from step 1 of **example 55** (70.0 mg, 0.108 mmol) and DIEA (41.8 mg, 0.323 mmol) in DCM (2 mL) was added benzyl chloroformate (55.1 mg, 0.323 mmol). After stirring at rt for 14 h, solvent was removed and

5 product was purified by reversed phase prep-HPLC to give **Compound 64** (26.9 mg, 31% yield): ¹HNMR (CD₃OD, 500 MHz) δ 1.00 (d, $J=2.14$ Hz, 1 H), 1.02 (d, $J=5.80$ Hz, 1 H), 1.04 (s, 9 H), 1.08-1.14 (m, 1 H), 1.16 (d, $J=6.71$ Hz, 1 H), 1.18-1.22 (m, 2 H), 1.43 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.87 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.17-2.22 (m, 1 H), 2.30-2.35 (m, 1 H), 2.62 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.90-2.95 (m, 1 H), 3.88 (s,

10 3 H), 4.08 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.31 (s, 1 H), 4.43 (d, $J=11.60$ Hz, 1 H), 4.55 (dd, $J=10.07, 7.32$ Hz, 1 H), 4.74 (d, $J=12.21$ Hz, 1 H), 4.81 (d, $J=6.10$ Hz, 1 H), 4.89 (d, $J=5.79$ Hz, 1 H), 5.10 (d, $J=9.16$ Hz, 1 H), 5.16 (s, 1 H), 5.28 (d, $J=17.09$ Hz, 1 H), 5.75-5.81 (m, 1 H), 5.83 (s, 1 H), 7.07 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.17 (d, $J=2.44$ Hz, 1 H), 7.20 (d, $J=7.32$ Hz, 2 H), 7.25 (t, $J=5.65$ Hz, 3 H), 7.30-7.33 (m, 1

15 H), 7.34-7.37 (m, 2 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.07 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.79 min.), MS m/z 748 (MH⁺).

Example 65: Preparation of Compound 65



Compound 65

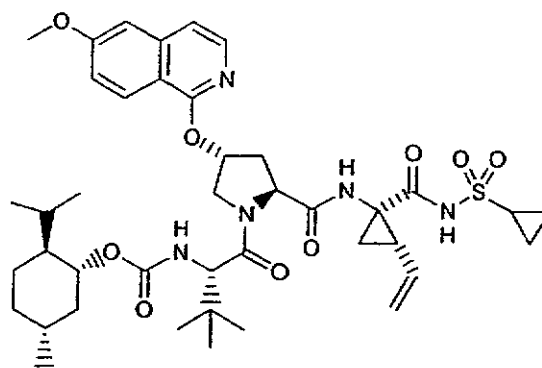
20

Compound 65 was prepared by the same method as **Compound 64** with the following modifications:

Modifications: (+)-Methyl chloroformate was used as a starting material to give **Compound 65** (28.8 mg, 36% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.72 (d, $J=6.71$ Hz, 3 H), 0.80 (t, $J=5.80$ Hz, 6H), 0.87 (d, $J=7.02$ Hz, 4 H), 0.90-0.95 (m, 6 H), 0.98-1.02 (m, 5 H), 1.05 (s, 9 H), 1.07-1.12 (m, 2 H), 1.18-1.23 (m, 2 H), 1.32-1.38 (m, 3 H), 1.41 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.46-1.48 (m, 1 H), 1.63-1.71 (m, 5 H), 1.85 (dd, $J=7.93$, 5.49 Hz, 1 H), 1.89-1.93 (m, 1 H), 2.00-2.03 (m, 1 H), 2.15 (q, $J=8.70$ Hz, 1 H), 2.34-2.38 (m, 1 H), 2.61 (dd, $J=13.73$, 7.33 Hz, 1 H), 2.89-2.93 (m, 1 H), 3.73 (s, 2 H), 3.92 (s, 3 H), 4.10 (dd, $J=11.60$, 3.36 Hz, 1 H), 4.33 (s, 1 H), 4.41 (d, $J=11.29$ Hz, 1 H), 4.46-4.52 (m, 1 H), 4.54 (dd, $J=9.76$, 7.90 Hz, 1 H), 4.81 (d, $J=5.80$ Hz, 1 H), 4.89 (m, 1 H), 5.08 (d, $J=11.60$ Hz, 1 H), 5.26 (d, $J=17.09$ Hz, 1 H), 5.77-5.81 (m, 1 H), 5.83 (d, $J=3.97$ Hz, 1 H), 7.11 (dd, $J=11.29$, 1.83 Hz, 1 H), 7.18 (d, $J=1.83$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.08 (d, $J=8.85$ Hz, 1 H); LC-MS (retention time: 2.06 min.), MS m/z 796 (MH^+).

15

Example 66: Preparation of Compound 66



Compound 66

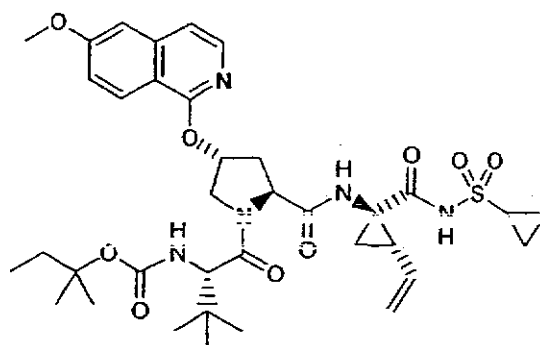
20 **Compound 66** was prepared by the same method as **Compound 64** with the following modifications:

Modifications: (-)-Methyl chloroformate was used as a starting material to give **Compound 66** (26.9 mg, 31% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.35 (d, $J=6.41$ Hz, 1 H), 0.51 (d, $J=6.71$ Hz, 2 H), 0.68 (d, $J=6.71$ Hz, 1 H), 0.73 (d, $J=7.02$

25

Hz, 2 H), 0.77-0.82 (m, 4 H), 0.88-0.98 (m, 10 H), 1.0-1.03 (m, 2H), 1.05 (s, 9 H),
 1.09-1.18 (m, 3 H), 1.25-1.29 (m, 1 H), 1.3-1.41 (m, 3 H), 1.60-1.71 (m, 3 H), 1.82-
 1.89 (m, 3 H), 2.00-2.04 (m, $J=2.14$ Hz, 1 H), 2.10 (q, $J=8.24$ Hz, 1 H), 2.39-2.43
 5 (m, 1 H), 2.61 (dd, $J=14.04, 7.32$ Hz, 1 H), 2.87-2.91 (m, 1 H), 3.73 (s, 1 H), 3.92 (s,
 3 H), 4.13 (dd, $J=11.75, 3.51$ Hz, 1 H), 4.22-4.27 (m, 2 H), 4.30 (s, 1 H), 4.39 (d,
 $J=11.90$ Hz, 1 H), 4.48-4.55 (m, 1 H), 4.79 (d, $J=5.19$ Hz, 1 H), 4.87 (d, $J=4.27$ Hz, 1
 H), 5.05 (d, $J=10.07$ Hz, 1 H), 5.22 (d, $J=16.79$ Hz, 1 H), 5.78-5.85 (m, 2 H), 7.09
 (dd, $J=9.16, 1.83$ Hz, 1 H), 7.17 (d, $J=1.83$ Hz, 1 H), 7.23 (d, $J=5.80$ Hz, 1 H), 7.88
 (d, $J=5.80$ Hz, 1 H) 8.09 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 2.05 min.), MS
 10 m/z 796 (MH^+).

Example 67: Preparation of Compound 67



Compound 67

15

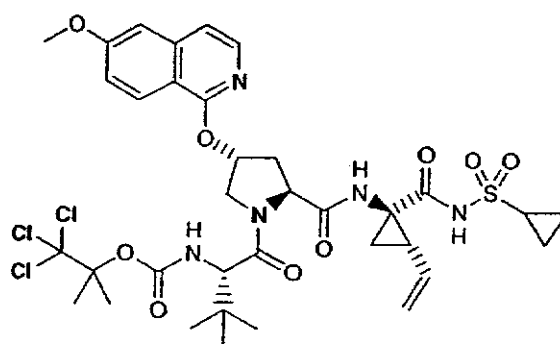
Compound 67 was prepared by the same method as Compound 64 with the following modifications:

Modifications: Di-tert-amyl dicarbonate was used as a starting material to give
 20 Compound 67 (35.3 mg, 41% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.78 (t, $J=7.17$
 Hz, 3 H), 0.89-0.95 (m, 6 H), 1.04 (s, 9 H), 1.005-1.09 (m, 3 H), 1.15 (s, 1 H), 1.22
 (d, $J=12.51$ Hz, 6 H), 1.40 (s, 2 H), 1.42-1.46 (m, 1 H), 1.48 (s, 3 H), 1.56-1.66 (m, 2
 H), 1.78 (q, $J=7.63$ Hz, 1 H), 1.84 (q, $J=7.53$ Hz, 1 H), 1.88 (d, $J=5.80$ Hz, 1 H), 2.22
 (d, $J=8.55$ Hz, 1 H), 2.27-2.31 (m, 1 H), 2.61 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.91-2.96
 25 (m, 1 H), 3.92 (s, 3 H), 4.08 (d, $J=12.21$ Hz, 1 H), 4.26 (d, $J=9.16$ Hz, 1 H), 4.42 (d,

$J=11.29$ Hz, 1 H), 4.52 (t, $J=7.93$ Hz, 1 H), 5.12 (d, $J=10.07$ Hz, 1 H), 5.29 (d, $J=17.09$ Hz, 1 H), 5.73-5.80 (m, 1 H), 5.84 (s, 1 H), 6.57 (d, $J=8.85$ Hz, 1 H), 7.09 (d, $J=8.54$ Hz, 1 H), 7.18 (s, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.08 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.82 min.), MS m/z 728 (MH^+).

5

Example 68: Preparation of Compound 68

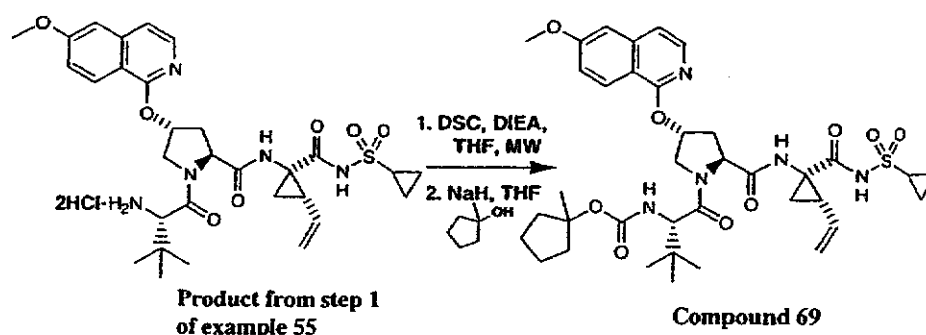


Compound 68

10 **Compound 68** was prepared by the same method as **Compound 64** with the following modifications:

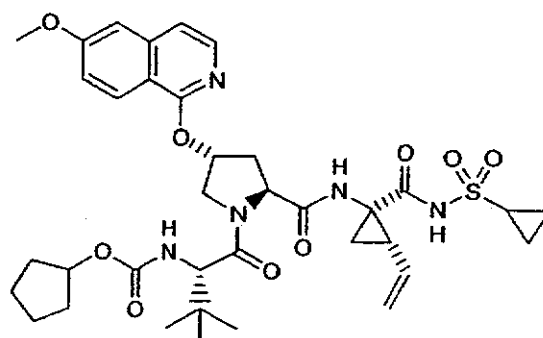
Modifications: 2,2,2-Trichloro-1,1-dimethyl chloroformate was used as a starting material to give **Compound 68** (30.5mg, 37% yield): ^1H NMR (CD_3OD , 500 MHz)
 15 δ 0.99 (s, 9 H), 1.04 (s, 6 H), 1.08-1.09 (m, 3H), 1.23-1.26 (m, 3 H), 1.44 (s, 2 H), 1.46 (d, $J=5.80$ Hz, 1 H), 1.71 (s, 2 H), 2.23-2.33 (m, 2 H), 2.60-2.64 (m, 1 H), 2.93-2.96 (m, 1 H), 3.70 (m, 1 H), 3.71 (s, 3 H), 3.93 (s, 3 H), 4.04-4.06 (m, 2 H), 4.27 (d, $J=9.16$ Hz, 1 H), 4.41 (d, $J=11.60$ Hz, 1 H), 4.57 (d, $J=10.98$, 6.11 Hz, 1 H), 5.14 (d, $J=12.21$ Hz, 1 H), 5.32 (d, $J=17.70$ Hz, 1 H), 5.75-5.80 (m, 1 H), 5.84 (s, 1 H), 7.10
 20 (dd, $J=9.16$, 2.44 Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.26 (d, $J=6.10$ Hz, 1 H), 7.90 (d, $J=5.80$ Hz, 1 H), 8.07 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.95 min.), MS m/z 816 (MH^+).

Example 69: Preparation of Compound 69



To a solution mixture of product from step 1 of example 55 (102 mg, 0.149 mmol) and DIEA (48.2, 0.373 mmol) in THF (2 mL) was added N,N'-dissuccinimidyl carbonate (57.1 mg, 0.223 mmol). The resulting suspension was irradiated in a microwave to 80 °C for 15 min. Then was added a slurry solution of sodium 1-methyl cyclopentoxide which was prepared by treating a 0 °C solution of 1-methyl cyclopentanol (149.2 mg, 1.49 mmol) in THF (1 mL) with NaH (60% in oil, 59.6 mg, 1.49 mmol) for 15 min at rt. After stirring at rt 15 min, the reaction was quenched with saturated aqueous ammonium chloride (3 mL) and extracted with EtOAc (10 mL). The organic layer was then passed through a celite hydromatrix column, concentrated and purified by reversed phase prep-HPLC to give Compound 69 (49.0 mg, 44%): ¹H NMR(CD₃OD, 500 MHz) δ 0.95-0.98 (m, 3 H), 0.99-1.01 (m, J=12.51 Hz, 1 H), 1.03 (s, 9 H), 1.14-1.18 (m, 2 H), 1.30 (s, 3 H), 1.40-1.47 (m, 3 H), 1.50-1.56 (m, 3 H), 1.60-1.64 (m, 1 H), 1.76-1.81 (m, 1 H), 1.83-1.85 (m, 1 H), 2.10-2.19 (m, 1 H), 2.36-2.43 (m, 1 H), 2.63 (dd, J=14.50, 7.17 Hz, 1 H), 2.86-2.90 (m, 1 H), 3.92 (s, 3 H), 4.09 (d, J=12.51 Hz, 1 H), 4.25 (d, J=1.53 Hz, 1 H), 4.43 (d, J=10.99 Hz, 1 H), 4.51-4.55 (m, 1 H), 5.06 (d, J=11.60 Hz, 1 H), 5.23 (d, J=16.78 Hz, 1 H), 5.80-5.85 (m, J=12.67, 12.67 Hz, 2 H), 7.09 (d, J=8.55 Hz, 1 H), 7.17 (s, 1 H), 7.24 (d, J=5.49 Hz, 1 H), 8.07 (d, J=9.16 Hz, 1 H); LC-MS (retention time: 1.87 min.), MS m/z 740 (MH⁺).

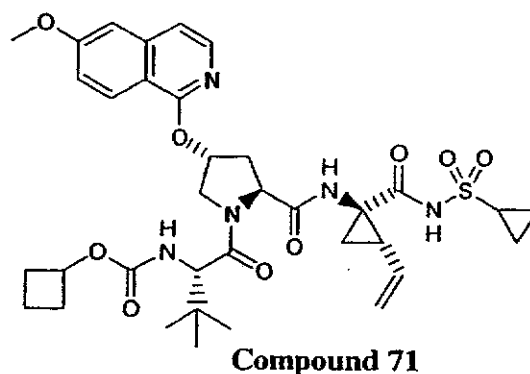
Example 70: Preparation of Compound 70

**Compound 70**

Compound 70 was prepared by the same method as **Compound 69** with the following modifications:

5

Modifications: Cyclopentanol was used as a starting material to give **Compound 70** (85.1 mg, 40% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz})$ δ 0.98 (s, 1 H), 1.00 (d, $J=4.88$ Hz, 1 H), 1.03 (s, 9 H), 1.06-1.10 (m, 2 H), 1.24-1.29 (m, 3 H), 1.36-1.40 (m, 2 H), 1.44 (dd, $J=9.31, 5.04$ Hz, 2 H), 1.57-1.62 (m, 5 H), 1.69-1.73 (m, 2 H), 1.88 (dd, $J=8.09, 5.65$ Hz, 1 H), 2.22-2.29 (m, 2 H), 2.59-2.62 (m, 1 H), 2.92-2.96 (m, 1 H), 3.93 (s, 3 H), 4.07 (dd, $J=10.99, 2.44$ Hz, 1 H), 4.29 (s, 1 H), 4.42 (dd, $J=12.51, 1.53$ Hz, 1 H), 4.55 (dd, $J=9.77, 7.93$ Hz, 1 H), 4.68-4.71 (m, 1 H), 4.81 (d, $J=8.55$ Hz, 1 H), 4.89 (d, $J=9.46$ Hz, 1 H), 5.13 (d, $J=10.68$ Hz, 1 H), 5.30 (d, $J=16.48$ Hz, 1 H), 5.73-5.78 (m, 1 H), 5.84 (s, 1 H), 7.12 (dd, $J=9.15, 1.83$ Hz, 1 H), 7.20 (d, $J=2.14$ Hz, 1 H), 7.27 (d, $J=5.80$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.09 (d, $J=8.85$ Hz, 1 H); LC-MS (retention time: 1.81 min.), MS m/z 726 (MH^+).

Example 71: Preparation of Compound 71

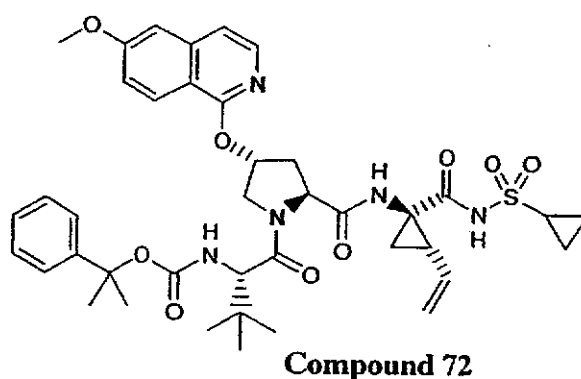
5

Compound 71 was prepared by the same method as **Compound 69** with the following modifications:

Modifications: Cyclobutanol was used as a starting material to give **Compound 71**
 10 (16.2 mg, 39% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.97 (s, 3 H), 1.03 (s, 9 H), 1.06-1.08 (m, 2 H), 1.17-1.22 (m, 3 H), 1.37-1.44 (m, 1 H), 1.82-1.85 (m, 1 H), 2.02-2.08 (m, 1 H), 2.15-2.21 (m, 1 H), 2.30-2.36 (m, 1 H), 2.49-2.54 (m, 0.4 H), 2.59-2.67 (m, 0.6 H), 2.90-2.94 (m, 1 H), 3.93 (s, 3H), 4.09 (dd, $J=8.09$, 4.73 Hz, 1 H), 4.20 (d, $J=10.68$ Hz, 0.4 H), 4.38 (d, $J=10.68$ Hz, 0.6 H), 4.46 (dd, $J=10.22$, 7.17 Hz, 0.4 H), 4.48-4.56 (m, 1 H), 5.07-5.11 (m, 1 H), 5.26 (d, $J=17.24$ Hz, 0.4 H), 5.28 (d, $J=17.24$ Hz, 0.6 H), 5.71-5.79 (m, 1 H), 5.84 (s, 1H), 7.07 (dd, $J=8.39$, 2.90 Hz, 1 H), 7.14 (d, $J=2.14$ Hz, 1 H), 7.20 (d, $J=2.44$ Hz, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.59 (d, $J=5.80$ Hz, 1 H), 7.88 (m, 1 H), 8.00 (d, $J=9.16$ Hz, 0.4 H), 8.07 (d, $J=8.85$ Hz, 0.6 H); LC-MS (retention time: 1.25 min.), MS m/z 712 (MH^+).

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Example 72: Preparation of Compound 72



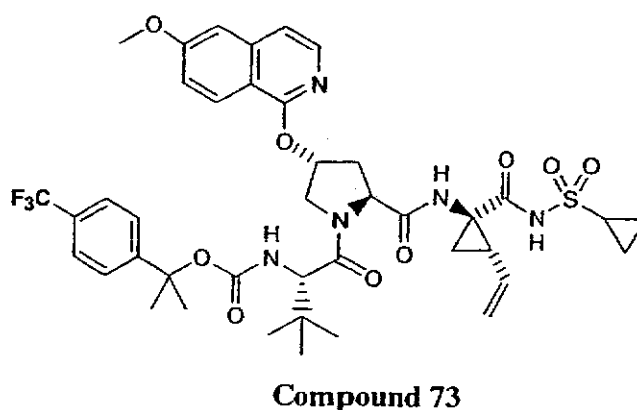
Compound 72 was prepared by the same method as **Compound 69** with the following modifications:

5

Modifications: 2-Phenyl-2-propanol was used as a starting material to give **Compound 72** (19.0 mg, 42% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz}) \delta$ 0.97 (m, 1 H), 1.03 (s, 9 H), 1.06-1.09 (m, 3 H), 1.16-1.22 (m, 4 H), 1.41-1.44 (m, 1 H), 1.57 (s, 3 H), 1.86 (t, $J=7.80 \text{ Hz}$, 1H), 2.14-2.18 (m, 1 H), 2.30-2.35 (m, 1 H), 2.57-2.61 (m, 1 H), 2.90-2.94 (m, 1 H), 3.92 (d, $J=4.27 \text{ Hz}$, 1 H), 3.94 (s, 3 H), 4.04 (dd, $J=10.99$, 3.66 Hz, 1 H), 4.18 (s, 1 H), 4.24 (d, $J=10.99 \text{ Hz}$, 1 H), 4.52 (s, 1 H), 5.09 (d, $J=10.07 \text{ Hz}$, 1 H), 5.26 (d, $J=14.95 \text{ Hz}$, 1 H), 5.78-5.82 (m, 2 H), 7.07-7.12 (m, 2 H), 7.16-7.20 (m, 3 H), 7.23 (d, $J=5.19 \text{ Hz}$, 1 H), 7.29 (d, $J=7.02 \text{ Hz}$, 2 H), 7.84 (d, $J=5.80 \text{ Hz}$, 1 H), 8.03 (d, $J=9.46 \text{ Hz}$, 1 H); LC-MS (retention time: 1.84 min.), MS m/z 776 (MH^+).

15

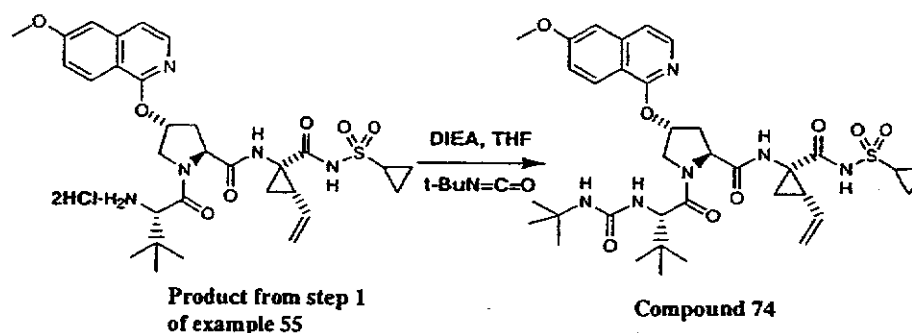
Example 73: Preparation of Compound 73



Compound 73 was prepared by the same method as **Compound 69** with the following modifications:

- 5 Modifications: 4-(Trifluoromethyl)phenyl dimethyl carbinol was used as a starting material to give **Compound 73** (22.1 mg, 45% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz})$ δ 0.91 (s, 1 H), 0.97-1.00 (m, $J=15.56 \text{ Hz}$, 4 H), 1.04 (s, 9 H), 1.07-1.10 (m, 2 H), 1.16-1.20 (m, 3 H), 1.30-1.31 (m, 1 H), 1.41 (dd, $J=9.61, 5.34 \text{ Hz}$, 1 H), 1.55 (d, $J=7.32 \text{ Hz}$, 6 H), 1.83-1.87 (m, 1 H), 2.11-2.14 (m, 1 H), 2.34-2.39 (m, 1 H), 2.57-
10 2.62 (m, 1 H), 2.89-2.92 (m, $J=11.60, 4.27 \text{ Hz}$, 1 H), 3.92 (s, 2 H), 3.94 (s, 3 H), 4.02-4.05 (m, 1 H), 4.17 (s, 1 H), 4.26 (d, $J=11.90 \text{ Hz}$, 1 H), 4.53 (t, $J=8.85 \text{ Hz}$, 1 H), 5.07 (d, $J=10.07 \text{ Hz}$, 1 H), 5.24 (d, $J=18.01 \text{ Hz}$, 1 H), 5.78-5.83 (m, 2 H), 7.08 (d, $J=7.02 \text{ Hz}$, 1 H), 7.19 (s, 1 H), 7.22 (d, $J=5.80 \text{ Hz}$, 1 H), 7.45 (dd, $J=13.74, 7.63 \text{ Hz}$, 3 H), 7.60 (d, $J=6.41 \text{ Hz}$, 1 H), 7.67 (d, $J=7.63 \text{ Hz}$, 1 H), 7.84 (d, $J=5.80 \text{ Hz}$, 1 H),
15 8.02 (d, $J=8.54 \text{ Hz}$, 1 H); LC-MS (retention time: 1.92 min.), MS m/z 844 (MH^+).

Example 74: Preparation of Compound 74

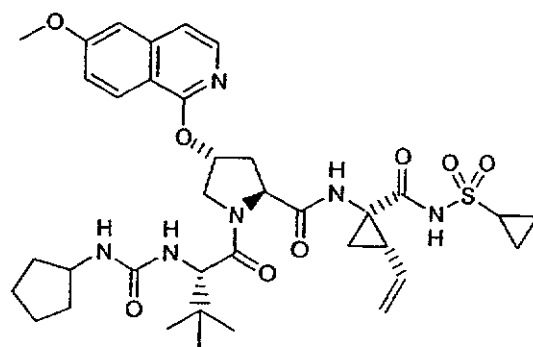


20

- To a solution mixture of the product from step 1 of **example 55** (70.0 mg, 0.108 mmol) and DIEA (41.8 mg, 0.323 mmol) in DCM (2 mL) was added *t*-butylisocyanate (32.0, 0.323 mmol). After stirring at rt overnight, the reaction was concentrated and purified by reversed-phase prep-HPLC to give **Compound 74** (42.3
25 mg, 55% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz})$ δ 0.96-1.00 (m, 1 H) 1.04 (s, 9 H) 1.08-1.10 (m, 3 H) 1.19 (s, 9 H) 1.22-1.31 (m, 2 H) 1.30 (m, 1 H) 1.41 (dd, $J=9.46$,

5.49 Hz, 1 H) 1.87 (dd, $J=8.24$, 5.49 Hz, 1 H) 2.20-2.29 (m, 2 H) 2.61 (dd, $J=14.04$, 6.72 Hz, 1 H) 2.92-2.97 (m, 1 H) 3.92 (s, 3 H) 4.08 (dd, $J=11.60$, 3.97 Hz, 1 H) 4.36 (s, 1 H) 4.47-4.52 (m, 2 H) 4.81 (d, $J=3.36$ Hz, 1 H) 4.88 (d, $J=8.85$ Hz, 1 H) 5.11 (dd, $J=10.22$, 1.68 Hz, 1 H) 5.28 (dd, $J=17.09$, 1.53 Hz, 1 H) 5.72-5.76 (m, 1 H) 5.85 (s, 1 H) 7.08 (dd, $J=9.16$, 2.44 Hz, 1 H) 7.18 (d, $J=2.14$ Hz, 1 H) 7.24 (d, $J=5.80$ Hz, 1 H) 7.88 (d, $J=6.10$ Hz, 1 H) 8.12 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.70 min.), MS m/z 713 (MH^+).

Example 75: Preparation of Compound 75



Compound 75

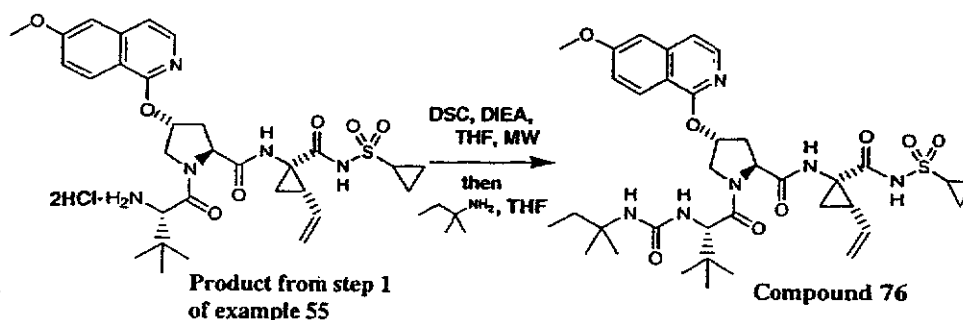
Compound 75 was prepared by the same method as Compound 74 with the following modifications:

15 Modifications: Cyclopentyl isocyanate was used as a starting material to give Compound 75 (38.5 mg, 49%): ^1H NMR(CD_3OD , 500 MHz) δ 0.92 (d, $J=7.63$ Hz, 1 H) 0.96 (s, 9 H) 0.98-1.02 (m, 1 H) 1.05 (s, 9 H) 1.07-1.10 (m, 2 H) 1.21-1.25 (m, 3 H) 1.28-1.34 (m, 1H) 1.36-1.55 (m, 8 H) 1.58-1.65 (m, 13 H) 1.81 (m, 1 H) 1.88 (m, 6 H) 2.23 (dd, $J=18.01$, 8.85 Hz, 1 H) 2.29 (m, 1 H) 2.59 (dd, $J=13.73$, 7.02 Hz, 1 H) 2.94 (m, 1 H) 3.27 (d, $J=1.83$ Hz, 1 H) 3.35 (d, $J=1.53$ Hz, 1 H) 3.75 (m, 1 H) 3.92 (s, 3 H) 3.95 (d, $J=6.41$ Hz, 1 H) 3.97 (s, 1 H) 4.09 (m, 2 H) 4.40 (s, 1 H) 4.45 (d, $J=11.90$ Hz, 1 H) 4.52 (dd, $J=10.07$, 7.02 Hz, 1 H) 4.81 (d, $J=7.02$ Hz, 1 H) 4.89 (d, $J=7.02$ Hz, 1 H) 5.11 (m, 1 H) 5.29 (d, $J=17.40$ Hz, 1 H) 5.75 (m, 1 H) 5.85 (s, 1 H) 7.11 (dd, $J=9.16$, 2.44 Hz, 1 H) 7.18 (d, $J=2.44$ Hz, 1 H) 7.25 (d, $J=5.80$ Hz, 1 H)

7.88 (d, $J=6.10$ Hz, 1 H) 7.95 (m, 1 H) 8.12 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.67 min.), MS m/z 725 (MH^+).

Example 76: Preparation of Compound 76

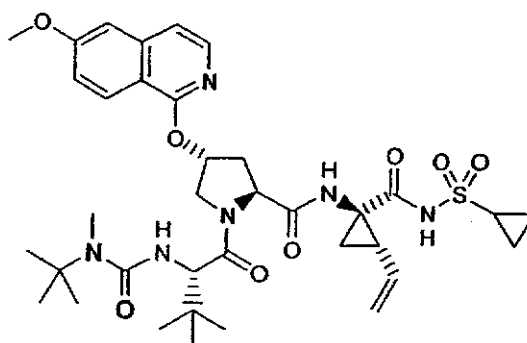
5



To a solution mixture of the product from step 1 of example 55 (70 mg, 0.102 mmol) and DIEA (33.0 mg, 0.255 mmol) in THF (2 mL) was added N,N' -dissuccinimidyl carbonate (39.2 mg, 0.153 mmol). The resulting suspension was irradiated in a microwave to 80 °C for 15 min. Then it was treated with tert-amylamine (88.9 mg, 1.02 mmol). After stirring at rt 15 min, the reaction was concentrated and purified by reversed phase prep-HPLC to give **Compound 76** (51 mg, 69%): ^1H NMR (CD_3OD , 500 MHz) δ 0.76 (t, $J=7.48$ Hz, 4 H), 0.97 (s, 1 H), 1.04 (s, 9 H), 1.13 (s, 6 H), 1.22-1.25 (m, 2 H), 1.41 (dd, $J=9.61$, 5.34 Hz, 1 H), 1.53 (dd, $J=13.89$, 7.48 Hz, 1 H), 1.58-1.62 (m, 1 H), 1.87 (dd, $J=7.93$, 5.49 Hz, 1 H), 2.20 (q, $J=8.65$ Hz, 1 H), 2.27-2.31 (m, 1 H), 2.60 (dd, $J=13.73$, 7.32 Hz, 1 H), 2.92-2.96 (m, 1 H), 3.92 (s, 3 H), 4.08 (dd, $J=11.75$, 3.81 Hz, 1 H), 4.36 (s, 1 H), 4.46 (d, $J=11.90$ Hz, 1 H), 4.50 (dd, $J=10.22$, 7.17 Hz, 1 H), 5.10 (dd, $J=10.22$, 1.37 Hz, 1 H), 5.27 (dd, $J=16.94$, 1.07 Hz, 1 H), 5.73-5.77 (m, 1 H), 5.84 (t, $J=3.51$ Hz, 1 H), 7.09 (dd, $J=9.16$, 2.44 Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.11 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.753 min.), MS m/z 727 (MH^+).

Example 77: Preparation of Compound 77

25

**Compound 77**

Compound 77 was prepared by the same method as **Compound 76** with the following modifications:

5

Modifications: tert-Butyl methylamine was used as a starting material to give **Compound 77** (160.7 mg, 74% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz})$ δ 0.96-1.10 (m, 1 H), 1.06 (s, 9 H), 1.08-1.12 (m, $J=5.80 \text{ Hz}$, 3 H), 1.26 (s, 9 H), 1.46 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.87 (dd, $J=7.93$, 5.49 Hz, 1 H), 2.21 (q, $J=8.75 \text{ Hz}$, 1 H), 2.26-2.31

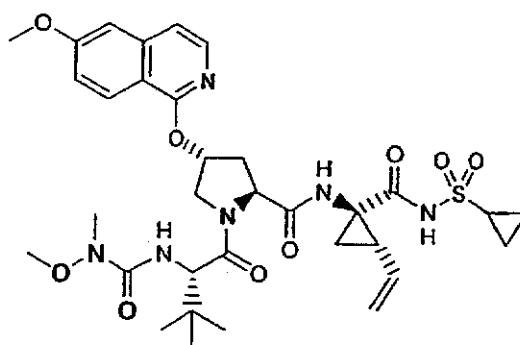
10

(m, 1 H), 2.57-2.62 (m, 1 H), 2.86 (s, 3 H), 2.91-2.95 (m, 1 H), 3.92 (s, 3 H), 4.09 (dd, $J=11.90$, 3.66 Hz, 1 H), 4.43 (s, 1 H), 4.46 (d, $J=11.90 \text{ Hz}$, 1 H), 4.52 (dd, $J=10.68$, 7.02 Hz, 1 H), 5.11 (dd, $J=10.22$, 1.37 Hz, 1 H), 5.29 (d, $J=17.09 \text{ Hz}$, 1 H), 5.75-5.82 (m, 1 H), 5.86 (s, 1 H), 7.09 (dd, $J=9.16$, 2.14 Hz, 1 H), 7.18 (d, $J=2.44 \text{ Hz}$, 1 H), 7.24 (d, $J=5.80 \text{ Hz}$, 1 H), 7.88 (d, $J=5.80 \text{ Hz}$, 1 H), 8.09 (d, $J=8.85 \text{ Hz}$, 1 H);

15

LC-MS (retention time: 1.76 min.), MS m/z 727 (MH^+).

Example 78: Preparation of Compound 78

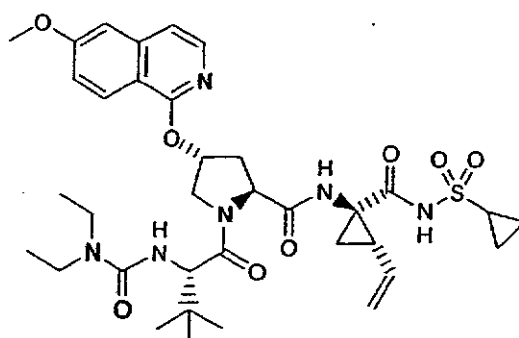
**Compound 78**

Compound 78 was prepared by the same method as **Compound 76** with the following modifications:

5

Modifications: *N,O*-Dimethylhydroxylamine hydrochloride was used as a starting material to give **Compound 78** (62.1 mg, 60% yield): $^1\text{H NMR}$ (CD_3OD , 500 MHz) δ 0.99 (t, $J=6.10$ Hz, 1 H), 1.07 (s, 11 H), 1.22-1.26 (m, $J=3.97$ Hz, 2 H), 1.47 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.88 (dd, $J=8.24, 5.49$ Hz, 1 H), 2.22 (d, $J=8.54$ Hz, 1 H), 2.3-30-2.33 (m, 1 H), 2.60 (dd, $J=13.43, 7.02$ Hz, 1 H), 2.92 (s, 3 H), 2.93-2.96 (m, 1 H), 3.66 (s, 3 H), 3.92 (s, 3 H), 4.12 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.34 (d, $J=12.21$ Hz, 1 H), 4.44 (d, $J=9.46$ Hz, 1 H), 4.54 (dd, $J=10.53, 6.87$ Hz, 1 H), 5.12 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=17.09$ Hz, 1 H), 5.75-5.83 (m, 1 H), 5.86 (t, $J=3.97$ Hz, 1 H), 6.70 (d, $J=9.77$ Hz, 1 H), 7.13 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.19 (d, $J=2.44$ Hz, 1 H), 7.25 (d, 15 $J=6.10$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.07 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.59 min.), MS m/z 701 (MH^+).

Example 79: Preparation of Compound 79

**Compound 79**

Compound 79 was prepared by the same method as **Compound 76** with the following modifications:

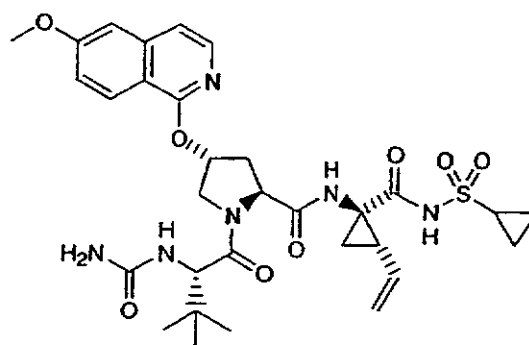
5

Modifications: Diethylamine was used as a starting material to give **Compound 79** (56.5 mg, 54% yield): $^1\text{H NMR}$ (CD_3OD , 500 MHz) δ 1.03 (q, $J=15.6$ Hz, 4 H), 1.06 (d, $J=1.53$ Hz, 9 H), 1.05-1.10 (m, 3 H), 1.13-1.23 (m, 4 H), 1.46 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.86 (dd, $J=7.93$, 5.30 Hz, 1 H), 2.17 (q, $J=8.85$ Hz, 1 H), 2.32-2.36 (m, 1 H), 2.60 (dd, $J=14.04$, 7.32 Hz, 1 H), 2.89-2.93 (m, 1 H), 3.16-3.24 (m, 4 H), 3.92 (s, 3 H), 4.14 (dd, $J=11.90$, 3.66 Hz, 1 H), 4.37 (d, $J=11.60$ Hz, 1 H), 4.51-4.55 (m, 2 H), 5.09 (d, $J=10.07$ Hz, 1 H), 5.27 (d, $J=17.09$ Hz, 1 H), 5.55 (d, $J=9.46$ Hz, 1 H), 5.79-5.84 (m, 1 H), 5.86 (s, 1 H), 7.11 (dd, $J=8.85$, 2.44 Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.08 (d, $J=9.16$ Hz, 1 H);

10 LC-MS (retention time: 1.68 min.), MS m/z 713 (MH^+).

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Example 80: Preparation of Compound 80

**Compound 80**

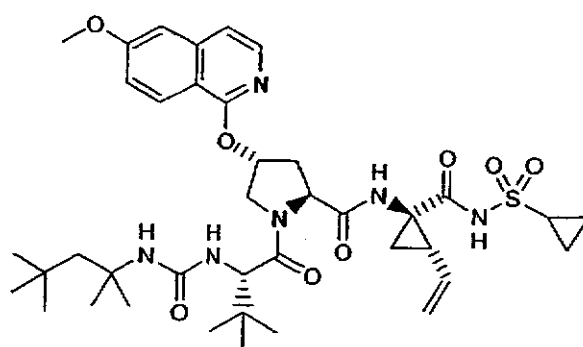
Compound 80 was prepared by the same method as **Compound 76** with the following modifications:

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Modifications: Saturated aqueous ammonium chloride was used as a starting material to give **Compound 76** (12.2 mg, 32% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz}) \delta$ 1.00-1.03 (m, 3 H), 1.06 (s, 9 H), 1.20-1.25 (m, 2 H), 1.42 (dd, $J=9.31, 5.34 \text{ Hz}$, 1 H), 2.22 (d, $J=9.77 \text{ Hz}$, 1 H), 2.29-2.35 (m, 1 H), 2.59 (dd, $J=13.28, 6.87 \text{ Hz}$, 1 H), 2.92-2.96 (m, 1 H), 3.92 (s, 3 H), 4.14 (dd, $J=11.75, 4.12 \text{ Hz}$, 1 H), 4.38-4.43 (m, 1 H), 4.51 (dd, $J=9.92, 6.87 \text{ Hz}$, 1 H), 5.11 (d, $J=11.90 \text{ Hz}$, 1 H), 5.28 (d, $J=17.70 \text{ Hz}$, 1 H), 5.72-5.79 (m, 1 H), 5.84 (s, 1 H), 7.15 (d, $J=2.44 \text{ Hz}$, 1 H), 7.17 (d, $J=2.75 \text{ Hz}$, 1 H), 7.23 (d, $J=5.80 \text{ Hz}$, 1H), 7.87 (d, $J=7.87 \text{ Hz}$, 1H), 8.10 (d, $J=8.85 \text{ Hz}$, 1H); LC-MS (retention time: 1.43 min.), MS m/z 657 (MH^+).

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Example 81: Preparation of Compound 81

**Compound 81**

Compound 81 was prepared by the same method as **Compound 76** with the following modifications:

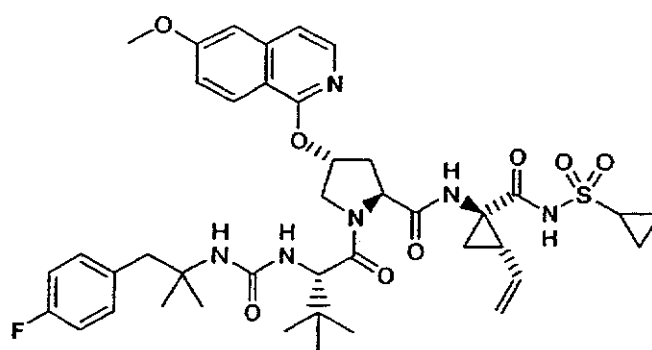
5

Modifications: tert-Octylamine was used as a starting material to give **Compound 81** (16.1 mg, 48% yield): $^1\text{H NMR}$ (CD_3OD , 500 MHz) δ 0.88 (s, 9 H), 1.00 (d, $J=9.77$ Hz, 5 H), 1.04 (s, 9 H), 1.17 (s, 3 H), 1.18-1.20 (m, 1 H), 1.21 (s, 3 H), 1.35 (d, $J=2.44$ Hz, 1 H), 1.40-1.43 (m, 1 H), 1.57 (d, $J=14.95$ Hz, 1 H), 1.67 (d, $J=14.65$ Hz, 1 H), 1.85 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.15 (d, $J=8.24$ Hz, 1 H), 2.34-2.43 (m, 1 H), 2.60 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.89-2.93 (m, 1 H), 3.92 (s, 3 H), 4.13 (dd, $J=11.60, 3.97$ Hz, 1 H), 4.38 (s, 1 H), 4.43 (d, $J=11.90$ Hz, 1 H), 4.50 (dd, $J=9.77, 7.32$ Hz, 1 H), 5.07 (d, $J=10.38$ Hz, 1 H), 5.24 (d, $J=17.09$ Hz, 1 H), 5.75-5.81 (m, 1 H), 5.84 (s, 1 H), 7.09 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.17 (d, $J=2.44$ Hz, 1 H), 7.23 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.92 min.), MS m/z 769 (MH^+).

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Example 82: Preparation of Compound 82

**Compound 82**

Compound 82 was prepared by the same method as **Compound 76** with the following modifications:

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Modifications: 1-(4-fluorophenyl)-2-methyl-2-propylamine was used as a starting material to give **Compound 82** (14.8 mg, 42% yield): ^1H NMR (CD_3OD , 500 MHz) δ 0.88 (s, 9 H), 1.00 (d, $J=9.46$ Hz, 6 H), 1.04 (s, 9 H), 1.17 (s, 3 H), 1.21 (s, 3 H), 1.32-1.37 (m, 2 H), 1.39-1.43 (m, 1 H), 1.57 (d, $J=14.65$ Hz, 1 H), 1.67 (d, $J=14.96$ Hz, 1 H), 1.82-1.86 (m, 1 H), 2.15 (t, $J=9.46$ Hz, 1 H), 2.33-2.43 (m, 2 H), 2.58-2.62 (dd, $J=14.50$, 7.76 Hz, 1 H), 2.89-2.95 (m, 1 H), 3.92 (s, 3 H), 4.12 (dd, $J=11.90$, 3.97 Hz, 1 H), 4.38 (s, 1 H), 4.43 (d, $J=12.82$ Hz, 1 H), 4.49-4.52 (m, 1 H), 5.24 (d, $J=16.48$ Hz, 1 H), 5.76-5.82 (m, 1 H), 5.83-5.85 (m, 1 H), 7.09 (dd, $J=9.00$, 2.59 Hz, 1 H), 7.17 (d, $J=2.14$ Hz, 1 H), 7.23 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.40 min.), MS m/z 807 (MH^+).

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Example 83: Preparation of Compound 83