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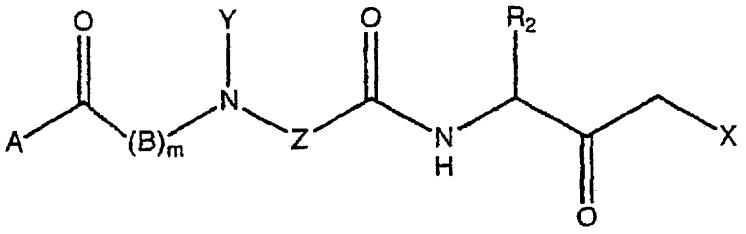
(54) Title: ANTICORONVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS



(I)

(57) Abstract: The invention relates to methods of inhibiting SARS-related coronavirus viral replication activity comprising contacting a SARS-related coronavirus protease with a therapeutically effective amount of a SARS 3C like protease inhibitor of formula (I), and compositions comprising the same.

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Anticoronaviral Compounds and Compositions, Their Pharmaceutical Uses and Materials for Their Synthesis

Background of the Invention

The invention relates to compounds and methods of inhibiting Severe Acute Respiratory Syndrome viral replication activity comprising contacting a SARS-related coronavirus 3C-like proteinase with a therapeutically effective amount of a SARS 3C-like protease inhibitor. The invention further relates to pharmaceutical compositions containing the SARS 3C like proteinase inhibitor in a mammal by administering effective amounts of such coronavirus 3C like proteinase inhibitor.

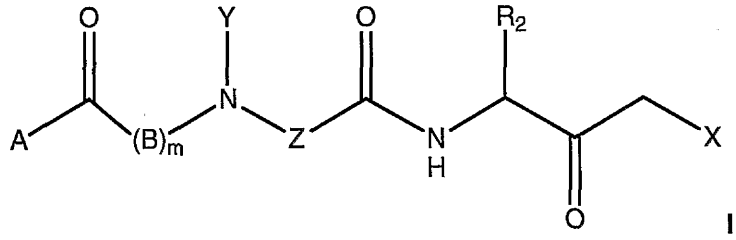
A worldwide outbreak of Severe Acute Respiratory Syndrome-related coronavirus ("SARS") has been associated with exposures originating from a single ill health care worker from Guangdong Province, China. Recently, the causative agent has been identified as a novel coronavirus. There is an acute need in the art for an effective treatment for the SARS-related coronavirus.

Recent evidence strongly implicates a new coronavirus as the causative agent of SARS (Centers for Disease Control, CDC). Coronavirus replication and transcription function is encoded by the so-called "replicase" gene (Thiel, Herold et al. 2001), which consists of two overlapping polyproteins that are extensively processed by viral proteases. The C-proximal region is processed at eleven conserved interdomain junctions by the coronavirus main or "3C-like" protease (Ziebuhr, Snijder et al. 2000). The name "3C-like" protease derives from certain similarities between the coronavirus enzyme and the well-known picornavirus 3C proteases (Gorbalenya, Koonin et al. 1989). These include substrate preferences, use of cysteine as an active site nucleophile in catalysis, and similarities in their putative overall polypeptide folds. Very recently Hilgenfeld and colleagues published a high-resolution X-ray structure of the porcine transmissible gastroenteritis coronavirus main protease (Anand, Palm et al. 2002). Atomic coordinates are available through the Protein Data Bank under accession code 1LVO.

Summary of The Invention

The present invention relates to compounds of formula I:

1. A compound comprising the following structure:



I

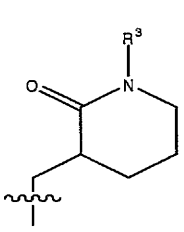
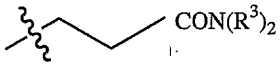
or a pharmaceutically acceptable salt, solvate or salt/solvate thereof;

wherein:

m is an integer selected from 0 and 1;

Y is selected from the group consisting of H, $-CH_3$, and $-CH_2CH_3$;

R^1 is C_1 to C_7 alkyl, C_3 to C_{10} cycloalkyl, and benzyl wherein said alkyl, benzyl and cycloalkyl is unsubstituted or independently substituted with 1 to 3 R^7 substituents;

R^2 is selected from  and 

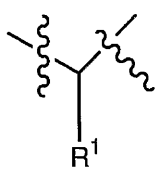
R^3 is independently selected from H and C_1 to C_3 alkyl;

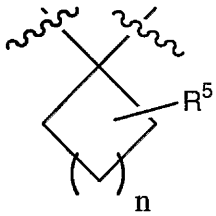
each R^4 and $R^{4'}$ is independently H, C_1 to C_3 alkyl or C_3 to C_6 cycloalkyl, wherein each alkyl and cycloalkyl is unsubstituted or substituted with oxo, 1 to 3 halogens or 1 to 3 hydroxyls;

R^5 is H or selected from R^7 substituents;

R^6 is C_6 to C_{10} aryl, benzyl, C_3 to C_{10} cycloalkyl, 4 to 10 member heterocycle or C_1 to C_7 alkyl wherein the foregoing R^6 substituents are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

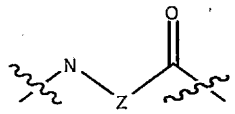
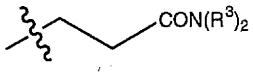
each R^7 is independently selected from halogen, oxo, C_1 to C_4 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_6 cycloalkyl, $-OR^4$, $-NR^4C(O)R^4$, $-NR^4R^{4'}$, SR^4, $-SOR^4$, $-SO^2R^4$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^{4'}$, $-SO_2NR^4R^{4'}$, $-NR^4SO_2NR^4R^{4'}$, 4 to 10 member heterocycle and $-OC(O)R^4$, wherein the foregoing alkyl, alkenyl, alkynyl, cycloalkyl and heterocycle groups are each optionally substituted with halogen, hydroxy, C_1 to C_6 alkoxy, and oxo;

Z is selected from the group consisting of 

and 

wherein n is 0 to 3;

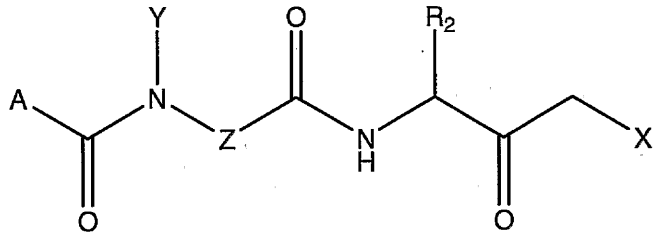
A is 4 to 10 member heterocycle, C_3 to C_{10} cycloalkyl, C_6 to C_{10} aryl and C_1 to C_7 alkyl , wherein said heterocycle, cycloalkyl, alkyl and aryl are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

B is  with the proviso that when R^2 is  then m is 0;

and

X is selected from –OH, -OR^6, Cl, Br, I, and -OC(O)R^6.

The compounds of the invention also include compounds with the following structure:



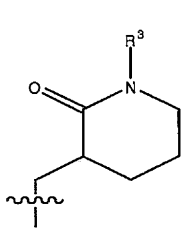
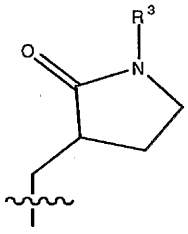
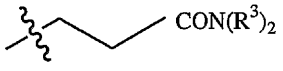
II

or a pharmaceutically acceptable salt, solvate or salt/solvate thereof;
wherein:

m is an integer selected from 0 and 1;

Y is selected from the group consisting of H, -CH_3, and –CH_2CH_3;

R^1 is C_1 to C_7 alkyl, C_3 to C_{10} cycloalkyl, and benzyl wherein said alkyl, benzyl and cycloalkyl is unsubstituted or independently substituted with 1 to 3 R^7 substituents;

R^2 is selected from  ,  and 

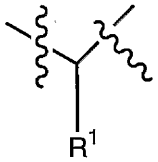
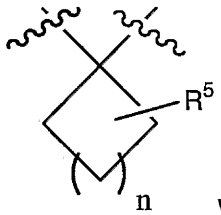
R^3 is selected from H and C_1 to C_3 alkyl;

each R^4 and $R^{4'}$ is independently H or C_1 to C_3 alkyl;

R^5 is H or selected from R^7 substituents;

R^6 is C_6 to C_{10} aryl, benzyl, C_4 to C_{10} cycloalkyl, 4 to 10 member heterocycle or C_1 to C_7 alkyl wherein the foregoing R^6 substituents are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

each R^7 is independently selected from halogen, oxo, C_1 to C_4 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, $-OR^4$, $-NC(O)R^4$, $-NR^4R^{4'}$, SR^4, $-SOR^4$, $-SO^2R^4$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^{4'}$, $-SO_2NR^4R^{4'}$, $-NR^4SO_2NR^4R^{4'}$, 4 to 10 member heterocycle and $-OC(O)R^4$, wherein the foregoing R^7 groups are each optionally substituted with halogen, hydroxy, C_1 to C_6 alkoxy, and C_3 to C_6 cycloalkyl wherein said cycloalkyl is unsubstituted or independently substituted with 1 to 3 of substituents independently selected from halogen, hydroxy and C_1 to C_6 alkoxy;

Z is selected from the group consisting of  and  wherein n is 0 to 3;

A is 4 to 10 member heterocycle, C_4 to C_{10} cycloalkyl, C_6 to C_{10} aryl and C_1 to C_7 alkyl, wherein said heterocycle, cycloalkyl, alkyl and aryl are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

X is selected from –OH, $-OR^6$, Cl, Br, I, and $-OC(O)R^6$.

The present invention provides methods of inhibiting the activity of a coronavirus 3C protease (also known as proteinase), comprising contacting the coronavirus 3C protease with an effective amount of a SARS 3C protease inhibitor compound or agent.

The present invention provides a novel method of interfering with or preventing SARS viral replication activity comprising contacting a SARS protease with a therapeutically effective amount of a rhinovirus protease inhibitor.

In one embodiment of the present invention, the SARS coronavirus 3C-like protease inhibitor is administered orally or intravenously.

The present invention also provides a method of treating a condition that is mediated by coronavirus 3C-like protease activity in a patient by administering to said patient a pharmaceutically effective amount of a SARS protease inhibitor.

The present invention also provides a method of targeting SARS inhibition as a means of treating indications caused by SARS-related viral infections.

The present invention also provides a method of targeting viral or cellular targets identified by using rhinovirus inhibitors against SARS coronavirus 3C-like protease for treating indications caused by SARS-related viral infections.

The present invention also provides a method of identifying cellular or viral pathways interfering with the functioning of the members of which could be used for treating indications caused by SARS infections by administering a SARS protease inhibitor.

The present invention also provides a method of using SARS protease inhibitors as tools for understanding mechanism of action of other SARS inhibitors.

The present invention also provides a method of using SARS 3C like protease inhibitors for carrying out gene profiling experiments for monitoring the up or down regulation of genes for the purposed of identifying inhibitors for treating indications caused by SARS infections.

The present invention further provides a pharmaceutical composition for the treatment of SARS in a mammal containing an amount of a SARS 3C like protease inhibitor that is effective in treating SARS and a pharmaceutically acceptable carrier.

For purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated and unsaturated monovalent hydrocarbon radicals having straight or branched moieties.

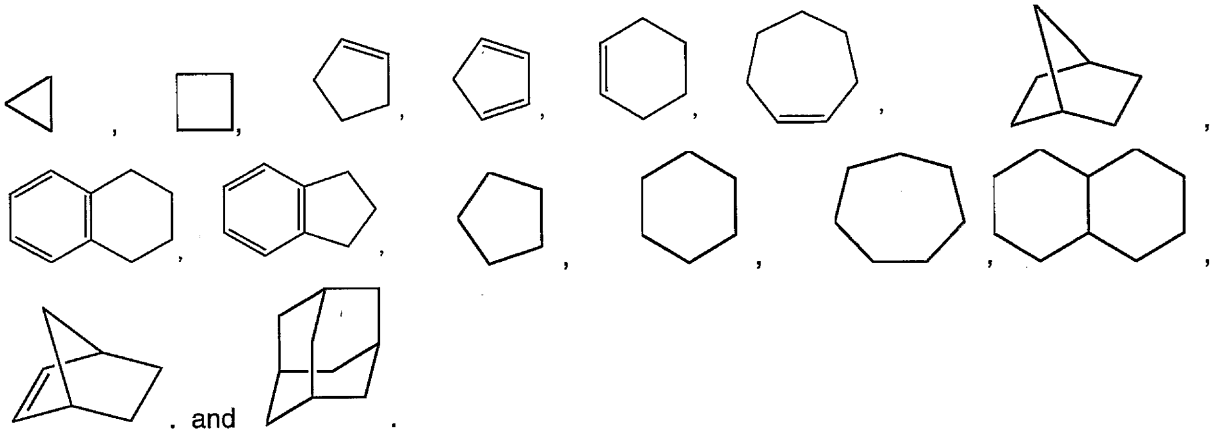
The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

The term "cycloalkyl", as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:

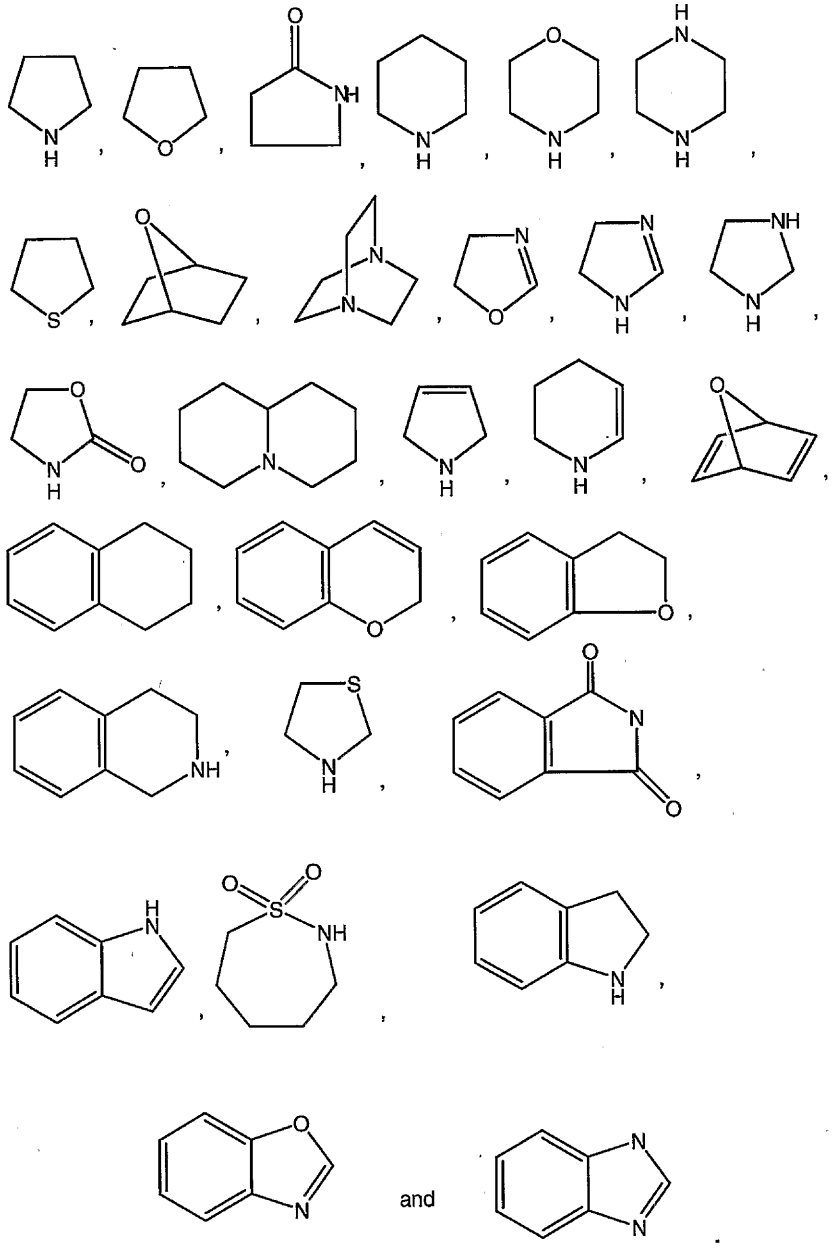


. and .

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "4 to 10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). The 4 to 10 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with

oxo moieties is 1,1-dioxo-thiomorpholinyl. Other illustrative examples of 4 to 10 membered heterocyclic are derived from, but not limited to, the following:



and

Unless otherwise indicated, the term "oxo" refers to =O.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula I. The compounds of formula I that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula I are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edislyate, estolate,

esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phospate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

Certain compounds of formula I may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula I, and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula I, the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods of treating SARS infections through administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more

(e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula I. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

The compounds of the invention can also be used in combination with other drugs. For example, dosing a SARS coronavirus infected patient with the SARS coronavirus 3CL protease inhibitor of the invention and an interferon, such as interferon alpha, or a pegylated interferon, such as PEG-Intron or Pegasus, may provide a greater clinical benefit than dosing either the interferon, pegylated interferon or the SARS coronavirus inhibitor alone. Examples of greater clinical benefits could include a larger reduction in symptoms, a faster time to alleviation of symptoms, reduced lung pathology, a larger reduction in the amount of SARS coronavirus in the patient (viral load), and decreased mortality.

The SARS coronavirus infects cells which express p-glycoprotein. Some of the SARS coronavirus 3CL protease inhibitors of the invention are p-glycoprotein substrates. Compounds which inhibit the SARS coronavirus which are also p-glycoprotein substrates may be dosed with p-glycoprotein inhibitor. Examples of p-glycoprotein inhibitors are verapamil, vinblastine, ketoconazole, nelfinavir, ritonavir or cyclosporine. The p-glycoprotein inhibitors act by inhibiting the efflux of the SARS coronavirus inhibitors of the invention out of the cell. The inhibition of the p-glycoprotein based efflux will prevent reduction of intracellular concentrations of the SARS coronavirus inhibitor due to p-glycoprotein efflux. Inhibition of the p-glycoprotein efflux will result in larger intracellular concentrations of the SARS coronavirus inhibitors. Dosing a SARS coronavirus infected patient with the SARS coronavirus 3CL protease inhibitors of the invention and a p-glycoprotein inhibitor may lower the amount of SARS coronavirus 3CL protease inhibitor required to achieve an efficacious dose by increasing the intracellular concentration of the SARS coronavirus 3CL protease inhibitor.

Among the agents that may be used to increase the exposure of a mammal to a compound of the present invention are those that can as inhibitors of at least one isoform of the cytochrome P450

(CYP450)enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. The compounds of the invention include compounds that are CYP3A4 substrates and are metabolized by CYP3A4. Dosing a SARS coronavirus infected patient with a SARS coronavirus inhibitor which is a CYP3A4 substrate, such as a SARS coronavirus 3CL protease inhibitor, and a CYP3A4 inhibitor, such as ritonavir, nelfinavir or delavirdine, will reduce the metabolism of the SARS coronavirus inhibitor by CYP3A4. This will result in reduced clearance of the SARS coronavirus inhibitor and increased SARS coronavirus plasma concentrations. The reduced clearance and higher plasma concentrations may result in a lower efficacious dose of the SARS coronavirus inhibitor.

The term "SARS-inhibiting agent" means any SARS related coronavirus 3C like protease inhibitor compound represented by formula I or a pharmaceutically acceptable salt, hydrate, prodrug, active metabolite or solvate thereof.

The term "interfering with or preventing" SARS-related coronavirus ("SARS") viral replication in a cell means to reduce SARS replication or production of SARS components necessary for progeny virus in a cell as compared to a cell not being transiently or stably transduced with the ribozyme or a vector encoding the ribozyme. Simple and convenient assays to determine if SARS viral replication has been reduced include an ELISA assay for the presence, absence, or reduced presence of anti-SARS antibodies in the blood of the subject (Nasoff et al., PNAS 88:5462-5466, 1991), RT-PCR (Yu et al., in Viral Hepatitis and Liver Disease 574-477, Nishioka, Suzuki and Mishiro (Eds.); Springer-Verlag Tokyo, 1994). Such methods are well known to those of ordinary skill in the art. Alternatively, total RNA from transduced and infected "control" cells can be isolated and subjected to analysis by dot blot or northern blot and probed with SARS specific DNA to determine if SARS replication is reduced. Alternatively, reduction of SARS protein expression can also be used as an indicator of inhibition of SARS replication. A greater than fifty percent reduction in SARS replication as compared to control cells typically quantitates a prevention of SARS replication.

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

If an inhibitor compound used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base (such as an amine (primary, secondary, or tertiary)), an alkali metal hydroxide, or alkaline earth metal hydroxide. Illustrative examples of suitable salts include organic salts derived from amino acids (such as glycine and arginine), ammonia, primary amines, secondary amines, tertiary amines, and cyclic amines (such as piperidine, morpholine, and piperazine), as well

as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of inhibitor compounds, prodrugs, salts, or solvates that are solids, it is understood by those skilled in the art that the hydroxamate compound, prodrugs, salts, and solvates used in the method of the invention, may exist in different polymorph or crystal forms, all of which are intended to be within the scope of the present invention and specified formulas. In addition, the hydroxamate compound, salts, prodrugs and solvates used in the method of the invention may exist as tautomers, all of which are intended to be within the broad scope of the present invention.

Solubilizing agents may also be used with the compounds of the invention to increase the compounds solubility in water or physiologically acceptable solutions. These solubilizing agents include cyclodextrans, propylene glycol, diethylacetamide, polyethylene glycol, Tween, ethanol and micelle forming agents. Oreffered solubilizing agents are cyclodextrans, particularly beta cyclodextrans and in particular hydroxypropyl betacyclodextran and sulfobutylether betacyclodextran.

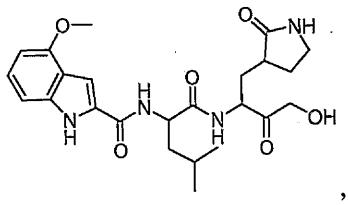
In some cases, the inhibitor compounds, salts, prodrugs and solvates used in the method of the invention may have chiral centers. When chiral centers are present, the hydroxamate compound, salts, prodrugs and solvates may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates, and mixtures thereof are intended to be within the broad scope of the present invention.

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

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. In a preferred embodiment of the present invention, "treating" or "treatment" means at least the mitigation of a disease condition in a human, that is alleviated by the inhibition of the activity of one or more coronaviral 3C-like proteases, including, but not limited to the 3C-like protease of the causative agent for SARS. In the case of SARS, representative disease conditions include fever, dry cough, dyspnea, headache, hypoxemia, lymphopenia, elevated aminotransferase levels as well as viral titer. Methods of treatment for mitigation of a disease condition include the use of one or more of the compounds in the invention in any conventionally acceptable manner. According to certain preferred embodiments of the invention, the compound or compounds of the present invention are administered to a mammal, such as a human, in need thereof. Preferably, the mammal in need thereof is infected with a coronavirus such as the causative agent of SARS.

The present invention also includes prophylactic methods, comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof to a mammal, such as a human, at risk for infection by a coronavirus. According to certain preferred embodiments, an effective amount of one or more compounds of the invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof is administered to a human at risk for infection by the causative agent for SARS. The prophylactic methods of the invention include the use of one or more of the compounds in the invention in any conventionally acceptable manner.

The following are examples of specific embodiments of the invention: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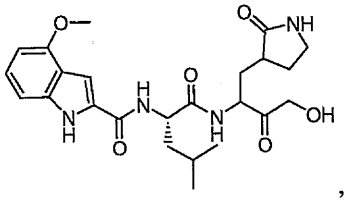
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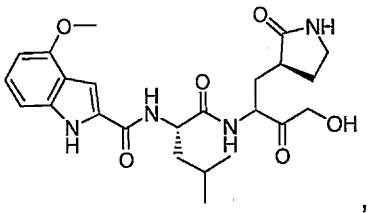
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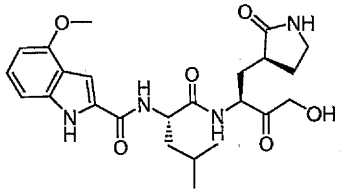

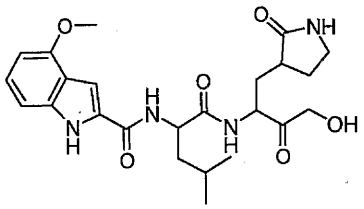
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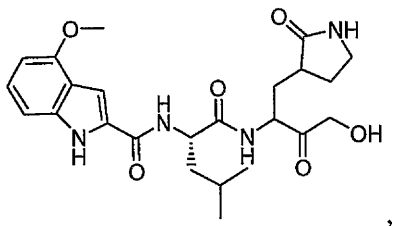
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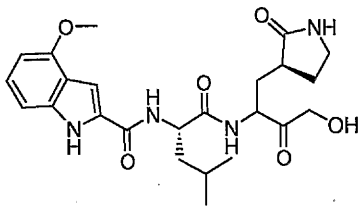
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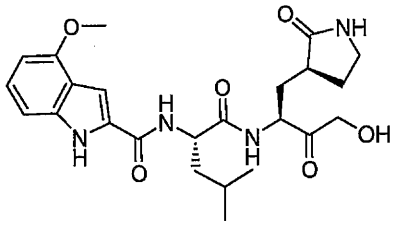
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Detailed Description Of The Invention And Preferred Embodiments

The compounds of the invention can be made by the following general procedure:

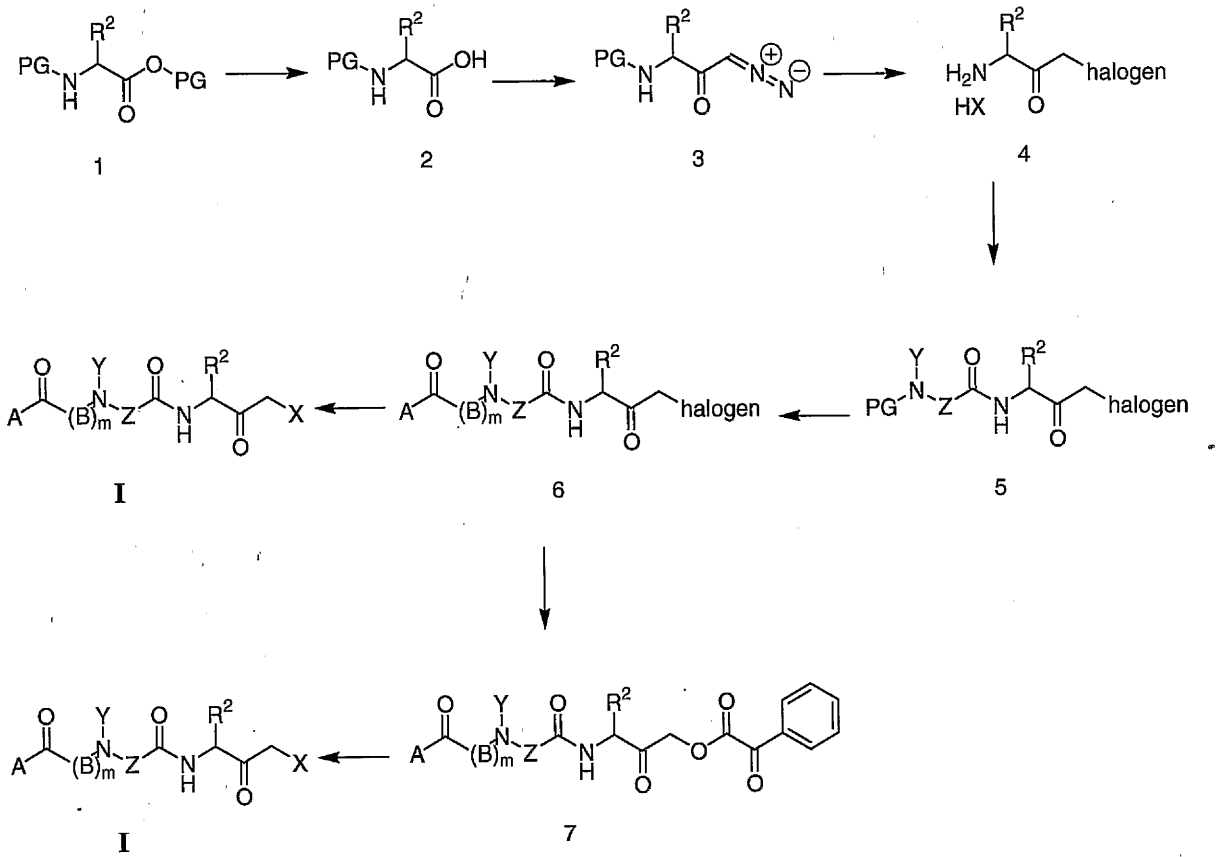


Chart 1 depicts the general preparation of compounds **I** wherein the definitions of R^2, Z, Y, X, A and B are given in the summary of the invention and PG is a suitable protecting group. Compound **1** is selectively de-protected employing standard conditions known in the art (see *Protective Groups in Organic Synthesis*, Greene & Wuts, Wiley-Interscience, New York, 3rd edition, **1999**) to provide the corresponding amino acid **2** wherein PG is a suitable protecting group. Compound **2** is converted to a mixed anhydride followed by treatment with diazomethane to generate the diazo ketone **3** (see Rich, D., *et al.*, *Journal of Medicinal Chemistry*, 35, **1992**, 3803-3812). Compound **3** is subjected to an excess of a mineral acid (such as hydrochloric acid or hydrobromic acid) to provide halomethylketone **4**. Halomethylketone **4** is reacted with an N-protected amino acid (such as a BOC-protected amino acid) employing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **5**. Compound **5** is subjected to standard nitrogen de-protecting conditions (such as HCL in a solvent such as dioxane) followed by reaction with a carboxylic acid utilizing standard peptide coupling conditions and/or methods known in the art to provide **6**. Compound **6** is reacted with a carboxylic acid in the presence of a suitable base (such as CsF or KF) and solvent (for example DMF) to produce I (see Krantz, A., et al., *Biochemistry*, 30, **1991**, 4678-4687). Alternatively to prepare compounds where X is OR^1, Compound **6** is reacted with benzoylformic acid and an appropriate base

(for example cesium fluoride or potassium fluoride) in a suitable solvent (such as DMF) to provide **7** (for general procedure see Marquis, R., *et al.*, *Bioorganic & Medicinal Chemistry*, 7, **1999**, 581-588). Compound **7** is reacted with methanol and catalytic amounts of an appropriate base (such as potassium carbonate) or alternatively with an aqueous base (for example 1M sodium bicarbonate) in a suitable solvent such as THF to provide hydroxymethylketone **I** where R^1 is hydrogen (see Mendonca, R., *et al.*, *Bioorganic & Medicinal Chemistry Letters*, 12, **2002**, 2887-2891 or Ellman, J., *et al.*, *Bioorganic & Medicinal Chemistry*, 11, **2003**, 21-29). Compound **I** is reacted with an alkylhalide in the presence of a suitable agent (such as silver(I) oxide) and an appropriate solvent (for example DCM, or 1,2-DCE) to afford alkoxymethylketones **I**.

Recent evidence indicates that a new coronavirus is the causative agent of SARS. The nucleotide sequence of the SARS-associated coronavirus has also recently been determined and made publicly available.

The activity of the inhibitor compounds as inhibitors of SARS-related viral activity may be measured by any of the suitable methods available in the art, including *in vivo* and *in vitro* assays. The activity of the compounds of the present invention as inhibitors of coronavirus 3C-like protease activity (such as the 3C-like protease of the SARS coronavirus) may be measured by any of the suitable methods known to those skilled in the art, including in vivo and in vitro assays. Examples of suitable assays for activity measurements include the antiviral cell culture assays described herein as well as the antiprotease assays described herein, such as the assays described in the Example section.

Administration of the inhibitor compounds and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, pulmonary, parenteral, topical, intravenous, injected, transdermal, and rectal. Oral, intravenous, and nasal deliveries are preferred.

A SARS-inhibiting agent may be administered as a pharmaceutical composition in any suitable pharmaceutical form. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyopholized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. The SARS-inhibiting agent may be prepared as a solution using any of a variety of methodologies. For example, the SARS-inhibiting agent can be dissolved with acid (e.g., 1 M HCl) and diluted with a sufficient volume of a solution of 5% dextrose in water (D5W) to yield the desired final concentration of SARS-inhibiting agent (e.g., about 15 mM). Alternatively, a solution of D5W containing about 15 mM HCl can be used to provide a solution of the SARS-inhibiting agent at the appropriate concentration. Further, the SARS-inhibiting agent can be prepared as a suspension using, for example, a 1% solution of carboxymethylcellulose (CMC).

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known or may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when

necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

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

A dose of the pharmaceutical composition may contain at least a therapeutically effective amount of an SARS-inhibiting agent and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of SARS-related coronavirus activity, by any known or suitable method of administering the dose, including topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; intravenously; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

The phrases "therapeutically effective amount" and "effective amount" are intended to mean the amount of an inventive agent that, when administered to a mammal in need of treatment, is sufficient to effect treatment for injury or disease conditions alleviated by the inhibition of SARS viral replication. The amount of a given SARS-inihibiting agent used in the method of the invention that will be therapeutically effective will vary depending upon factors such as the particular SARS-inihibiting agent, the disease condition and the severity thereof, the identity and characteristics of the mammal in need thereof, which amount may be routinely determined by artisans.

It will be appreciated that the actual dosages of the SARS-inhibiting agents used in the pharmaceutical compositions of this invention will be selected according to the properties of the particular agent being used, the particular composition formulated, the mode of administration and the particular site, and the host and condition being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests. For oral administration, e.g., a dose that may be employed is from about 0.01 to about 1000 mg/kg body weight, preferably from about 0.1 to about 500 mg/kg body weight, and even more preferably from about 1 to about 500 mg/kg body weight, with courses of treatment repeated at appropriate intervals. For intervenous dosing a dose of up to 5 grams per day may be employed.

The terms "cytochrome P450-inhibiting amount" and "cytochrome P450 enzyme activity-inhibiting amount," as used herein, refer to an amount of a compound required to decrease the activity of cytochrome P450 enzymes or a particular cytochrome P450 enzyme isoform in the

presence of such compound. Whether a particular compound of decreases cytochrome P450 enzyme activity, and the amount of such a compound required to do so, can be determined by methods known to those of ordinary skill in the art and the methods described herein.

Protein functions required for coronavirus replication and transcription are encoded by the so-called "replicase" gene. Two overlapping polyproteins are translated from this gene and extensively processed by viral proteases. The C-proximal region is processed at eleven conserved interdomain junctions by the coronavirus main or "3C-like" protease. The name "3C-like" protease derives from certain similarities between the coronavirus enzyme and the well-known picornavirus 3C proteases. These include substrate preferences, use of cysteine as an active site nucleophile in catalysis, and similarities in their putative overall polypeptide folds. A comparison of the amino acid sequence of the SARS-associated coronavirus 3C-like protease to that of other known coronaviruses shows the amino acid sequence to be highly conserved, particularly in the catalytically important regions of the protease.

Amino acids of the substrate in the protease cleavage site are numbered from the N to the C terminus as follows : -P3-P2-P1-P1´-P2´-P3´, with cleavage occurring between the P1 and P1' residues (Schechter & Berger, 1967). Substrate specificity is largely determined by the P2, P1 and P1´ positions. Coronavirus main protease cleavage site specificities are highly conserved with a requirement for glutamine at P1 and a small amino acid at P1' (Journal of General Virology 83, pp. 595-599 (2002)).

Recently, Hilgenfeld and colleagues published a high-resolution x-ray structure of the porcine transmissible gastroenteritis coronavirus main protease (The EMBO Journal, Vol. 21, pp. 3213-3224 (2002)). Atomic coordinates are available through the Protein Data Bank under accession code 1LVO. Our observations of the catalytic and structural similarities between rhinovirus 3C protease and coronavirus "3C-like" main protease, lead to the conclusion that selected inhibitors of rhinovirus 3C protease would be useful against the coronavirus main (3C-like) protease.

EXAMPLES

In the examples described below, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents may be purchased from commercial suppliers, such as Sigma-Aldrich Chemical Company, or Lancaster Synthesis Ltd. and may be used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and N, N-dimethylformamide (DMF) may be purchased from Aldrich in Sure Seal bottles and used as received. All solvents may be purified using standard methods known to those skilled in the art, unless otherwise indicated.

The structures of the compounds of the following examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, elemental microanalysis and melting point. Proton magnetic resonance (^{1}H NMR) spectra were determined using a Bruker spectrometers operating at a field strength of 300 to 400 megahertz (MHz). Chemical shifts are reported in parts per

million (ppm, δ) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced to residual protic solvent signals as follows: $CHCl_3$ = 7.26 ppm; DMSO = 2.49 ppm, C_6HD_5 = 7.15 ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; br, broad resonance; m, multiplet. Coupling constants are given in Hertz. Elemental microanalyses were performed by Atlantic Microlab Inc., Norcross, GA and gave results for the elements stated within ±0.4% of the theoretical values. Flash column chromatography was performed using Silica gel 60 (Merck Art 9385) or various MPLC systems. Analytical thin layer chromatography (TLC) was performed using precoated sheets of Silica 60 F_{254} (Merck Art 5719). All reactions were performed in septum-sealed flasks under a slight positive pressure of argon or dry nitrogen unless otherwise noted.

Preferred compounds in accordance with the invention may be prepared in manners analogous to those specifically described below.

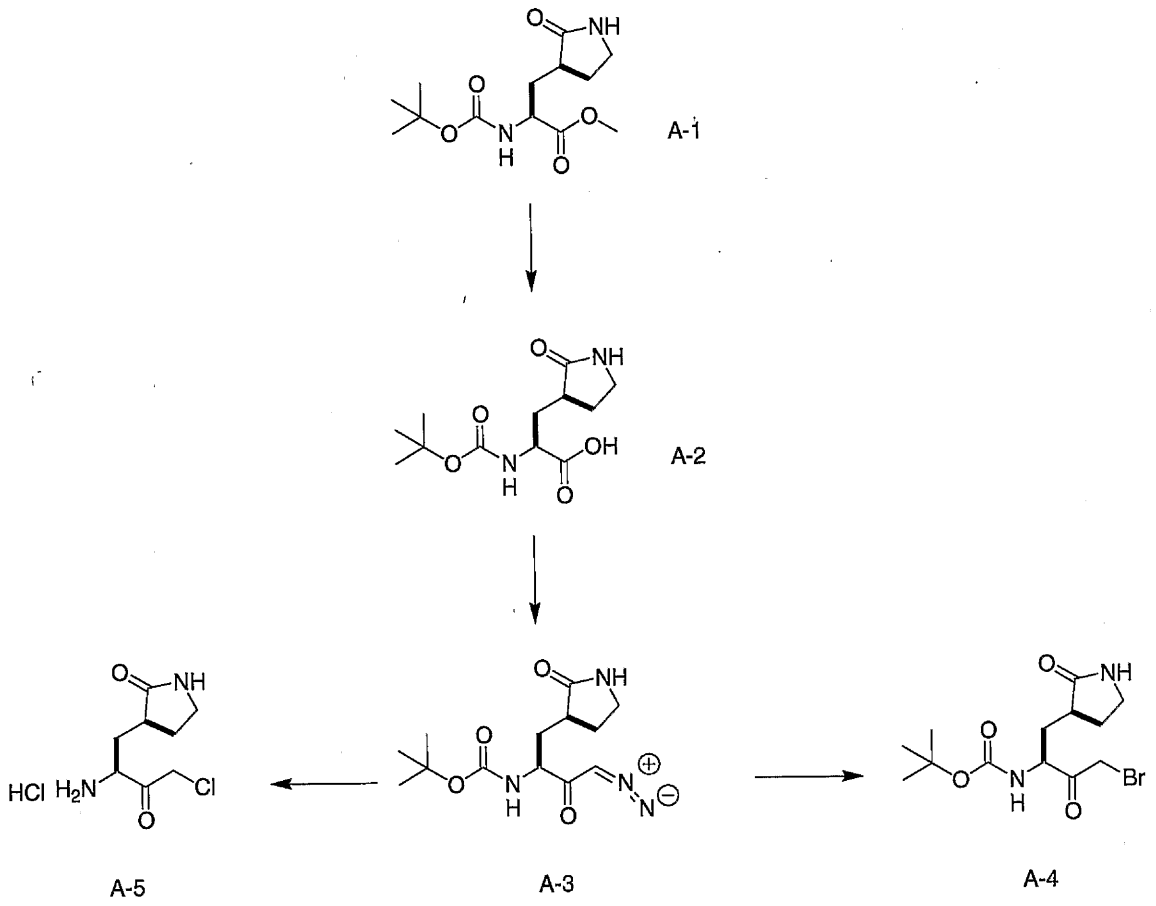
The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAXμ RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 mm interior diameter. The samples are run on a Hewlett Packard- 1100 systemA gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 ml / minute.

In the examples and specification, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "ETOAC" or "ETOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl Et_2O refers to diethyl ether, DMF refers to *N,N*-dimethylformamide. DMSO refers to dimethylsulfoxide. MTBE refers to *tert*-butyl methyl ether. Other abbreviations include: CH_3OH (methanol), EtOH (ethanol), EtOAc (ethyl acetate), DME (ethylene glycol dimethyl ether) DCM refers to dichloromethane, 1,2 DCE referes to 1,2 dichloroethane, Ph (phenyl), Tr (triphenylmethyl), Cbz (benzyloxycarbonyl), Boc (*tert*-butoxycarbonyl), TFA (trifluoroacetic acid), DIEA (*N,N*-diisopropylethylamine), TMEDA (*N,N,N',N'*-tetramethylethylenediamine), AcOH (acetic acid), Ac_2O (acetic anhydride), NMM (4-methylmorpholine), HOBt (1-hydroxybenzotriazole hydrate), HATU [*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate], EDC [1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride], TEA triethylamine, LDA lithium

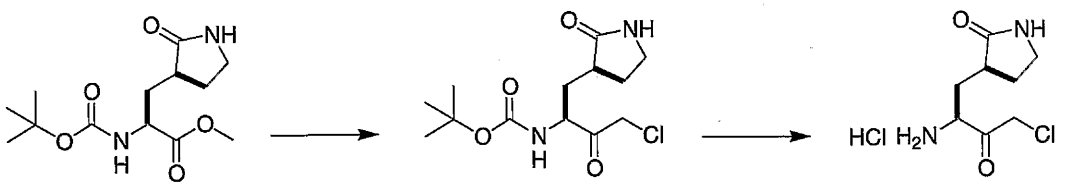
diisopropyl amide, DCC (dicyclohexyl-carbodiimide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), DMAP (4-dimethylaminopyridine), Gln (glutamine), Leu (leucine), Phe (phenylalanine), Phe(4-F) (4-fluorophenylalanine), Val (valine), amino-Ala (2,3-diaminopropionic acid), and (*S*)-Pyrrol-Ala [(2*S*,3'*S*)-2-amino-3-(2'-oxopyrrolidin-3'-yl)-propionic acid]. Additionally, "L" represents the configuration of naturally occurring amino acids.

The compounds of the invention are made by the following general procedure:



As depicted in Chart A, amino ester **A-1** (described by Tian, Q., *et al.*, *Tetrahedron Letters*, 42, **2001**, 6807-6809) is converted under standard conditions known in the art (such as aqueous LiOH and methanol) to the corresponding amino acid **A-2**. Compound **A-2** is converted to a mixed anhydride followed by treatment with diazomethane to generate the diazo ketone **A-3** (Rich, D., *et al.*, *Journal of Medicinal Chemistry*, 35, **1992**, 3803-3812). Compound **A-3** is subjected to excess hydrochloric acid to provide chloromethylketone **A-5** with concomitant removal of the *tert*-butoxycarbonyl (Boc) nitrogen protecting group. Alternatively, **A-3** is reacted with stoichiometric quantities of hydrobromic acid to generate the nitrogen Boc-protected bromomethylketone **A-4**.

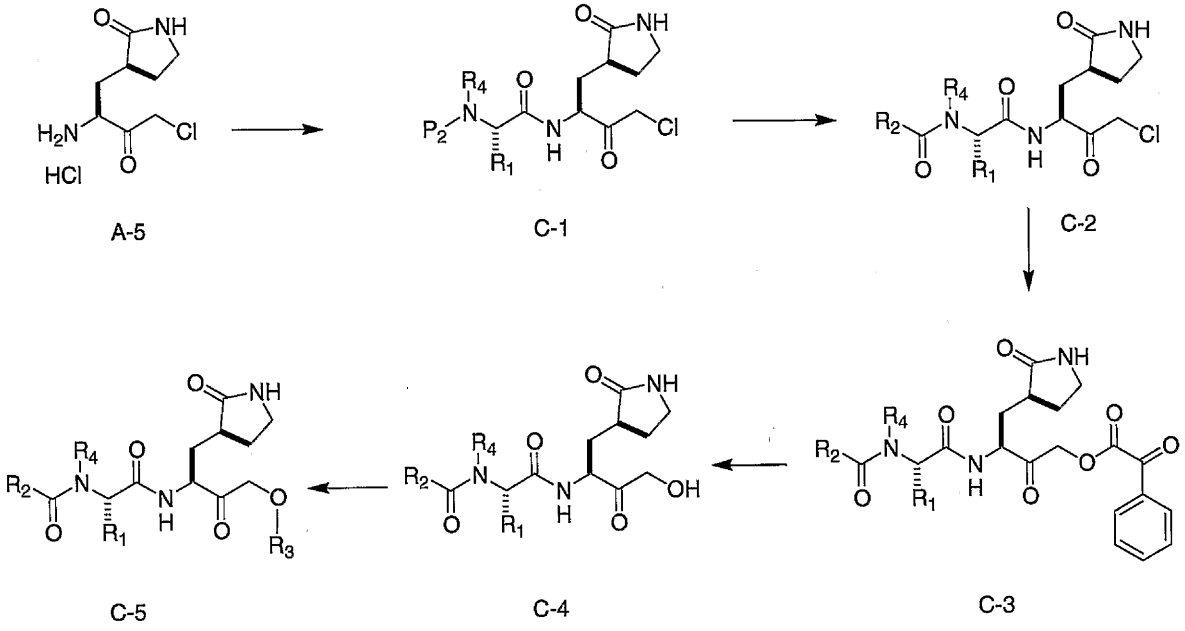
Chart B



A-1 B-1 A-5

Chart B describes an alternative preparation of **A-5**. Amino ester **A-1** is reacted with a species produced by the action of a suitable base (for example n-BuLi or LDA) and chloroiodomethane to generate **B-1** (see Chen, P., *et al.*, *Tetrahedron Letters*, 38, **1997**, 3175-78). Compound **B-1** is subjected to standard N-Boc de-protection procedures (such as HCL in a solvent such as dioxane) to afford **A-5** (see *Protective Groups in Organic Synthesis*, Greene & Wuts, Wiley-Interscience, New York, 3rd edition, **1999**).

Chart C



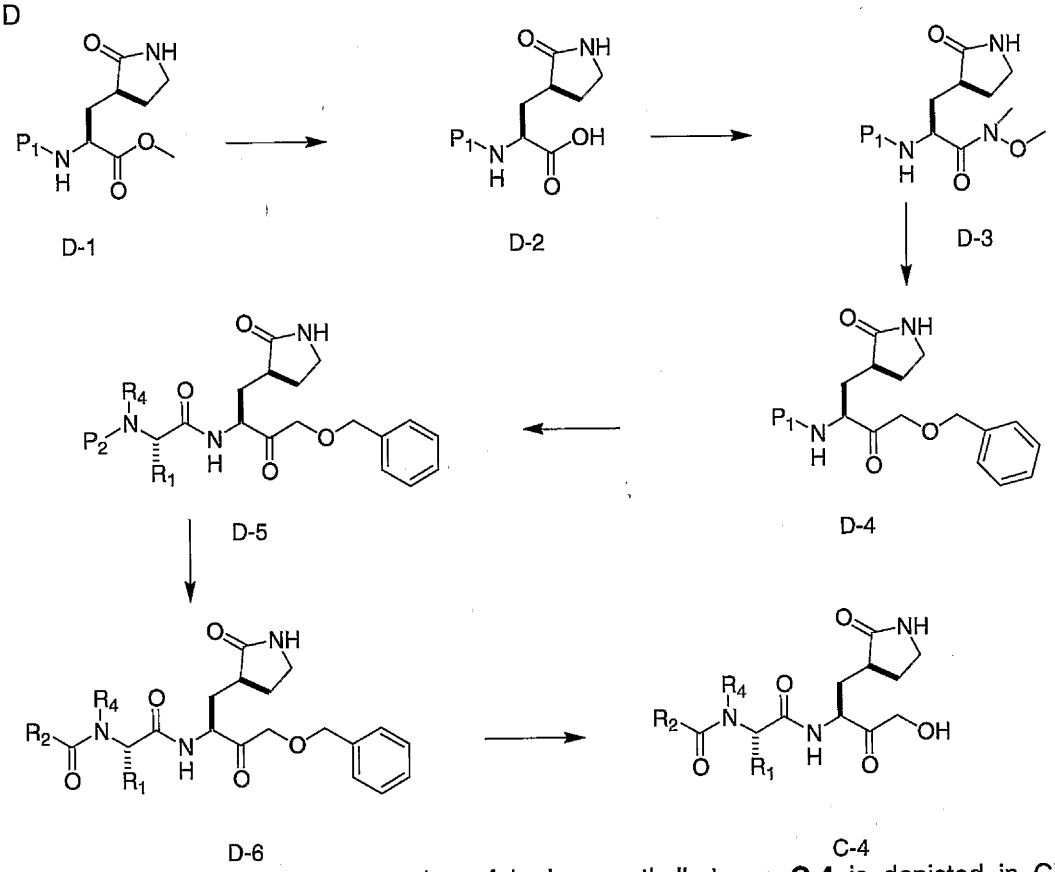
A-5 C-1 C-2

C-5 C-4 C-3

As depicted in Chart C, chloromethylketone **A-5** is reacted with an N-protected amino acid employing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **C-1**. Compound **C-1** is subjected to standard nitrogen de-protecting conditions (such as HCL in a solvent such as dioxane) followed by reaction with a carboxylic acid utilizing standard peptide coupling conditions and/or methods known in the art to provide **C-2**. Compound **C-2** is reacted with benzoylformic acid and an appropriate base (for example cesium fluoride or potassium fluoride) in a suitable solvent (such as DMF) to generate **C-3** (for general procedure see Marquis, R., *et al.*, *Bioorganic & Medicinal Chemistry*, 7, **1999**, 581-588). Compound **C-3** is reacted with methanol and catalytic amounts of an appropriate base (such as potassium carbonate) or alternatively with an aqueous base (for example 1M sodium bicarbonate) in

a suitable solvent such as THF to provide hydroxymethylketone **C-4** (see Mendonca, R., *et al.*, *Bioorganic & Medicinal Chemistry Letters*, 12, **2002**, 2887-2891 or Ellman, J., *et al.*, *Bioorganic & Medicinal Chemistry*, 11, **2003**, 21-29). Compound **C-4** is reacted with an alkylhalide in the presence of a suitable agent (such as silver(I) oxide) and an appropriate solvent (for example DCM, or 1,2-DCE) to afford alkoxymethylketones **C-5**.

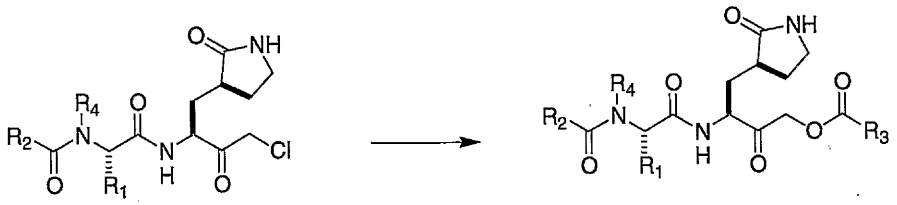
Chart D



An alternative method for the preparation of hydroxymethylketones **C-4** is depicted in Chart D. Compound **D-1** where P1 is an appropriate protecting group for nitrogen (for example Boc, CBZ, Ac), is hydrolyzed under standard conditions known in the art (for example aqueous LiOH and methanol) to the corresponding carboxylic acid **D-2**. Compound **D-2** is converted to the Weinreb amide utilizing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **D-3**. Compound **D-3** is treated with an excess of an organometallic species generated from benzyloxymethyl chloride (see Mendonca, R.V., *et al.*, *Bioorganic & Medicinal Chemistry Letters*, 11, **2002**, 2887-91 for Grignard procedure or Buchanan, J.L., *et al.*, *Tetrahedron Letters*, 40, **1999**, 3985-3988 for organostanane procedure) to provide (benzyloxy)methyl ketone **D-4**. Compound **D-4** is subjected to standard nitrogen de-protecting conditions followed by reaction with a N-protected amino acid employing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **D-5**. Compound **D-5** is subjected to standard nitrogen de-protecting conditions (such as HCl in a solvent such as dioxane) followed by reaction with a carboxylic acid utilizing standard peptide coupling conditions and/or methods known in the art to

provide **D-6**. Compound **D-6** is reacted with a suitable palladium catalyst in the presence of hydrogen (see *Protective Groups in Organic Synthesis*, Greene & Wuts, Wiley-Interscience, New York, 3rd edition, **1999**) to provide hydroxymethylketone **C-4**.

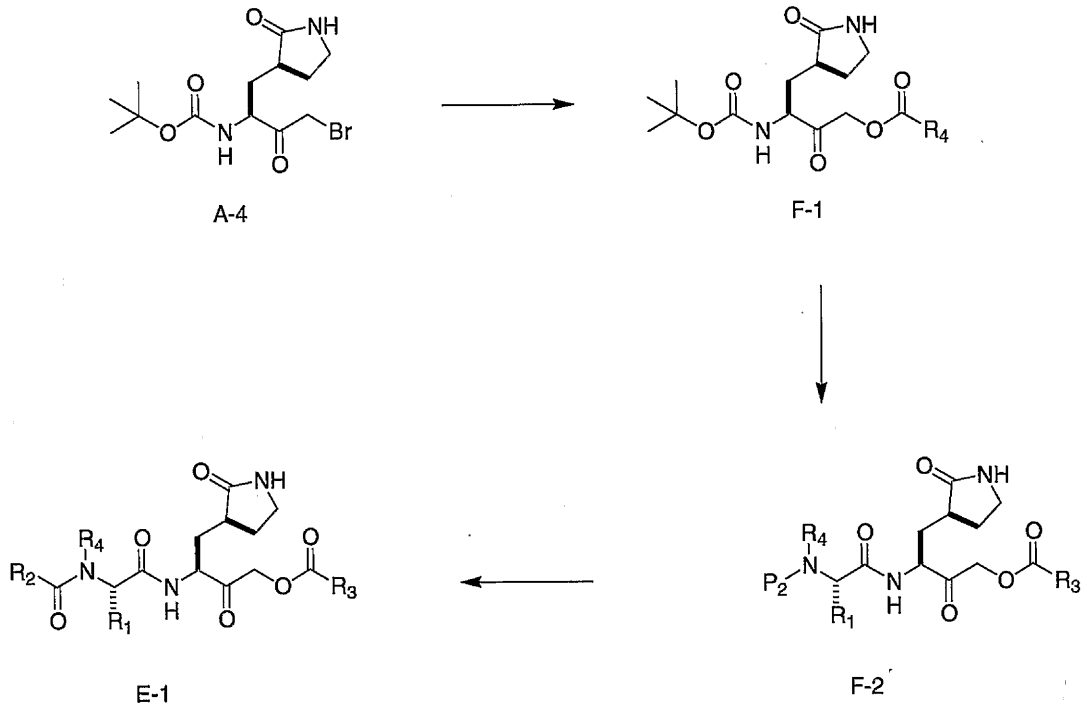
Chart E



C-2 E-1

Chart E depicts the preparation of (acyloxy)methylketones **E-1**. Compound **C-2** is reacted with a carboxylic acid in the presence of a suitable base (such as CsF or KF) and solvent (for example DMF) to produce **E-1** (see Krantz, A., et al., *Biochemistry*, 30, **1991**, 4678-4687).

Chart F

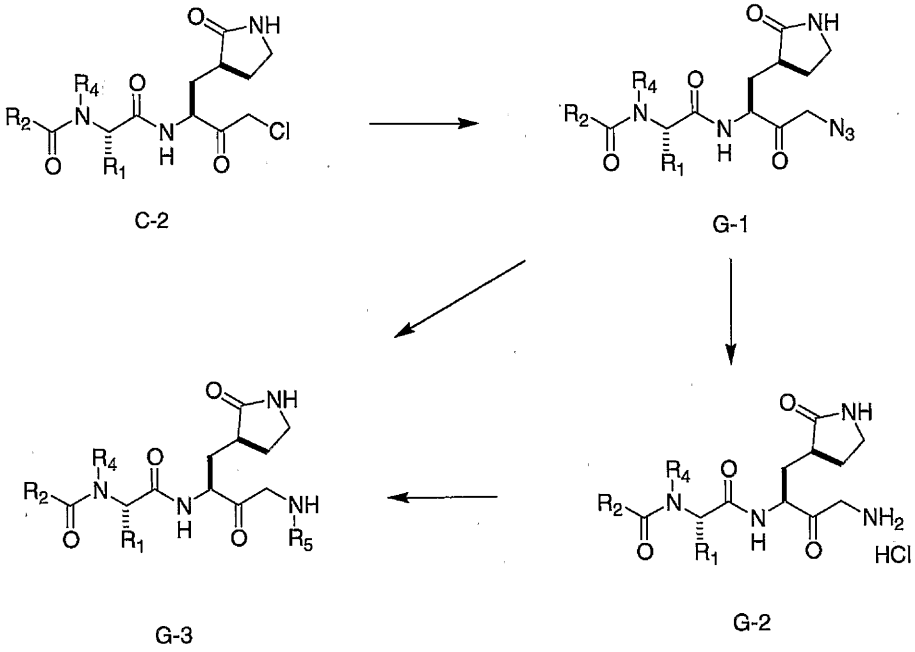


A-4 F-1 F-2 E-1

An alternative method for the preparation of (acyloxy)methylketones **E-1** is depicted in Chart F. **A-4** is reacted with a carboxylic acid in the presence of a suitable base (such as CsF or KF) and solvent (for example DMF) to produce **F-1** (see Krantz, A., et al., *Biochemistry*, 30, **1991**, 4678-4687). Compound **F-1** is subjected to standard nitrogen de-protecting conditions (such as HCl in a solvent such as dioxane) followed by reaction with a N-protected amino acid employing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **F-2**. Compound **F-2** is subjected to standard nitrogen de-

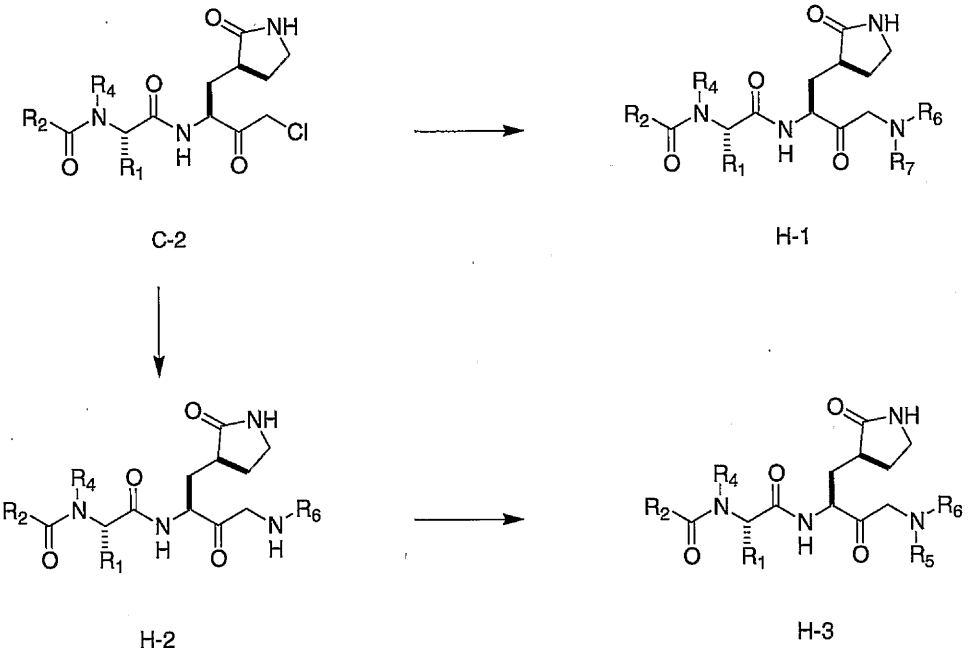
protecting conditions followed by reaction with a carboxylic acid utilizing standard peptide coupling conditions and/or methods known in the art to provide **E-1.**

Chart G



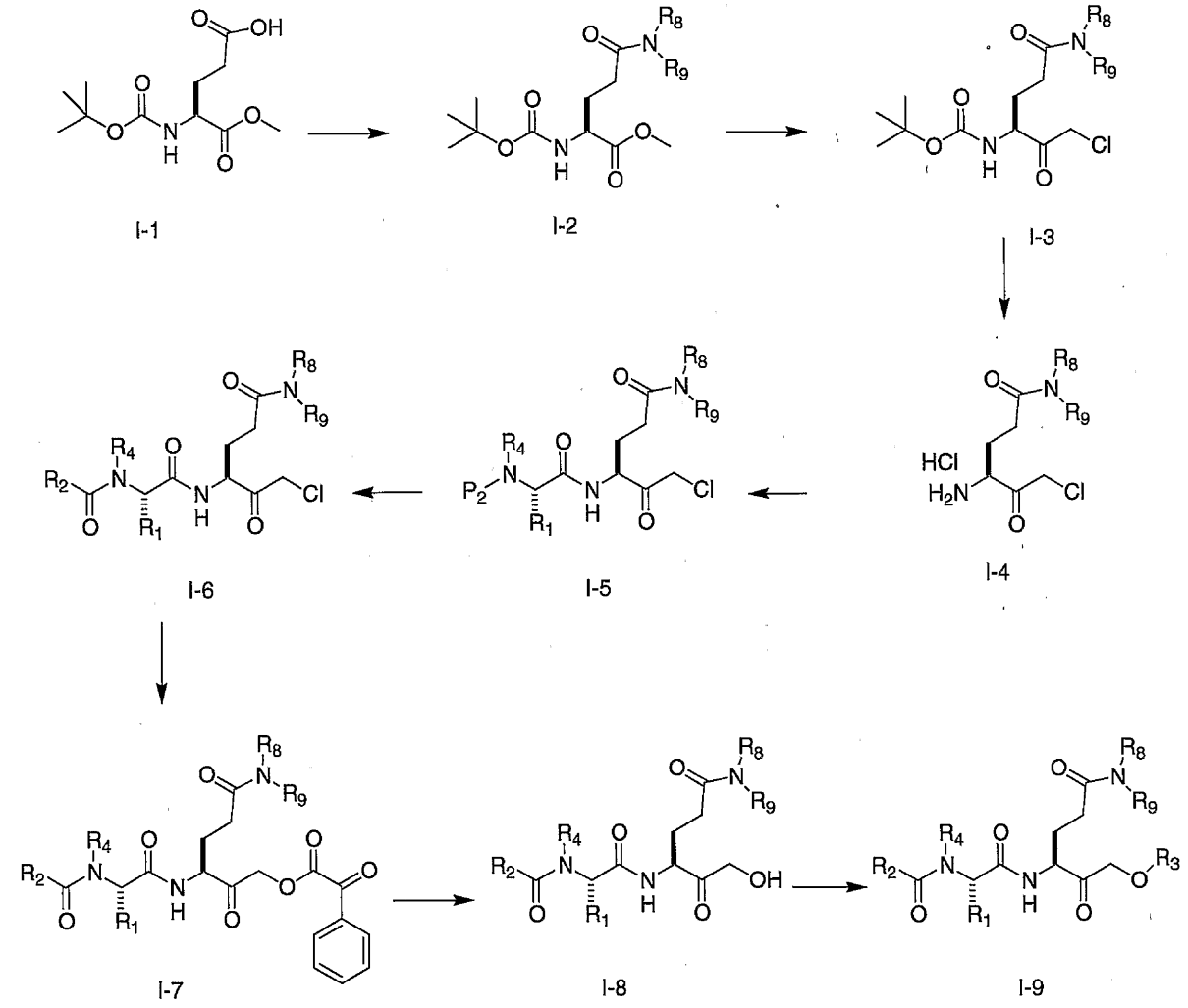
As depicted in Chart G, chloromethylketone **C-2** is converted to the corresponding azidomethylketone **G-1** employing sodium azide in a suitable solvent (see Ellman, J.A., *et al.*, *Bioorganic & Medicinal Chemistry Letters*, 12, **2002**, 2993-2996). Compound **G-1** is reacted with a suitable palladium catalyst in the presence of hydrogen and hydrochloric acid to provide aminomethylketone **G-2** (see DeGraw, J.I., *et al*, *Journal of Medicinal Chemistry*, 33, **1990**, 212-215). Compound **G-2** is reacted with various acid halides, carboxylic acids, sulfonylchlorides, or isocyanates under standard methods and conditions known in the art to afford **G-3.** Alternatively, in certain instances azide **G-1** is reduced in the presence of a suitable reagent (such as acetic acid anhydride) to directly afford **G-3** (see US 4,325,877).

Chart H



Another preparation of aminomethylketones is illustrated in Chart H. Compound **C-2** is reacted with secondary amines in a suitable solvent (such as THF or DMF) to afford tertiary amines **H-1** (see Norbeck, D.W., *et al.*, *Journal of Medicinal Chemistry*, 33, **1990**, 1285-1288). Compound **C-2** is also reacted with primary amines to provide **H-2**. Compound **H-2** is reacted with various acid halides, carboxylic acids, sulfonylchlorides, or isocyanates under standard conditions and methods known in the art (for example see Digenis, G.A., *et al.*, *Journal of Medicinal Chemistry*, 29, **1986**, 1468-1476) to provide **H-3.**

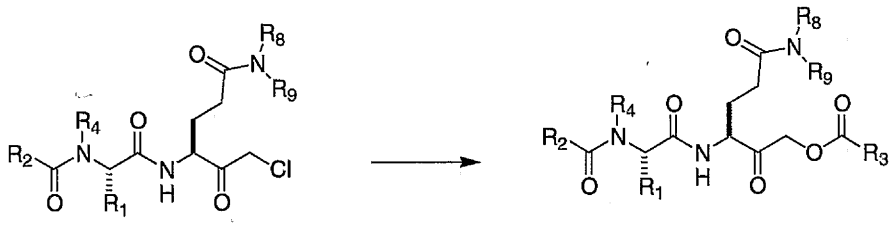
Chart I



As depicted in Chart I, commercially available amino ester **I-1** is reacted with primary and/or secondary amines employing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **I-2**. Compound **I-2** is treated with a species produced by the action of a suitable base (for example n-BuLi or LDA) and chloroiodomethane to generate **I-3** (see Chen, P., *et al.*, *Tetrahedron Letters*, 38, **1997**, 3175-78). Compound **I-3** is subjected to standard N-Boc de-protection procedures to afford **I-4** (see *Protective Groups in Organic Synthesis*, Greene & Wuts, Wiley-Interscience, New York, 3rd edition, **1999**). Compound **I-4** is reacted with a N-protected amino acid utilizing standard peptide coupling conditions and/or methods known in the art to provide **I-5**. Compound **I-5** is subjected to standard nitrogen de-protecting conditions (such as HCl in a solvent such as dioxane) followed by reaction with a carboxylic acid utilizing standard peptide coupling conditions and/or methods known in the art (for example HATU in the presence of a suitable base such as NMM or TEA) to provide **I-6**. Compound **I-6** is reacted with benzoylformic acid and an appropriate base (for example cesium fluoride or potassium fluoride) in a suitable solvent (such as DMF) to generate **I-7** (for general procedure see Marquis, R., *et al.*, *Bioorganic & Medicinal Chemistry*, 7, **1999**, 581-588). Compound **I-7** is reacted

with methanol and catalytic amounts of an appropriate base (such as potassium carbonate) or alternatively with an aqueous base (for example 1M sodium bicarbonate) in a suitable solvent such as THF to provide hydroxymethylketone **I-8** (see Mendonca, R., *et al.*, *Bioorganic & Medicinal Chemistry Letters*, 12, **2002**, 2887-2891 or Ellman, J., *et al.*, *Bioorganic & Medicinal Chemistry*, 11, **2003**, 21-29. Compound **I-8** is reacted with an alkyl halide in the presence of a suitable agent (such as silver(I) oxide) and an appropriate solvent (for example DCM, or 1,2-DCE) to afford alkoxymethylketones **I-9**.

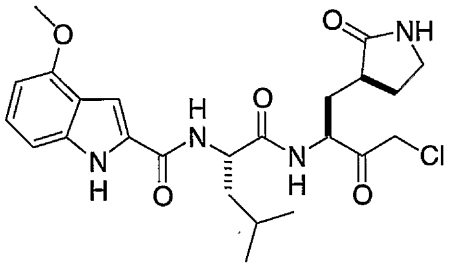
Chart J



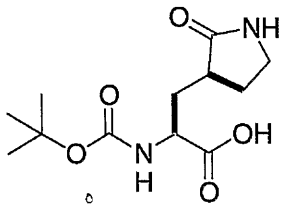
I-6 J-1

Chart J depicts the preparation of (acyloxy)methylketones **J-1**. Compound **I-6** is reacted with a carboxylic acid in the presence of a suitable base (such as CsF or KF) and solvent (for example DMF) to produce **J-1** (see Krantz, A., et al., *Biochemistry*, 30, **1991**, 4678-4687).

Example 1: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



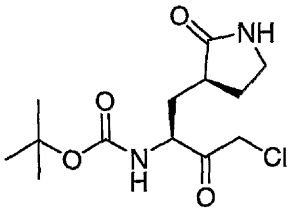
Preparation of Intermediate: *N*-(*tert*-butoxycarbonyl)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-L-alanine



A 3-L multi-neck flask equipped with overhead stirrer and internal thermometer was charged with methyl *N*-(*tert*-butoxycarbonyl)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-L-alaninate (205 g, 716 mmol) followed by

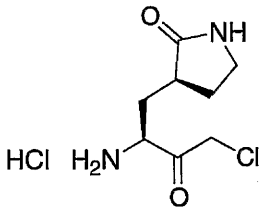
methanol (1 L) and the solution cooled to 0 °C using ice/NaCl bath. NaOH (115 g in 950 mL water, 2.875 mol) solution was pre-cooled to 0 °C then added to the flask *via* pressure-equalizing dropping funnel at such a rate to maintain internal temperature below 5 °C. The resulting solution was stirred at 0 °C for 1 hour before neutralizing with conc. hydrochloric acid (keeping internal temp below 10 °C), then removing the methanol *in vacuo*. The residue was diluted with ethyl acetate (400 mL), acidified to pH 3 with conc. hydrochloric acid, then the mixture transferred to a sep funnel, and the organics removed. The aqueous was extracted with ethyl acetate (2 x 400 mL), and the combined organics washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the title compound as a white foam, 95%. ^{1}H NMR (400 MHz, MeOD) δ 3.98 - 4.28 (1 H, m), 3.25 - 3.41 (2 H, m), 2.44 - 2.57 (1 H, m), 2.29 - 2.41 (1 H, m), 2.03 - 2.14 (1 H, m), 1.73 - 1.90 (2 H, m), 1.44 (9 H, s); MS (APCI-) for $C_{12}H_{20}N_2O_5$ *m/z* 272.3 $(M-H)^-$.

Preparation of Intermediate: *tert*-butyl ((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate



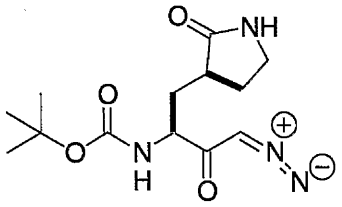
A three-neck flame dried flask equipped with nitrogen inlet and internal thermometer was charged with methyl *N*-(*tert*-butoxycarbonyl)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-L-alaninate (10 g, 35 mmol), THF (200 mL) and chloroiodomethane (10.2 mL, 140 mmol) and the solution cooled to -77 °C. LDA (140 mL, 210 mmol, 1.5M mono-THF complex in cyclohexane) was added via pressure equalizing dropping funnel at such a rate to keep the internal temperature below –70 °C. After complete addition, the reaction was stirred for an additional hour and quenched with a mixture of AcOH (33 mL) and THF (200 mL) with rate of addition regulated to maintain the internal temperature below –65 °C. After complete addition, the dark suspension was stirred for 10 minutes then warmed to ambient temperature. The reaction was diluted with ethyl acetate (500 mL) and the organics were washed with water (250 mL), satd. $NaHCO_3$ (250 mL), brine (250 mL), dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to yield the crude product as a dark oil which was purified by flash chromatography eluting with ethyl acetate. The resulting solid was triturated with diethyl ether to afford the title compound as a pale yellow solid, 5.7 g, 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (1 H, s), 7.75 (1 H, d, *J*=7.6 Hz), 4.73 - 4.94 (2 H, m), 4.37 (1 H, m), 3.28 - 3.43 (2 H, m), 2.46 (1 H, m), 2.30 - 2.40 (1 H, m), 2.02 - 2.14 (1 H, m), 1.77 - 1.95 (2 H, m), 1.60 (9 H, s); MS (API-ES +) for $C_{13}H_{21}N_2O_4Cl$ *m/z* 327.1 $(M+Na)^+$.

Preparation of Intermediate: (3*S*)-3-[(2*S*)-2-amino-4-chloro-3-oxobutyl]pyrrolidin-2-one, hydrochloride salt



A solution of *tert*-butyl ((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate (6.5 g, 21.3 mmol) in dioxane (90 mL) was placed under nitrogen, cooled to 13 °C, and treated with 4M hydrochloric acid/dioxane (90 mL). The reaction mixture was stirred at 10-15 °C for 1 hour. The solvents were removed *in vacuo*, keeping water bath below 30 °C, to yield an orange solid that was azeotroped with dioxane/methanol to afford the title compound as an orange foam, 5.14 g, 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (2 H, s), 7.98 (1 H, s), 4.93 (d, J = 16 Hz, 1 H), 4.80 (d, J = 16 Hz, 1 H), 4.25 - 4.33 (1 H, m), 3.11 - 3.27 (2 H, m), 2.52 - 2.65 (1 H, m), 2.23 - 2.35 (1 H, m), 1.81 - 1.96 (1 H, m), 1.64 - 1.78 (1 H, m).

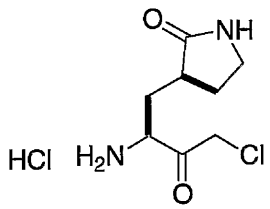
Preparation of Intermediate: *tert*-butyl ((1*S*)-3-diazo-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl) carbamate



A solution of *N*-(*tert*-butoxycarbonyl)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-L-alanine (2.72 g, 10.0 mmol) in THF (100 mL) was placed under an atmosphere of N_2 and cooled to –23 °C. The resulting clear colorless solution was successively treated with triethylamine (2.1 mL, 15.0 mmol) followed by isobutylchloroformate (1.6 mL, 12.0 mmol). The reaction mixture gradually became opaque with a fine white precipitate and after 1 hr was filtered. The colorless filtrate was transferred to a non-ground joint flask, cooled to 0 °C, and slowly treated with a solution of diazomethane (~35 mL, ~16.6 mmol) in diethyl ehter. Note: The diazomethane was generated employing a Diazald kit according to the procedure described in the Aldrich Technical Bulletin AL-180. The resulting yellow clear solution was gradually warmed to RT over 16 hr. At this time, N_2 was bubbled thru the reaction to remove excess diazomethane followed by *in vacuo* concentration. The resulting residue was diluted with ethyl acetate (100 mL), washed once with sat. $NaHCO_3$ (50 mL), once with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude yellow foam. This material was purified by LC (150

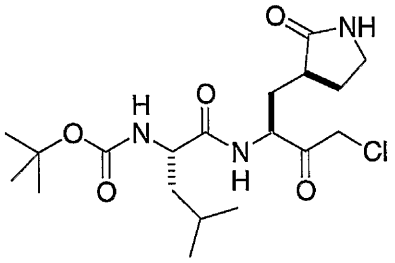
g 230-400 SiO2, 3-4% methanol/chloroform) to afford 2.72 g (92%) of the title compound as a light yellow foam. ^{1}H NMR (DMSO-d_6) δ 7.63 (bs, 1 H), 7.42 (d, J = 8 Hz, 1 H), 6.06 (bs, 1 H), 3.96 (m, 1 H), 3.13 (m, 2 H), 2.21 (m, 1 H), 2.01 (m, 1 H), 1.86 (m, 1 H), 1.63-1.52 (m, 2 H), 1.38 (s, 9 H); MS (ESI+) for $C_{13}H_{20}N_4O_4$ *m/z* 319.0 $(M+Na)^+$.

Alternative Preparation of Intermediate: (3S)-3-[(2S)-2-amino-4-chloro-3-oxobutyl]pyrrolidin-2-one hydrochloride



A solution of *tert*-butyl ((1*S*)-3-diazo-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl) carbamate (592 mg, 2.0 mmol) in 1,4-dioxane (7 mL) was placed under an atmosphere of N_2 and cooled to 0°C. This clear pale yellow solution was drop-wise treated with a solution of 4M hydrochloric acid in 1,4-dioxane (5 mL, 20 mmol) with copious gas evolution observed. Upon complete addition, the reaction was warmed to RT over 1 hr with the formation of white precipitate. The solid was collected by filtration, washed with diethyl ether, and dried to give 401 mg (83%) of the title compound as a white powder. ^{1}H NMR (DMSO-d_6) δ 8.76 (bs, 3 H), 7.96 (s, 1 H), 4.93 (d, J = 16 Hz, 1 H), 4.80 (d, J = 16 Hz, 1 H), 4.28 (m, 1 H), 3.18 (m, 2 H), 2.61 (m, 1 H), 2.30 (m, 1 H), 1.93 (m, 2 H), 1.70 (m, 1 H); MS (ESI+) for $C_8H_{13}ClN_2O_2$ *m/z* 205.0 $(M+H)^+$.

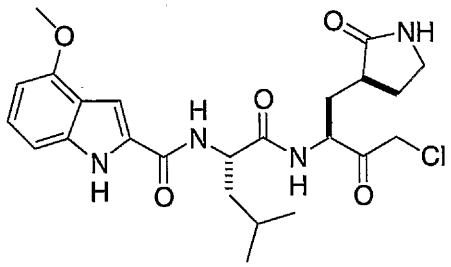
Preparation of Intermediate: N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide



A solution of (3*S*)-3-[(2*S*)-2-amino-4-chloro-3-oxobutyl]pyrrolidin-2-one hydrochloride (391 mg, 1.6 mmol) and Boc-Leu-OH (412 mg, 1.8 mmol) in DMF (9 mL) was placed under an atmosphere of N_2 and cooled to 0°C. This clear pale yellow solution was successively treated with HATU (678 mg, 1.8 mmol) followed by N-methylmorpholine (0.41 mL, 3.7 mmol). The reaction mixture gradually became opaque and after 1hr was quenched with 1:1 ice / sat aqueous $NaHCO_3$ (40 mL) and extracted three

times with ethyl acetate (40 mL). The combined organics were washed once with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow syrup. This material was purified by LC (50 g 230-400 SiO_2, 3-5% methanol/chloroform) to afford 636 mg (40%) of the title compound as a white foam. ^{1}H NMR (DMSO-d_6) δ 8.47 (d, J = 8 Hz, 1 H), 7.64 (s, 1 H), 7.04 (d, J = 8 Hz, 1 H), 4.60 (d, J = 16 Hz, 1 H), 4.53 (d, J = 16 Hz, 1 H), 4.40 (m, 1 H), 3.90 (m, 1 H), 3.16 (m, 1 H), 3.08 (m, 1 H), 2.24 (m, 1 H), 2.10 (m, 1 H), 1.98 (m, 1 H), 1.63 (m, 2 H), 1.45-1.37 (m, 11 H), 0.89 (d, J = 4 Hz, 3H), 0.85 (d, J = 4 Hz, 3H); MS (ESI+) for $C_{19}H_{32}ClN_3O_5$ *m/z* 418.1 $(M+H)^+$. Anal. Calcd for $C_{19}H_{32}ClN_3O_5$ • 0.6 H_2O: C, 53.22; H, 7.81; N, 9.80. Found: C, 53.00; H, 7.65; N, 9.54. HRMS (ESI+) Calcd for $C_{19}H_{32}ClN_3O_5$+H1 418.2103, found 418.2091.

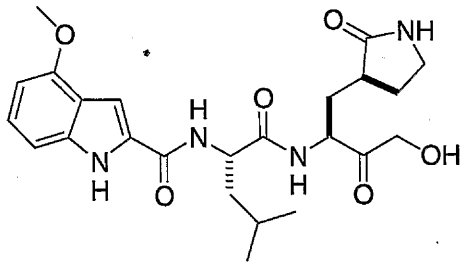
Preparation of Product: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



A solution of N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide (244 mg, 0.59 mmol) in 1,4-dioxane (1.0 mL) was placed under an atmosphere of N_2. This clear colorless solution was treated with a solution of 4M hydrochloric acid in 1,4-dioxane with no observable change. The reaction gradually became opaque with the formation of a gummy precipitate. After 2hr, the volatiles were removed *in vacuo*, diluted with 1:1 ethanol / 1,4-dioxane, concentrated, and high vacuum dried to give N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide hydrochloride as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 9.18 (d, J = 8 Hz, 1 H), 8.40 (bs, 3 H), 7.69 (s, 1 H), 4.68 (s, 2 H), 4.49 (m, 1 H), 3.81 (m, 1 H), 3.15 (m, 2 H), 2.37 (m, 1 H), 2.17 (m, 1 H), 1.92 (m, 1 H), 1.67 (m, 3 H), 1.55 (m, 2 H), .92 (d, J = 4 Hz, 3 H), .88 (d, J = 4 Hz, 3 H); MS (ESI+) for $C_{14}H_{24}ClN_3O_3$ *m/z* 318.1 $(M+H)^+$. A solution of the crude hydrochloride salt and 4-methoxy-1*H*-indole-2-carboxylic acid (123 mg, 0.64 mmol) in DMF (2.5 mL) was placed under an atmosphere of N_2 and cooled to 0 °C. This pale yellow solution was successively treated with HATU (245 mg, 0.64 mmol) and N-methylmorpholine (0.14 mL, 1.29 mmol) turning a brighter color. After 30 min, the reaction was quenched with 1:1 ice / sat $NaHCO_3$ (25 mL) and extracted three times with ethyl acetate (20 mL). The combined organics were washed once with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow syrup. This material was purified by LC (30 g 230-400 SiO_2, 4% methanol/chloroform) to afford 167 mg (58%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.59 (s, 1 H), 8.62 (d, J = 8 Hz, 1 H), 8.44 (d,

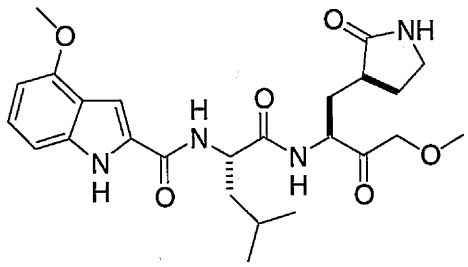
J = 4 Hz, 1 H), 7.65 (s, 1 H), 7.38 (s, 1 H), 7.10 (t, *J* = 8 Hz, 1 H), 7.02 (d, *J* = 8 Hz, 1 H), 6.51 (d, *J* = 8 Hz, 1 H), 4.60 (d, *J* = 16 Hz, 1 H), 4.58 (d, *J* = 16 Hz, 1 H), 4.46 (m, 2 H), 3.89 (s, 3 H), 3.11 (m, 2 H), 2.29 (m, 1 H), 2.11 (m, 1 H), 1.99 (m, 1 H), 1.76-1.54 (m, 5 H), 0.95 (d, *J* = 8 Hz, 3 H), 0.9 (d, *J* = 8 Hz, 3 H); MS (ESI+) for $C_{24}H_{31}ClN_4O_5$ *m/z* 491.1 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{24}H_{31}ClN_4O_5$+H1 491.2056, found 491.2058.

Example 2: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



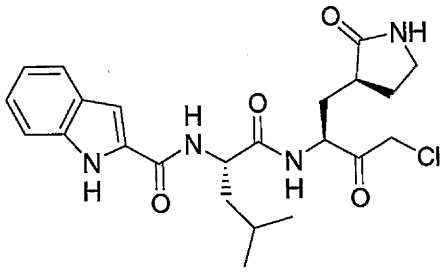
A solution of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (488 mg, 0.99 mmol) and benzoylformic acid (195 mg, 1.3 mmol) in DMF (6.5 mL) was placed under an atmosphere of N_2. This clear pale yellow solution was treated with cesium fluoride (350 mg, 2.3 mmol) followed by heating to 65 °C. After 4 hr, the now yellow suspension was cooled to RT, diluted with ethyl acetate (60 mL), washed three times water (30 mL), once with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to give (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl oxo(phenyl)acetate as a crude yellow foam. MS (ESI+) for $C_{32}H_{36}N_4O_8$ *m/z* 605.2 $(M+H)^+$. A solution of the crude (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl oxo(phenyl)acetate in methanol (40 mL) was placed under an atmosphere of N_2 and treated with potassium carbonate (7 mg, 0.05 mmol) with vigorous stirring. After 1hr the volatiles were removed *in vacuo* (bath < 30 °C) to give a crude yellow glass. This material was purified by Biotage MPLC (25M column, 6% methanol/chloroform) to afford 346 mg (73%) of the title compound as an off-white solid. ^1H NMR (DMSO-d_6) δ 11.56 (s, 1 H), 8.44 (d, *J* = 8 Hz, 1 H), 8.39 (d, *J* = 8 Hz, 1 H), 7.61 (s, 1 H), 7.35 (s, 1 H), 7.08 (t, *J* = 8 Hz, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 6.49 (d, *J* = 8 Hz, 1 H), 5.04 (t, *J* = 8 Hz, 1 H), 4.46 (m, 2 H), 4.25 (dd, *J* = 8, 20 Hz, 1 H), 4.13 (dd, *J* = 8, 20 Hz, 1 H), 3.87 (s, 3 H), 3.10 (m, 2 H), 2.28 (m, 1 H), 2.08 (m, 1 H), 1.92 (m, 1 H), 1.70-1.53 (m, 5 H), 0.93 (d, *J* = 8 Hz, 3 H), 0.89 (d, *J* = 8 Hz, 3 H); MS (ESI+) for $C_{24}H_{32}N_4O_6$ *m/z* 473.2 $(M+H)^+$.

Example 3: 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide



A solution of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (185 mg, 0.39 mmol), iodomethane (0.12 mL, 2.0 mmol), and silver(I) oxide (182 mg, 0.79 mmol) in dichloromethane (12 mL) was placed under an atmosphere of N_2. The resulting black thick suspension was heated to reflux for 18 hours, treated with a second portion of iodomethane (0.12 mL, 2.0 mmol), and returned to reflux for an additional 24 hrs. The reaction was cooled to RT, diluted with dichloromethane (20 mL), washed once with water (20 mL), once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude tan solid. This material was purified by Biotage MPLC (25M column, 3.5-4.5% methanol/chloroform) to afford 19 mg (10%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1 H), 8.48 (d, J = 8 Hz, 1 H), 8.40 (d, J = 8 Hz, 1 H), 7.63 (s, 1 H), 7.35 (s, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 4.47 (m, 1 H), 4.38 (m, 1 H), 4.25 (d, J = 16 Hz, 1 H), 4.11 (d, J = 16 Hz, 1 H), 3.87 (s, 3 H), 3.23 (s, 3 H), 3.08 (m, 2 H), 2.31 (m, 1 H), 2.08 (m, 1 H), 1.92 (m, 1 H), 1.72-1.51 (m, 5 H), 0.93 (d, J = 8 Hz, 3 H), 0.88 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{25}H_{34}N_4O_6$ *m/z* 487.2 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{25}H_{34}N_4O_6$+H1 487.2551, found 487.2563.

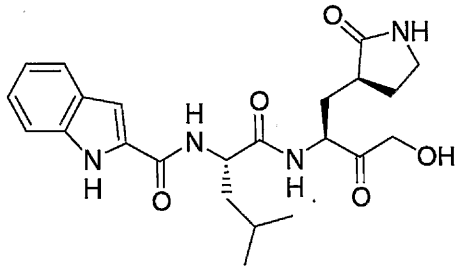
Example 4: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting indole-2-carboxylic acid and making non-critical variations provided a crude orange foam. This material was purified by Biotage flash chromatography, eluting with

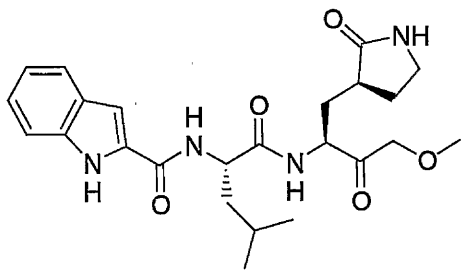
methanol/dichloromethane to afford the title compound as an off-white solid, 1.75 g, 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (1 H, s), 8.64 (1 H, d, *J*=7.8 Hz), 8.50 (1 H, d, *J*=7.8 Hz), 7.55 - 7.69 (2 H, m), 7.42 (1 H, d, *J*=8.3 Hz), 7.26 (1 H, d, *J*=1.5 Hz), 7.16 (1 H, m), 7.02 (1 H, t, *J*=7.5 Hz), 4.53 - 4.66 (2 H, m), 4.39 - 4.52 (2 H, m), 2.94 - 3.18 (2 H, m), 2.22 - 2.35 (1 H, m), 2.03 - 2.16 (1 H, m), 1.89 - 2.02 (1 H, m), 1.45 - 1.82 (5 H, m), 0.93 (d, *J*=6.3 Hz, 3 H), 0.88 (d, *J*=6.3 Hz, 3 H); MS (APCI-) for $C_{23}H_{29}N_4O_4Cl$ *m/z* 459.1 $(M-H)^-$.

Example 5: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide



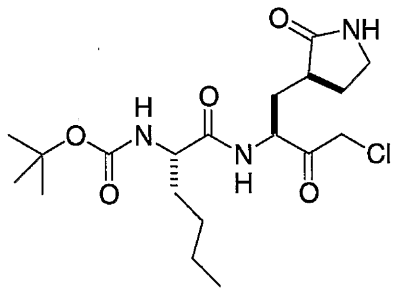
Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide and making non-critical variations provided a crude black gum. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as an off-white solid, 218 mg, 18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (1 H, s), 8.42 - 8.61 (2 H, m), 7.61 (2 H, d, *J*=8.6 Hz), 7.41 (1 H, d, *J*=8.1 Hz), 7.26 (1 H, s), 7.17 (1 H, t, *J*=7.6 Hz), 7.02 (1 H, t, *J*=7.5 Hz), 5.02 (1 H, t), 4.38 - 4.58 (2 H, m), 4.09 - 4.32 (2 H, m), 3.01 - 3.17 (2 H, m), 2.24 - 2.38 (1 H, m), 2.03 - 2.22 (2 H, m), 1.92 (1 H, m), 1.46 - 1.77 (4 H, m), 0.85 - 0.99 (6 H, m); MS (APCI+) for $C_{23}H_{30}N_4O_5$ *m/z* 443.1 $(M+H)^+$.

Example 6: *N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide and making non-critical variations provided a crude pale brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a white foam, 15 mg, 7%. ^{1}H NMR (CDCl3) δ 9.52 (1 H, s), 8.38 (1 H, d, *J*=6.1 Hz), 7.62 (1 H, d, *J*=8.1 Hz), 7.40 (1 H, dd, *J*=8.1, 3.8 Hz), 7.20 - 7.29 (1 H, m), 7.11 (1 H, t, *J*=7.5 Hz), 6.98 (1 H, dd, *J*=11.4, 1.5 Hz), 6.87 (1 H, d, *J*=8.3 Hz), 5.98 (1 H, d, *J*=13.1 Hz), 4.71 - 4.88 (1 H, m), 4.63 (1 H, m), 4.08 - 4.33 (2 H, m), 3.38 - 3.44 (3 H, s), 3.08 - 3.33 (2 H, m), 2.28 - 2.63 (2 H, m), 2.13 - 2.25 (1 H, m), 1.55 - 2.10 (4 H, m), 0.85 - 1.03 (6 H, m); MS (APCI-) for $C_{24}H_{32}N_4O_5$ *m/z* 455.2 $(M-H)^-$.

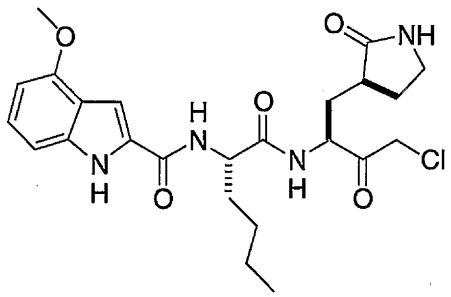
Preparation of Intermediate: *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-norleucinamide



Following the procedure described for the preparation of *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting Boc-NorLeu-OH and making non-critical variations provided a golden syrup. This material was purified by LC (100 g 230-400 SiO_2, 2.5-3.5% methanol/chloroform) to afford 727 mg (42%) of the title compound as a light yellow foam. ^{1}H NMR (DMSO-d_6) δ 8.45 (d, *J* = 8 Hz, 1 H), 7.62 (s, 1 H), 7.00 (d, *J* = 8 Hz, 1 H), 4.59 (d, *J* = 16 Hz, 1 H), 4.53 (d, *J* = 16 foam in 42% isolated yield. ^{1}H Hz, 1 H), 4.38 (m, 1 H), 3.80 (m, 1

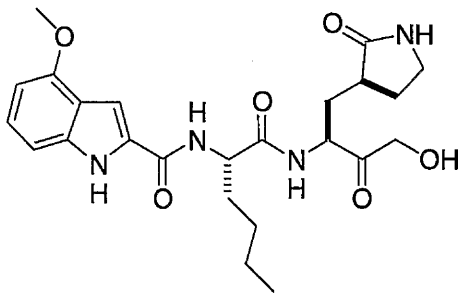
H), 3.15 (m, 1 H), 3.06 (m, 1 H), 2.22 (m, 1 H), 2.07 (m, 1 H), 1.98 (m, 1 H), 1.63-1.51 (m, 4 H), 1.36 (m, 9 H), 1.24 (m, 4H), 0.83 (t, J = 8 Hz, 3 H); MS (ESI+) for $C_{19}H_{32}ClN_3O_5$ *m/z* 418.1 $(M+H)^+$.

Example 7: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}pentyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-norleucinamide and making no other critical variations provided crude yellow foam. This material was purified by Biotage MPLC (25M column, 3% methanol/chloroform) to afford 254 mg (63%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1 H), 8.57 (d, J = 8 Hz, 1 H), 8.39 (d, J = 4 Hz, 1 H), 7.62 (s, 1 H), 7.36 (s, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 4.58 (d, J = 16 Hz, 1 H), 4.56 (d, J = 16 Hz, 1 H), 4.43 (m, 1 H), 4.35 (m, 1H), 3.87 (s, 3 H), 3.09 (m, 2 H), 2.27 (m, 1 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.74-1.54 (m, 4 H), 1.30 (m, 4 H), 0.86 (t, J = 8 Hz, 3 H); MS (ESI+) for $C_{24}H_{31}N_4O_5Cl$ *m/z* 491.1 $(M+H)^+$; Anal. Calcd for $C_{24}H_{31}ClN_4O_5$: C, 58.71; H, 6.36; N, 11.41. Found: C, 58.66; H, 6.45; N, 11.22.

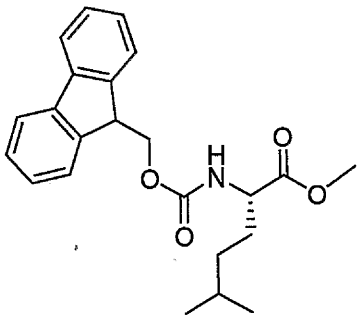
Example 8: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}pentyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide

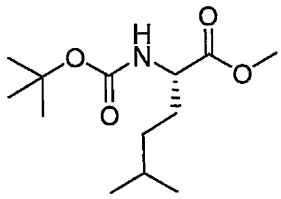
but substituting of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}pentyl)-4-methoxy-1*H*-indole-2-carboxamide and making non critical variations provided a crude yellow foam. This material was purified by Biotage MPLC (25M column, 5-6% methanol/chloroform) to afford 82 mg (35%) of the title compound as a white foam. ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1 H), 8.42 (d, *J* = 8 Hz, 1 H), 8.38 (d, *J* = 8 Hz, 1 H), 7.62 (s, 1 H), 7.35 (s, 1 H), 7.09 (t, *J* = 8 Hz, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 6.49 (d, *J* = 8 Hz, 1 H), 5.06 (t, *J* = 8 Hz, 1 H), 4.44 (m, 2 H), 4.25 (dd, *J* = 8, 20 Hz, 1 H), 4.14 (dd, *J* = 8, 20 Hz, 1 H), 3.87 (s, 3 H), 3.08 (m, 2 H), 2.28 (m, 1 H), 2.10 (m, 1 H), 1.91 (m, 1 H), 1.74-1.54 (m, 4 H), 1.32 (m, 4 H), 0.87 (t, *J* = 8 Hz, 3 H); MS (ESI+) for $C_{24}H_{32}N_4O_6$ *m/z* 473.2 $(M+H)^+$; Anal. Calcd for $C_{24}H_{32}N_4O_6 \cdot 0.6\ H_2O$ & • 0.2 ethyl acetate: C, 59.46; H, 7.01; N, 11.18. Found: C, 53.37; H, 6.94; N, 11.23; HRMS (ESI+) Calcd for $C_{24}H_{32}N_4O_6$+H1 473.2395, found 473.2382.

Preparation of Intermediate: methyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-5-methyl-L-norleucinate



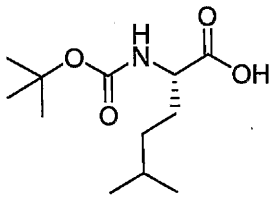
To a solution of *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-5-methyl-L-norleucine (2.14 g, 5.8 mmol) in methanol (15 mL) is added toluene (30 mL) followed by dropwise addition of TMS-diazomethane (2.9 mL, 2M in Hexane, 5.8 mmol). TLC analysis indicated incomplete reaction and TMS-diazomethane was added drop-wise until a yellow color persisted. At this time, the reaction was quenched by the addition of AcOH (1 mL) followed by concentration *in vacuo*. The residue was purified by Biotage flash chromatography, eluting with ethyl acetate/Hexane to afford the title compound as a white solid, 2.18 g, 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2 H, d, *J*=7.6 Hz), 7.60 (2 H, dd, *J*=7.2, 3.9 Hz), 7.40 (2 H, t, *J*=7.2 Hz), 7.31 (2 H, t, *J*=7.5 Hz), 5.26 (1 H, d, *J*=8.6 Hz), 4.31 - 4.51 (3 H, m), 4.23 (1 H, t, *J*=7.1 Hz), 3.75 (3 H, s), 1.78 - 1.93 (1 H, m), 1.60 - 1.76 (1 H, m), 1.45 - 1.60 (1 H, m), 1.05 - 1.34 (2 H, m), 0.88 (d, *J* = 4 Hz, 3 H), 0.86 (d, *J* = 4 Hz, 3 H); MS (APCI+) for $C_{23}H_{27}NO_4$ *m/z* 160.1 $(M-Fmoc+H)^+$.

Preparation of Intermediate: methyl *N*-(*tert*-butoxycarbonyl)-5-methyl-L-norleucinate



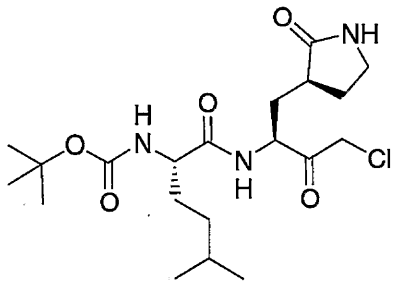
To a solution of methyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-5-methyl-L-norleucinate (2.18 g, 5.72 mmol) in DMF (50 mL) was added KF (2.33 g, 40.04 mmol) followed by triethylamine (1.70 mL, 12.24 mmol) and di-*tert*-butyl dicarbonate (7.39 mmol) and the mixture stirred at ambient temperature. After 4 hours, TLC analysis indicated incomplete reaction and the reaction mixture was treated with a second portion of KF (2.7g, 46.55 mmol) and BOC_2O (800 mg, 3.67 mmol). After 16 hours, the mixture was diluted with diethyl ether (300 mL), washed with satd. $NaHCO_3$ (2 x 50 mL), 1M hydrochloric acid (2 x 50 mL), $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and the solvents evaporated *in vacuo* to yield the crude product, which was purified by Biotage flash chromatography eluting with dichloromethane/hexane to afford the title compound as a clear oil, 980 mg, 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (1 H, d, *J*=6.8 Hz), 4.21 - 4.32 (1 H, m), 3.72 (3 H, s), 1.72 - 1.85 (1 H, m), 1.46 - 1.66 (2 H, m), 1.43 (9 H, s), 1.11 - 1.29 (2 H, m), 0.88 (d, *J* = 4 Hz, 3 H), 0.86 (d, *J* = 4 Hz, 3 H); MS (API-ES+) for $C_{13}H_{25}NO_4$ *m/z* 282.2 $(M+Na)^+$.

Preparation of Intermediate: *N*-(*tert*-butoxycarbonyl)-5-methyl-L-norleucine



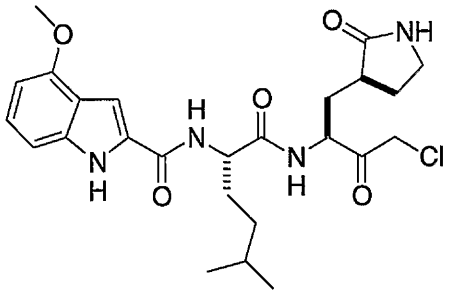
To a solution of methyl *N*-(*tert*-butoxycarbonyl)-5-methyl-L-norleucinate (980 mg, 3.78 mmol) in THF (30 mL) at 0 °C was added a solution (pre-cooled to 5 °C) of LiOH (1M, 11.3 mL, 11.33 mmol) and the resulting mixture stirred at 0 °C for 1 hour, then allowed to warm to ambient temperature. The reaction was acidified to *p*H 2 with 1M hydrochloric acid and extracted with ethyl acetate (3 x 60mL). The combined organics were washed with brine (100 mL) dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield the title compound as a clear oil, 990 mg, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (1 H, d, *J*=7.8 Hz), 4.23 - 4.34 (1 H, m), 1.75 - 1.93 (2 H, m), 1.60 - 1.72 (1 H, m), 1.50 - 1.59 (1 H, m), 1.44 (9 H, s), 1.19 - 1.30 (1 H, m), 0.88 (d, *J* = 4 Hz, 3 H), 0.86 (d, *J* = 4 Hz, 3 H); MS (API-ES+) for $C_{12}H_{23}NO_4$ *m/z* 268.1 $(M+Na)^+$.

Preparation of Intermediate: N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-5-methyl-L-norleucinamide



Following the procedure described for the preparation of N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting *N*-(*tert*-butoxycarbonyl)-5-methyl-L-norleucine and making non-critical variations provided a crude golden oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as an off-white solid, 360 mg, 41%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (1 H, d, *J*=8.1 Hz), 7.62 (1 H, s), 7.02 (1 H, d, *J*=7.1 Hz), 4.49 - 4.62 (2 H, m), 4.33 - 4.44 (1 H, m), 3.78 (1 H, m), 3.15 (1 H, t, *J*=8.7 Hz), 3.00 - 3.10 (1 H, m), 2.18 - 2.30 (1 H, m), 2.04 - 2.14 (1 H, m), 1.92 - 2.02 (1 H, m), 1.40 - 1.68 (5 H, m), 1.36 (9 H, s), 1.05 - 1.25 (2 H, m, *J*=7.3 Hz), 0.83 (3 H, d, *J*=1.52 Hz), 0.82 (3 H, d, *J*=1.52 Hz); MS (API-ES+) for $C_{20}H_{34}N_3O_5Cl$ *m/z* 454.2 $(M+Na)^+$.

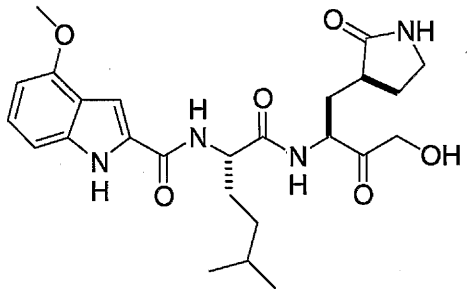
Example 9: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-5-methyl-L-norleucinamide and making no other critical variations provided a crude yellow foam. This material was purified by Biotage MPLC (25M column, 2.5-3.5% methanol/chloroform) to afford 307 mg (73%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1 H), 8.59 (d, *J* = 8 Hz, 1 H), 8.41 (d, *J* = 4 Hz, 1 H), 7.64 (s, 1 H), 7.37 (s, 1 H), 7.09 (t, *J* = 8 Hz, 1 H), 7.00 (d, *J* = 8 Hz, 1 H), 6.49 (d, *J* = 8 Hz, 1 H), 4.59 (s, 2 H), 4.44 (m, 1 H), 4.35 (m, 1H), 3.87 (s, 3 H), 3.08 (m, 2 H), 2.26 (m, 1 H), 2.07 (m, 1 H), 1.98 (m, 1 H), 1.70-1.51 (m, 5

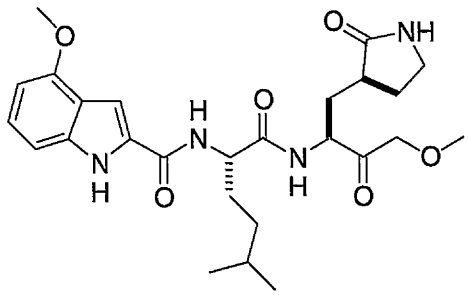
H), 1.25 (m, 2 H), 0.88 (d, J = 4 Hz, 3 H), 0.86 (d, J = 4 Hz, 3 H); MS (ESI+) for $C_{25}H_{33}ClN_4O_5$ *m/z* 505.2 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{25}H_{33}ClN_4O_5$+H1 505.2212, found 505.2204.

Example 10: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide and making non critical variations provided a crude yellow foam. This material was purified by Biotage MPLC (25M column, 5-5.5% methanol/chloroform) to afford 135 mg (50%) of the title compound as a white foam. ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1 H), 8.42 (d, J = 8 Hz, 1 H), 8.38 (d, J = 8 Hz, 1 H), 7.62 (s, 1 H), 7.35 (s, 1 H), 7.09 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 5.06 (t, J = 8 Hz, 1 H), 4.47-4.30 (m, 2 H), 4.25 (dd, J = 8, 20 Hz, 1 H), 4.14 (dd, J = 8, 20 Hz, 1 H), 3.87 (s, 3 H), 3.09 (m, 2 H), 2.30 (m, 1 H), 2.08 (m, 1 H), 1.92 (m, 1 H), 1.72-1.51 (m, 5 H), 1.25 (m, 2 H), 0.87 (d, J = 4 Hz, 3 H), 0.86 (d, J = 4 Hz, 3 H); MS (ESI+) for $C_{25}H_{34}N_4O_6$ *m/z* 487.1 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{25}H_{34}N_4O_6$ 487.2551, found 487.2541.

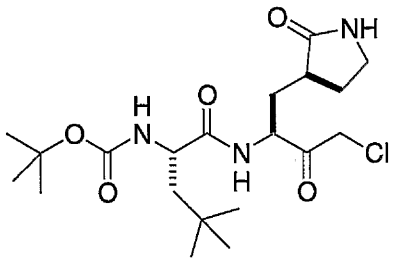
Example 11: 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-carboxamide



A solution of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide (112 mg, 0.23 mmol), iodomethane (0.29 mL, 4.6 mmol), and silver(I) oxide (107 mg, 0.46 mmol) in dichloroethane

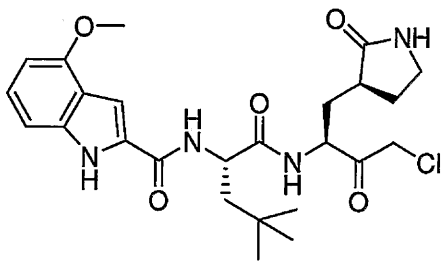
(7.5 mL) was placed under an atmosphere of N_2. The resulting thick black suspension was heated to 85 °C for 15 minutes *via* microwave. The reaction was cooled to RT, diluted with dichloromethane (20 mL), washed once with water (20 mL), once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude tan solid. This material was purified by Biotage MPLC (25M column, 3-5% methanol/chloroform) to afford 23 mg (20%) of the title compounds as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1 H), 8.47 (d, J = 8 Hz, 1 H), 8.38 (d, J = 8 Hz, 1 H), 7.62 (s, 1 H), 7.36 (s, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 4.38 (m, 2 H), 4.26 (d, J = 16 Hz, 1 H), 4.13 (d, J = 16 Hz, 1 H), 3.87 (s, 3 H), 3.23 (s, 3 H), 3.06 (m, 2 H), 2.27 (m, 1 H), 2.09 (m, 1 H), 1.89 (m, 1 H), 1.68-1.50 (m, 5 H), 1.22 (m, 2H), 0.93 (d, J = 4 Hz, 3 H), 0.92(d, J = 4 Hz, 6 H); MS (ESI+) for $C_{26}H_{36}N_4O_6$ *m/z* 501.2 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{26}H_{36}N_4O_6$ 501.2708, found 501.2703.

Preparation of Intermediate: *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-L-leucinamide



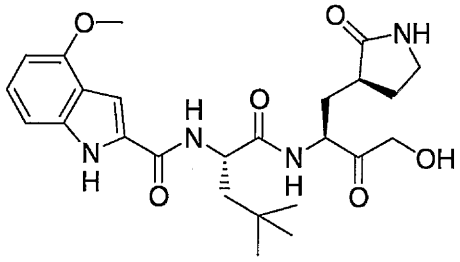
Following the procedure described for the preparation of *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting Boc-(beta t-butyl)-Ala-OH and making non-critical variations provided a golden syrup. This material was purified by Biotage MPLC (65i column, 2.5-3.5% methanol/chloroform) to afford 3.41g (40%) of the title compound as a white foam. ^{1}H NMR (DMSO-d_6) δ 8.39 (d, J = 8 Hz, 1 H), 7.64 (s, 1 H), 7.00 (d, J = 8 Hz, 1 H), 4.58 (d, J = 16 Hz, 1 H), 4.52 (d, J = 16 Hz, 1 H), 4.38 (m, 1 H), 3.92 (m, 1 H), 3.15 (t, J = 8 Hz, 1 H), 3.07 (q, J = 8 Hz, 1 H), 2.22 (m, 1 H), 2.09 (m, 1 H), 1.97 (m, 1 H), 1.62 (m, 2 H), 1.50 (m, 2 H), 1.36 (s, 9H), 0.88 (s, 9H); MS (ESI+) for $C_{20}H_{34}ClN_3O_6$ *m/z* 432.1 $(M+H)^+$.

Example 12: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-L-leucinamide and making non critical variations provided a pale yellow solid. This material was purified by Biotage MPLC (40M column, 2-4.5% methanol/chloroform) to afford 920 g (60%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (d, *J*=1.8 Hz, 1 H), 8.54 (d, *J*=7.8 Hz, 1 H), 8.45 (d, *J*=8.1 Hz, 1 H), 7.64 (s, 1 H), 7.32 (d, *J*=1.8 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 7.00 (d, *J*=8.3 Hz, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.52 - 4.62 (m, 1 H), 4.40 - 4.51 (m, 2 H), 3.87 (s, 3 H), 3.01 - 3.16 (m, 2 H), 2.19 - 2.31 (m, 1 H), 2.03 - 2.12 (m, 1 H), 1.91 - 2.01 (m, 1 H), 1.81 (dd, *J*=14.1, 9.9 Hz, 1 H), 1.54 - 1.72 (m, 3 H), 0.93 (s, 9 H); MS (ESI+) for $C_{25}H_{33}ClN_4O_5$ *m/z* 505.1 $(M+H)^+$; HRMS (ESI+) Calcd for $(M+H)^+$ 505.2212, found 505.2204.

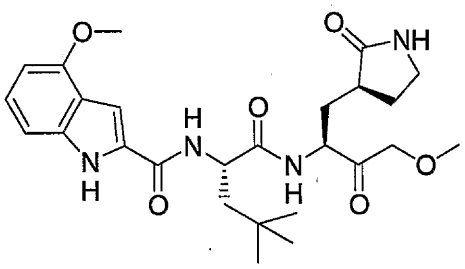
Example 13: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide and making non critical variations provided a crude brown glass. This material was purified by Biotage MPLC (40M column, 2-10% methanol/chloroform) to afford 415 mg (53%) of the title compound as a white solid. MS (ESI+) for $C_{25}H_{34}N_4O_6$ *m/z* 487.2 $(M+H)^+$. Alternatively, following the procedure described

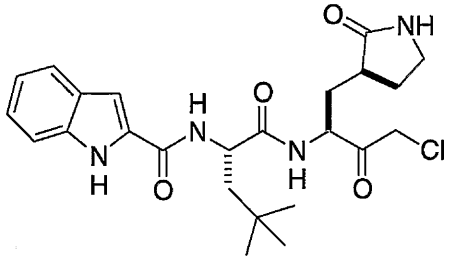
for the preparation of *N*-{(1*S*)-1-(cyclohexylmethyl)-2-[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-2-oxoethyl}-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide and making non critical variations provided a tan solid. This material was purified by Biotage MPLC (25M column, 6-7% methanol/chloroform) to afford 100 mg (77%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1 H), 8.42 (d, J = 8 Hz, 1 H), 8.37 (d, J = 8 Hz, 1 H), 7.62 (s, 1 H), 7.32 (s, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 5.04 (t, J = 8 Hz, 1 H), 4.52 (m, 1 H), 4.42 (m, 1H), 4.24 (dd, J = 8, 20 Hz, 1 H), 4.12 (dd, J = 8, 20 Hz, 1 H), 3.87 (s, 3 H), 3.09 (m, 2 H), 2.25 (m, 1 H), 2.06 (m, 1 H), 1.93 (m, 1 H), 1.80 (dd, J = 8, 16 Hz, 1 H), 0.93 (s, 9 H); MS (ESI+) for $C_{25}H_{34}N_4O_6$ *m/z* 487.2 $(M+H)^+$; Anal. Calcd for $C_{25}H_{34}N_4O_6 \cdot 0.3\,H_2O$: C, 61.03; H, 7.09; N, 11.39. Found: C, 61.07; H, 7.09; N, 11.22; HRMS (ESI+) Calcd for $C_{25}H_{34}N_4O_6$ 487.2551, found 487.2541.

Example 14: 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide



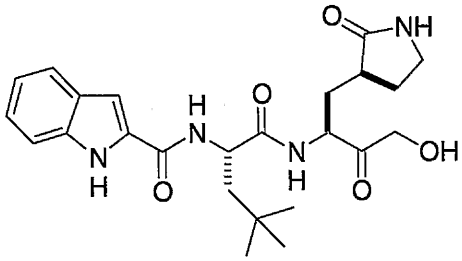
Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide and making non critical variations provided a crude product. This material was purified by Biotage MPLC (40S column, 2-5% methanol/chloroform) to afford 21 mg (9%) of the title compound as a pale tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1 H), 8.42 (d, J=6.8 Hz, 1 H), 7.62 (s, 1 H), 7.32 (s, 1 H), 7.08 (t, J=7.7 Hz, 1 H), 7.00 (d, J=7.8 Hz, 1 H), 6.49 (d, J=7.3 Hz, 1 H), 4.49 - 4.55 (m, 1 H), 4.32 - 4.41 (m, 1 H), 4.21 - 4.30 (m, 1 H), 4.12 (t, J=16.9 Hz, 1 H), 3.87 (s, 3 H), 3.23 (s, 3 H), 3.01 - 3.16 (m, 2 H), 2.20 - 2.32 (m, 1 H), 2.03 - 2.15 (m, 1 H), 1.87 - 1.98 (m, 1 H), 1.73 - 1.85 (m, 1 H), 1.54 - 1.70 (m, 3 H), 0.93 (s, 9 H); MS (ESI+) for $C_{26}H_{36}N_4O_6$ *m/z* 501.2 $(M+H)^+$; HRMS (ESI+) Calcd for $(M+H)^+$ 501.2708, found 501.2701.

Example 15: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-L-leucinamide and indole-2-carboxylic acid and making no other critical variations provided a crude yellow foam. This material was purified by Biotage MPLC (40M column, 2.5-3.5% methanol/chloroform) to afford 1.06 g (62%) of the title compound as a light yellow foam. ^{1}H NMR (DMSO-d_6) δ 11.59 (s, 1 H), 8.58 (d, J = 8 Hz, 1 H), 8.50 (d, J = 8 Hz, 1 H), 7.64 (s, 1 H), 7.61 (d, J = 8 Hz, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.23 (s, 1H), 7.17 (t, J = 8 Hz, 1 H), 7.02 (t, J = 8 Hz, 1 H), 4.62-4.50 (m, 3 H), 4.45 (m, 1 H), 3.10 (m, 2 H), 2.25 (m, 1 H), 2.08 (m, 1 H), 1.96 (m, 1 H), 1.80 (m, 1H), 1.72-1.58 (m, 3 H), 0.94 (s, 9H); MS (ESI+) for $C_{24}H_{31}ClN_4O_4$ *m/z* 475.1 $(M+H)^+$; Anal. Calcd for $C_{24}H_{31}ClN_4O_4 \cdot 0.35\ CHCl_3$: C, 56.59; H, 6.12; N, 10.84. Found: C, 56.38; H, 6.18; N, 10.75; HRMS (ESI+) Calcd for $C_{24}H_{31}ClN_4O_4$ 475.2107, found 475.2122.

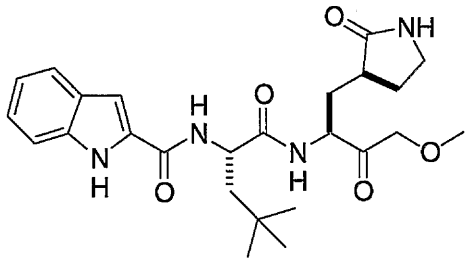
Example 16: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide and making non critical variations provided a crude yellow foam. This material was purified by Biotage MPLC (40M column, 4.5-5.5% methanol/chloroform) to afford 730 mg (72%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.59 (s, 1 H), 8.49 (d, J = 8 Hz, 1 H), 8.43 (d, J = 8 Hz, 1 H), 7.62 (s, 1 H), 7.60 (s, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.23 (s, 1H), 7.17 (t, J = 8 Hz, 1 H), 7.02 (t, J = 8 Hz, 1 H), 5.05 (t, J =

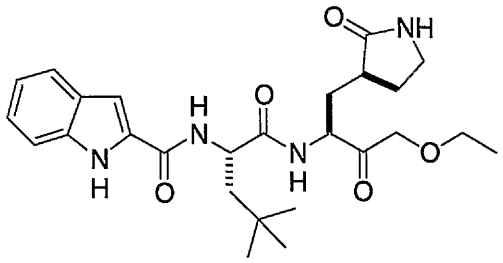
8 Hz, 1 H), 4.56 (m, 1 H), 4.43 (m, 1H), 4.25 (dd, *J* = 8, 20 Hz, 1 H), 4.13 (dd, *J* = 8, 20 Hz, 1 H), 3.10 (m, 2 H), 2.25 (m, 1 H), 2.07 (m, 1 H), 1.93 (m, 1 H), 1.80 (m, 1H), 1.64 (m, 3 H), 0.94 (s, 9H); MS (ESI+) for $C_{24}H_{32}N_4O_5$ *m/z* 457.1 $(M+H)^+$; Anal. Calcd for $C_{24}H_{32}N_4O_5 \bullet 0.2\ CHCl_3 \bullet 0.2$ ethyl acetate • 0.25 H_2O: C, 59.75; H, 6.88; N, 11.15. Found: C, 59.67; H, 6.72; N, 11.03; HRMS (ESI+) Calcd for $C_{24}H_{32}N_4O_5$ 457.2446, found 457.2439.

Example 17: *N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide



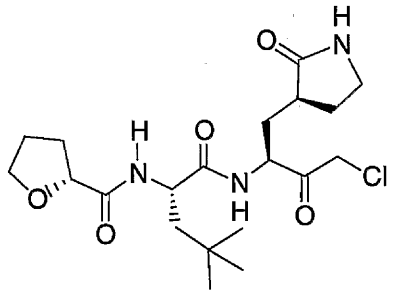
Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide and making non critical variations provided a crude tan foam. This material was purified by Biotage MPLC (25M column, 3.5-4.5% methanol/chloroform) to afford 43 mg (15%) of the title compound as a white solid. ^1H NMR (DMSO-d_6) δ 11.58 (s, 1 H), 8.48 (apar t, *J* = 8 Hz, 2 H), 7.61 (apar d, *J* = 8 Hz, 2 H), 7.41 (d, *J* = 8 Hz, 1 H), 7.23 (s, 1H), 7.17 (t, *J* = 8 Hz, 1 H), 7.02 (t, *J* = 8 Hz, 1 H), 4.55 (m, 1 H), 4.37 (m, 1H), 4.25 (d, *J* = 20 Hz, 1 H), 4.10 (d, *J* = 20 Hz, 1 H), 3.23 (s, 3 H), 3.06 (m, 2H), 2.27 (m, 1 H), 2.07 (m, 1 H), 1.91 (m, 1 H), 1.79 (m, 1H), 1.69 (m, 3 H), 0.94 (s, 9H); MS (ESI+) for $C_{25}H_{34}N_4O_5$ *m/z* 471.2 $(M+H)^+$; Anal. Calcd for $C_{25}H_{34}N_4O_5 \bullet 0.2$ ethyl acetate • 0.75 H_2O: C, 61.76; H, 7.46; N, 11.17. Found: C, 61.85; H, 7.15; N, 11.02; HRMS (ESI+) Calcd for $C_{25}H_{34}N_4O_5$ 471.2602, found 471.2595.

Example 18: *N*-((1*S*)-1-{[((1*S*)-3-ethoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide



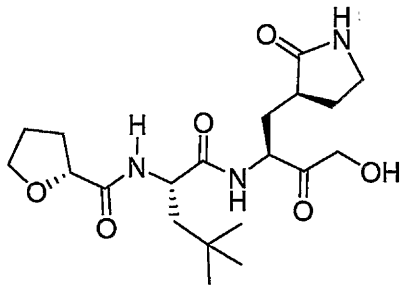
Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide but substituting iodoethane and making non critical variations provided a crude tan foam. This material was purified by Biotage MPLC (25M column, 3-5% methanol/chloroform) to afford 19 mg (6%) of the title compound as an off- white solid. ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1 H), 8.48 (d, J = 8 Hz, 1 H), 8.45 (d, J = 8 Hz, 1 H), 7.61 (apar d, J = 8 Hz, 2 H), 7.41 (d, J = 8 Hz, 1 H), 7.23 (s, 1H), 7.17 (t, J = 8 Hz, 1 H), 7.02 (t, J = 8 Hz, 1 H), 4.56 (m, 1 H), 4.40 (m, 1H), 4.28 (d, J = 16 Hz, 1 H), 4.13 (d, J = 16 Hz, 1 H), 3.41 (m, 2 H), 3.06 (m, 2H), 2.26 (m, 1 H), 2.09 (m, 1 H), 1.91 (m, 1 H), 1.82 (m, 1H), 1.63 (m, 3 H), 1.08 (t, J = 8 Hz, 3 H), 0.94 (s, 9H); MS (ESI+) for $C_{26}H_{36}N_4O_5$ *m/z* 485.2 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{26}H_{36}N_4O_5$ 485.2759, found 485.2756.

Example 19: *N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-*N*^{2}-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide



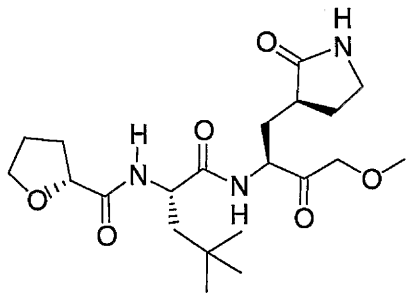
Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-L-leucinamide and (2*R*)-tetrahydrofuran-2-carboxylic acid and making non-critical variations provided a crude product. This crude material was purified by Biotage MPLC (40 M cartridge, chloroform mobile phase with 2% methanol followed by 3% methanol, sample loaded in chloroform) resulting in the isolation of 1.13 g (61%) of the title compound as a light yellow foam. R_f = 0.27 (95:5 dichloromethane-methanol); ^{1}H NMR (400 MHz, DMSO-D6) δ 8.47 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.68 (s, 1H), 4.55 (s, 2H), 4.44 - 4.36 (m, 1H), 4.35 - 4.27 (m, 1H), 4.21 (dd, J = 8, 5 Hz, 1H), 3.95 - 3.86 (m, 1H), 3.79 - 3.71 (m, 1H), 3.18 - 3.07 (m, 2H), 2.21 (td, J = 9, 4 Hz, 1H), 2.13 - 2.03 (m, 2H), 1.97 - 1.88 (m, 1H), 1.85 - 1.74 (m, 3H), 1.68 - 1.56 (m, 4H), 0.88 (s, 9H); MS (ESI+) for $C_{20}H_{32}ClN_3O_5$ *m/z* 430 (M+H).

Example 20: N^1-((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide and making non critical variations provided a crude product. This material was purified by a series of two radial chromatographies (1st - 2mm plate, 90:10 dichloromethane-methanol to 90:20, sample loaded in 90:10)(2nd -1 mm plates, 90:10 dichloromethane-methanol to 95:5, sample loaded in dichloromethane) to provide 0.402 g (46%) of the title compound as a light yellow foam. R_f = 0.44 (90:10 dichloromethane – methanol); ^{1}H NMR (400 MHz, DMSO-D6) δ 8.27 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 9 Hz, 1H), 7.65 (s, 1H), 5.11 (t, *J* = 6 Hz, 1H), 4.46 - 4.38 (m, 1H), 4.37 - 4.30 (m, 1H), 4.24 – 4.15 (m, 2H), 4.14 – 4.08 (m, 1H), 3.96 – 3.87 (m, 1H), 3.79 – 3.70 (m, 1H), 3.18 - 3.06 (m, 2H), 2.25 - 2.16 (m, 1H), 2.13 - 2.02 (m, 2H), 1.87 - 1.75 (m, 4H), 1.66 - 1.54 (m, 4H), 0.88 (s, 9H); MS (ESI+) for $C_{20}H_{33}N_3O_6$ *m/z* 412 (M+H). Anal. Calcd for $C_{20}H_{33}N_3O_6 \cdot 0.5H_2O$: C, 57.12; H, 8.16; N, 9.99. Found: C, 57.25; H, 7.93; N, 9.68. HRMS (ESI+) Calcd for $C_{20}H_{33}N_3O_6$+H 412.2442, found 412.2447.

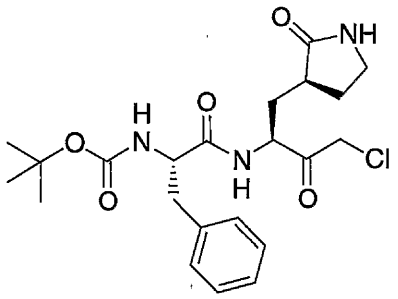
Example 21: N^1-((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide



Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-

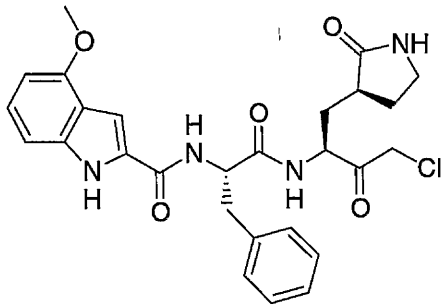
carboxamide but substituting N^1-((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide and making non critical variations provided a crude product. This material was purified by radial chromatography (1 mm plate, 95:5 dichloromethane-methanol, sample loaded in dichloromethane) resulting in the isolation of 45.6 mg (22%) of the title compound as a light orange gum and as a mixture of diastereomers. R_f = 0.30 (95:5 dichloromethane – methanol); ^{1}H NMR (400 MHz, DMSO-D6, major diastereomer) δ 8.33 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 9 Hz, 1H), 7.66 (s, 1H), 4.39 - 4.28 (m, 2H), 4.24 - 4.07 (m, 3H), 3.94 - 3.86 (m, 1H), 3.75 (q, *J* = 7 Hz, 1H), 3.24 (s, 3H), 3.18 - 3.06 (m, 2 H), 2.27 - 2.15 (m, 1H), 2.14 - 2.03 (m, 2H), 1.92 - 1.73 (m, 4 H), 1.67 - 1.53 (m, 4 H), 0.88 (s, 9H); MS (ESI+) for $C_{21}H_{35}N_3O_6$ *m/z* 426 (M+H). HRMS (ESI+) Calcd for $C_{21}H_{35}N_3O_6$+H1 426.2599, found 426.2604.

Preparation of Intermediate: *N*-(*tert*-butoxycarbonyl)-*N*-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-phenylalaninamide



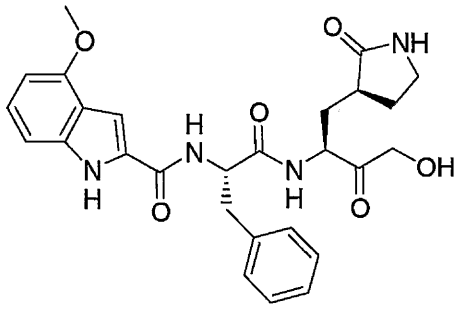
Following the procedure described for the preparation of N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting Boc-Phe-OH and making non-critical variations provided a crude brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a white solid, 351 mg, 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1 H, s), 7.19 - 7.31 (5 H, m), 5.77 (1 H, s), 5.10 (1 H, d, *J*=6.1 Hz), 4.52 - 4.57 (1 H, m), 4.44 (1 H, m), 4.01 - 4.12 (2 H, m), 3.26 – 3.37 (2 H, m), 3.01 - 3.08 (2 H, m), 2.29 - 2.37 (1 H, m), 2.15 - 2.25 (1 H, m), 1.98 – 2.06 (1 H, m), 1.75 - 1.91 (2 H, m), 1.40 (9 H, s); MS (API-ES -) for $C_{22}H_{30}N_3O_5Cl$ *m/z* 450.2 $(M-H)^-$.

Example 22: *N*-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-phenylalaninamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-(*tert*-butoxycarbonyl)-*N*-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-phenylalaninamide and making non-critical variations provided a crude green solid. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a white solid, 300 mg, 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (1 H, d, *J*=2.0 Hz), 8.68 (1 H, d, *J*=7.8 Hz), 8.61 (1 H, d, *J*=7.8 Hz), 7.61 (1 H, s), 7.37 (2 H, d, *J*=7.1 Hz), 7.31 (1 H, d, *J*=1.8 Hz), 7.26 (2 H, t, *J*=7.6 Hz), 7.16 (1 H, t, *J*=7.2 Hz), 7.07 (1 H, t), 6.97 (1 H, d, *J*=8.1 Hz), 6.49 (1 H, d, *J*=7.6 Hz), 4.68 (1 H, m), 4.38 - 4.49 (3 H, m), 3.88 (3 H, s), 2.97 - 3.17 (4 H, m), 2.20 - 2.32 (1 H, m), 2.02 - 2.14 (1 H, m), 1.93 - 2.02 (1 H, m), 1.52 - 1.69 (2 H, m); MS (APCI-+) for $C_{27}H_{29}N_4O_5Cl$ *m/z* 526.0 $(M+H)^+$.

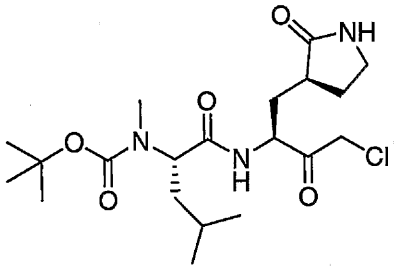
Example 23: *N*-((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-phenylalaninamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-phenylalaninamide and making non-critical variations provided a crude greenish

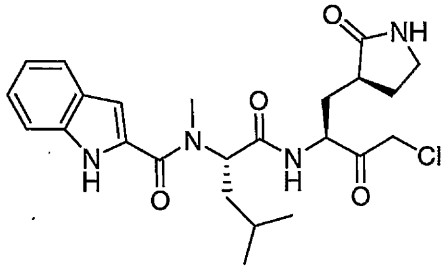
gum. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as an off-white solid, 123 mg, 44%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (1 H, d, *J*=2.0 Hz), 8.58 (2 H, dd, *J*=8.2, 3.9 Hz), 7.63 (1 H, s), 7.35 - 7.43 (2 H, m), 7.31 (1 H, d, *J*=1.8 Hz), 7.27 (2 H, t, *J*=7.6 Hz), 7.17 (1 H, t, *J*=7.3 Hz), 7.08 (1 H, t, *J*=8.0 Hz), 6.98 (1 H, d, *J*=8.1 Hz), 6.48 (1 H, d, *J*=7.8 Hz), 5.06 (1 H, t, *J*=6.1 Hz), 4.72 (1 H, m), 4.48 (1 H, m), 4.16 (2 H, m), 3.89 (3 H, s), 2.97 - 3.18 (4 H, m), 2.24 - 2.36 (1 H, m), 2.04 - 2.18 (1 H, m), 1.88 - 2.01 (1 H, m), 1.55 - 1.76 (2 H, m); MS (APCI+) for $C_{27}H_{30}N_4O_6$ *m/z* 507.1 $(M+H)^+$.

Preparation of Intermediate: *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*^{2}-methyl-L-leucinamide



Following the procedure described for the preparation of *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting Boc-N-methyl-Leu-OH and making non-critical variations provided a crude green gum. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as an orange foam, 2.08 g, 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (1 H, d, *J*=7.1 Hz), 7.69 (1 H, d, *J*=11.1 Hz), 4.58 (2 H, s), 4.48 (1 H, d, *J*=11.9 Hz), 4.40 (1 H, s), 3.02 - 3.22 (2 H, m), 2.69 - 2.79 (3 H, m), 2.14 - 2.27 (1 H, m), 2.03 - 2.14 (1 H, m), 1.87 - 2.00 (1 H, m), 1.48 - 1.76 (4 H, m), 1.38 (9 H, brd, *J*=5.8 Hz), 0.79 - 0.97 (6 H, m).

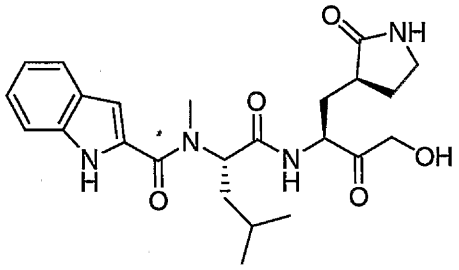
Example 24: *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-*N*-methyl-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide

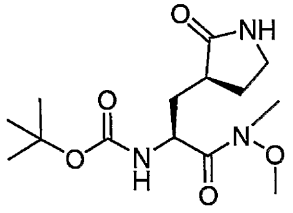
but substituting N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-N^2-methyl-L-leucinamide and indole-2-carboxylic acid and making non-critical variations provided a crude brown gum. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford 1.16 g (52%) of the title compound as an orange foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (1 H, s), 8.65 (1 H, s), 7.70 (1 H, s), 7.60 (1 H, s), 7.43 (1 H, d, *J*=8.1 Hz), 7.19 (1 H, t, *J*=7.6 Hz), 7.01 - 7.08 (1 H, m), 6.97 (1 H, s), 5.14 (1 H, s), 4.64 (2 H, s), 4.47 (1 H, s), 3.26 (2 H, s), 3.13 (3 H, s), 2.27 (1 H, s), 2.14 (1 H, s), 1.90 - 2.04 (1 H, m), 1.77 - 1.89 (1 H, m), 1.68 (3 H, s), 1.55 (1 H, s), 0.74 - 1.03 (6 H, m); MS (APCI-) for $C_{24}H_{31}N_4O_4Cl$ *m/z* 473.1 $(M-H)^-$.

Example 25: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-*N*-methyl-1*H*-indole-2-carboxamide



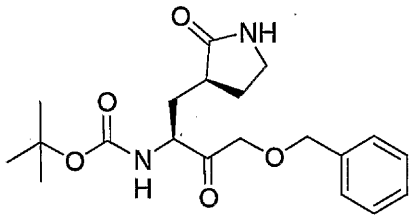
Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-*N*-methyl-1*H*-indole-2-carboxamide and making non-critical variations provided a crude brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford 491 mg (44%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (1 H, s), 8.73 (1 H, s), 7.89 (1 H, s), 7.75 - 7.85 (1 H, m), 7.65 (1 H, d, *J*=8.1 Hz), 7.40 (1 H, t, *J*=7.6 Hz), 7.25 (1 H, t, *J*=7.6 Hz), 7.18 (1 H, s), 5.35 (2 H, bs), 4.67 (1 H, s), 4.46 (2 H, m), 3.25 - 3.51 (4 H, m), 2.49 (1 H, s), 2.35 (1 H, s), 2.09 - 2.23 (1 H, m), 1.55 - 2.07 (6 H, m), 1.03 - 1.21 (6 H, m); MS (APCI-) for $C_{24}H_{32}N_4O_5$ *m/z* 455.2 $(M-H)^-$.

Preparation of Intermediate: *tert*-butyl ((1*S*)-2-[methoxy(methyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}ethyl)carbamate



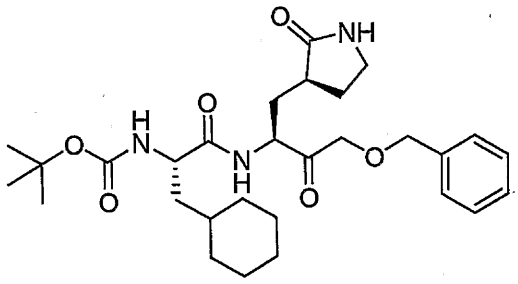
To a 3-L multi necked flask equipped with overhead stirrer, nitrogen inlet and internal thermometer was charged *N*-(*tert*-butoxycarbonyl)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-L-alanine (190g, 698 mmol) followed by dichloromethane (1100 mL) and the solution cooled to 0 °C employing an ice/NaCl bath. *N,O*-dimethylhydroxylamine hydrochloric acid salt (68 g, 698 mmol) was added followed by N-methyl morpholine (230 mL, 2.09 mol), HOBt.hydrate (106 g, 698 mmol) and EDCI (147g, 768 mmol) and the mixture stirred at 0 °C under nitrogen for 6 hours before quenching with water (500 mL). The bi-phasic mixture was transferred to a sep-funnel and the organics isolated, washed with 1M hydrochloric acid (2 x 500 mL), water (400 mL) satd. $NaHCO_3$ (2 x 700 mL) and brine (300 mL), then dried over $MgSO_4$, filtered and the solvents evaporated in vacuo to yield a pale yellow solid, 173 g, 79%. ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (1 H, s), 5.39 (1 H, d, *J*=8.8 Hz), 4.66 (1 H, td, *J*=9.6, 2.8 Hz), 3.77 (3 H, s), 3.33 (2 H, dd, *J*=9.3, 4.0 Hz), 3.19 (2 H, s), 2.41 - 2.62 (2 H, m), 2.05 - 2.16 (1 H, m), 1.75 - 1.95 (1 H, m), 1.67 (1 H, m), 1.41 (9 H, s).

Preparation of Intermediate: *tert*-butyl ((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate



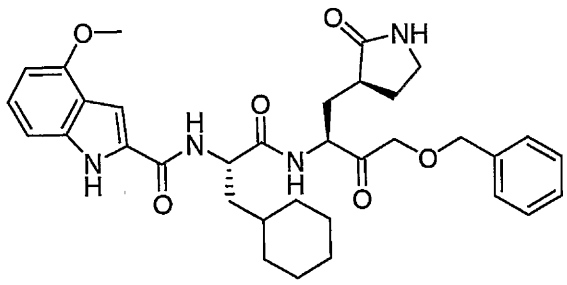
To a 100 mL multi necked flask equipped with stirrer bar, nitrogen inlet and internal thermometer was charged magnesium turnings (dried in oven at 100 °C overnight, 1.04 g, 43 mmol) and $HgCl_2$ (774 mg, 2.85 mmol) and the flask purged with nitrogen for 10 min. THF (50 mL) was added, and the suspension cooled to –45 °C before adding BOM-Cl (5.94 mL, 43 mmol), and the resulting suspension stirred for 5 hours, the temperature returning to 5 °C. The suspension was re-cooled to –50 °C, and *tert*-butyl ((1*S*)-2-[methoxy(methyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}ethyl)carbamate (1.5 g, 4.76 mmol) was added and the thick suspension stirred for 48 hours under nitrogen and was allowed to come to ambient temperature. The reaction was quenched by careful addition of satd. NH_4Cl solution (25 mL), and the mixture stirred until effervescence ceased then extracted with ethyl acetate (3 x 120 mL). The combined organics were dried over $MgSO_4$, filtered and the solvents evaporated *in vacuo* to yield a crude orange gum, which was purified by flash chromatography, eluting with 1 – 3% methanol/dichloromethane to afford the title compound as a clear glass, 900 mg, 50%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.33 (5 H, m), 5.63 - 5.73 (2 H, m), 4.52 (3 H, m), 4.19 (2 H, q, *J*=17.4 Hz), 3.19 - 3.25 (2 H, m), 2.29 - 2.42 (2 H, m), 1.68 - 1.93 (3 H, m), 1.35 (9 H, s); MS (APCI+) for $C_{20}H_{28}N_2O_5$ *m/z* 378.1. $(M+H)^+$.

Preparation of Intermediate: *tert*-butyl [(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]carbamate



To a solution of *tert*-butyl ((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate (200 mg, 0.53 mmol) in dioxane (5 mL) was added 4M hydrochloric acid / dioxane (5 mL) and the solution stirred at ambient temperature for 4 hours before removing the solvents *in vacuo*, azeotroping the residue with toluene (2 x 10 mL) and drying *in vacuo* for one hour. The crude hydrochloride salt was taken into DMF (3 mL) and the solution cooled to 0 °C before adding *N*-BOC-cyclohexylalanine-OH (139mg, 0.53 mmol), collidine (156 µL, 1.22 mmol) and HATU (194 mg, 0.53 mmol) in order, and the resulting suspension stirred at 0 °C for 5 hours. The reaction was quenched by the addition of water (30 mL) and the mixture extracted with diethyl ether (3 x 75 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvents removed *in vacuo* to yield the crude product which was purified by flash chromatography, eluting with 1 – 3% methanol/dichloromethane to afford the title compound as a pale brown gum, 205 mg, 76%. The product was contaminated with ~20% of another diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1 H, d, *J*=5.6 Hz), 7.26 - 7.42 (5 H, m), 5.93 (1 H, s), 4.94 (1 H, d, *J*=7.6 Hz), 4.72 (1 H), 4.60 (1 H, d, *J*=11.6 Hz), 4.55 (1 H, d, *J*=11.6 Hz), 4.14 - 4.34 (3 H, m), 3.27 (2 H, m), 2.23 - 2.51 (3 H, m), 1.56 - 2.05 (9 H, m), 1.33 - 1.48 (9 H, m), 1.05 - 1.29 (4 H, m), 0.80 - 1.03 (2 H, m).

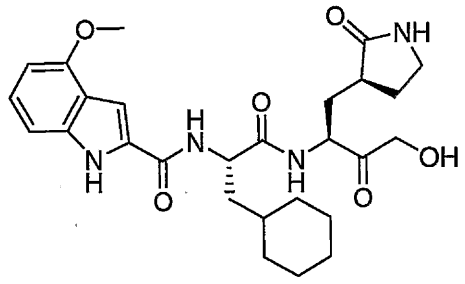
Example 26: *N*-[(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide



To a solution of *tert*-butyl [(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]carbamate (200 mg, 0.38 mmol) in dioxane

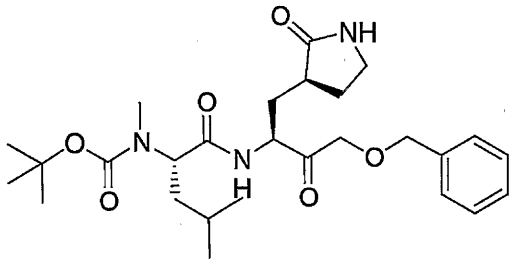
(4 mL) was added 4M hydrochloric acid / dioxane (4 mL) and the solution stirred at ambient temperature for 2 hours before removing the solvents *in vacuo*, azeotroping the residue with toluene (2 x 10 mL) and drying *in vacuo* for one hour. The crude hydrochloride salt was taken into DMF (3 mL) and the solution cooled to 0 °C before adding 4-methoxy-indole-2-carboxylic acid (73 mg, 0.38 mmol), collidine (125 µL, 0.95 mmol) and HATU (144 mg, 0.38 mmol) in order, and the resulting suspension stirred at 0 °C for 6 hours. The reaction was quenched by the addition of water (20 mL) and the mixture extracted with diethyl ether (3 x 50 mL). The combined organics were washed with water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered, and the solvents removed *in vacuo* to yield the crude product which was purified by Biotage flash chromatography, eluting with 1 – 3% methanol/dichloromethane to afford the title compound as a pale brown gum, 90 mg, 39%. The product was contaminated with ~20% of another diastereoisomer from previous step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (1 H, s), 8.13 (1 H, d, *J*=6.6 Hz), 7.21 - 7.32 (5 H, m), 7.11 (1 H, t, *J*=8.0 Hz), 7.02 (1 H, d, *J*=1.5 Hz), 6.94 (1 H, d, *J*=8.3 Hz), 6.72 - 6.78 (1 H, m), 6.42 (1 H, d, *J*=7.8 Hz), 5.97 (1 H, s), 4.73 (1 H, m), 4.64 (1 H, m), 4.53 (1 H, d, *J*=11.6 Hz), 4.46 (1 H, d, *J*=11.6 Hz), 4.26 (1 H, d, *J*=17.2 Hz), 4.15 (1 H, d, *J*=17.4 Hz), 3.87 (3 H, s), 3.08 - 3.16 (2 H, m), 2.27 - 2.38 (1 H, m), 1.92 (1 H, m), 1.49 - 1.84 (9 H, m), 1.26 - 1.42 (1 H, m), 0.98 - 1.23 (4 H, m), 0.78 - 0.98 (2 H, m); MS (APCI+) for $C_{34}H_{42}N_4O_6$ *m/z* 603.2. $(M+H)^+$.

Example 27: *N*-{(1*S*)-1-(cyclohexylmethyl)-2-[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-2-oxoethyl}-4-methoxy-1*H*-indole-2-carboxamide



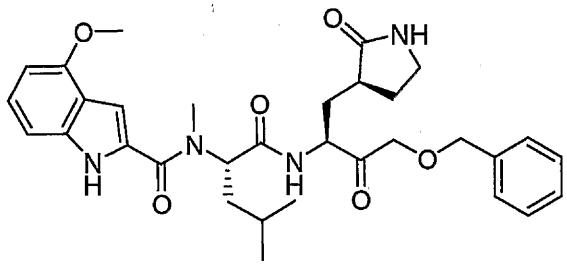
To a solution of *N*-[(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide (80 mg, 0.13 mmol) in EtOH (3 mL) was added 10% Pd/C (50mg) and the suspension hydrogenated at ambient temperature under H_2 (1atm balloon) for 5 hours. The catalyst was removed by filtration, and the solvents evaporated *in vacuo* to yield the crude product which was purified by Biotage flash chromatography, eluting with 2 – 10% methanol/dichloromethane to afford the title compound, 37 mg, 55% as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.19 (1 H, s), 7.05 (1 H, t, *J*=8.0 Hz), 6.93 (1 H, d, *J*=8.1 Hz), 6.41 (1 H, d, *J*=7.8 Hz), 4.52 - 4.59 (2 H, m), 4.27 (2 H, m), 3.83 (3 H, s), 3.08 - 3.21 (2 H, m), 2.47 (1 H, m), 2.13 - 2.24 (1 H, m), 1.92 - 2.03 (1 H, m), 1.53 - 1.79 (9 H, m), 1.31 - 1.45 (1 H, m), 1.04 - 1.29 (3 H, m), 0.81 - 1.02 (2 H, m); MS (APCI+) for $C_{27}H_{36}N_4O_6$ *m/z* 513.2. $(M+H)^+$.

Preparation of Intermediate: N^1-((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-N^2-(*tert*-butoxycarbonyl)-N^2-methyl-L-leucinamide



Following the procedure described for the preparation of *tert*-butyl [(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]carbamate but substituting Boc-N-methyl-Leu and making non-critical variations provided a crude brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound (123 mg, 47%) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.33 (5 H, m), 5.76 (1 H, bd), 4.73 (1 H, s), 4.46 - 4.59 (2 H, m), 4.08 - 4.27 (2 H, m), 3.14 - 3.28 (2 H, m), 2.68 (3 H, s), 2.16 - 2.38 (2 H, m), 1.88 - 2.00 (1 H, m), 1.56 - 1.86 (5 H, m), 1.41 (9 H, s), 0.94 (d, *J* = 8 Hz, 3 H), 0.89 (d, *J* = 8 Hz, 3 H).

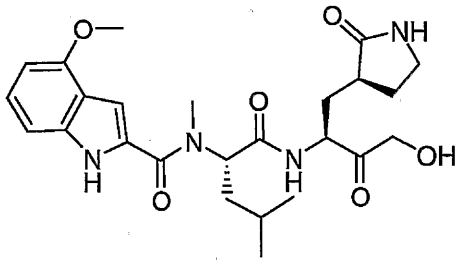
Example 28: *N*-((1*S*)-1-{[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-[(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide but substituting N^1-((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-N^2-(*tert*-butoxycarbonyl)-N^2-methyl-L-leucinamide and making non critical variations provided a crude brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a clear oil, 67 mg, 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (1 H, s), 7.95 (1 H, s), 7.26 - 7.36 (5 H, m), 7.18 (1 H, t, *J*=8.0 Hz), 7.04 (1 H, d, *J*=8.3 Hz), 7.00 (1 H, s), 6.48 (1 H, d, *J*=7.8 Hz), 5.87 (1 H, s), 5.18 - 5.27 (1 H, m), 4.70 (1 H, s), 4.50

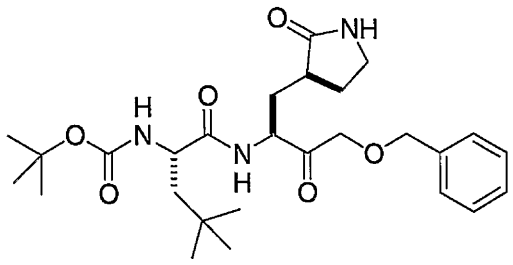
- 4.63 (2 H, m), 4.16 - 4.36 (2 H, m), 3.93 (3 H, s), 3.32 (3 H, s), 3.03 - 3.18 (2 H, m), 2.22 (2 H, s), 1.91 - 2.02 (1 H, m), 1.81 (3 H, t, *J*=7.3 Hz), 1.66 - 1.72 (1 H, m), 1.55 (1 H, s), 0.87 - 1.01 (6 H, m); MS (API-ES -) for $C_{32}H_{40}N_4O_6$ *m/z* 576.7. $(M-H)^-$.

Example 29: *N*-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of *N*-{(1*S*)-1-(cyclohexylmethyl)-2-[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-2-oxoethyl}-4-methoxy-1*H*-indole-2-carboxamide but substituting N-((1S)-1-{[((1S)-3-(benzyloxy)-2-oxo-1-{[(3S)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-N-methyl-1H-indole-2-carboxamide and making non critical variations provided a crude clear glass. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a white foam, 42 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (1 H, s), 8.26 (1 H, s), 7.18 (1 H, t, *J*=8.0 Hz), 7.05 (1 H, d, *J*=8.1 Hz), 6.99 (1 H, d, *J*=2.3 Hz), 6.48 (1 H, d, *J*=7.6 Hz), 6.09 (1 H, s), 5.14 - 5.27 (1 H, m), 4.51 - 4.65 (1 H, m), 4.25 - 4.50 (2 H, m), 3.94 (3 H, s), 3.26 - 3.46 (3 H, m), 3.11 - 3.24 (1 H, m), 3.01 - 3.11 (1 H, m), 1.48 - 2.39 (9 H, m), 0.88 - 1.02 (6 H, m); MS (API-ES-) for $C_{25}H_{34}N_4O_6$ *m/z* 485.3 $(M-H)^-$.

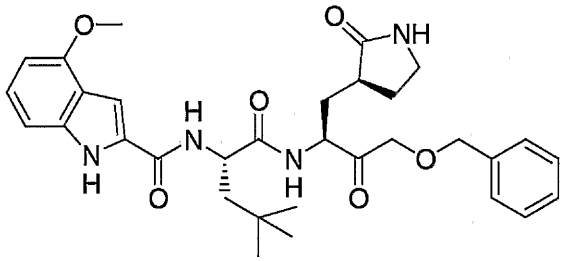
Preparation of Intermediate: N^1-((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-N^2-(*tert*-butoxycarbonyl)-4-methyl-L-leucinamide



Following the procedure described for the preparation of *tert*-butyl [(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]carbamate but

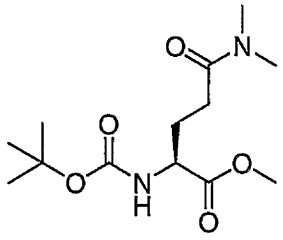
substituting Boc-(beta t-butyl)-Ala-OH and making non-critical variations provided a brown syrup. This material was purified by LC (33 g 230-400 SiO_2, 1-2.5% methanol/chloroform) to afford 258 mg (55%) of the title compound as a light yellow foam. ^{1}H NMR (DMSO-d_6) δ 8.23 (d, J = 8 Hz, 1 H), 7.62 (s, 1 H), 7.32 (m, 5 H), 6.96 (d, J = 8 Hz, 1 H), 4.46 (s, 2 H), 4.35-4.33 (m, 2 H), 4.21 (d, J = 16 Hz, 1 H), 3.95 (m, 1 H), 3.09 (m, 2 H), 2.24 (m, 1 H), 2.07 (m, 1 H), 1.92 (m, 1 H), 1.58 (m, 2 H), 1.46 (m, 2 H), 1.35 (s, 9 H), 0.87 (m, 9 H); MS (ESI+) for $C_{27}H_{41}N_3O_6$ *m/z* 504.2 $(M+H)^+$.

Example 30: *N*-((1*S*)-1-{[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



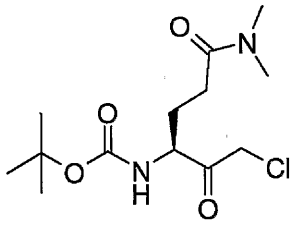
Following the procedure described for the preparation of *N*-[(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide but substituting N^1-((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-N^2-(*tert*-butoxycarbonyl)-4-methyl-L-leucinamide and making non critical variations provided a golden syrup. This material was purified by Biotage MPLC (25M column, 3% methanol/chloroform) to afford 173 mg (60%) of the title compound as an off-white foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1 H), 8.43 (app t, J = 8 Hz, 2 H), 7.62 (s, 1 H), 7.32 (m, 6 H), 7.08 (t, J = 8 Hz, 1 H), 7.00 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 4.52 (m, 1 H), 4.47-4.35 (m, 4 H), 4.22 (d, J = 16 Hz, 1 H), 3.87 (s, 3 H), 3.05 (m, 2 H), 2.28 (m, 1 H), 2.06 (m, 1 H), 1.93 (m, 1 H), 1.64-1.57 (m, 3 H), 0.92 (s, 9 H); MS (ESI+) for $C_{32}H_{40}N_4O_6$ *m/z* 577.2 $(M+H)^+$; Anal. Calcd for $C_{32}H_{40}N_4O_6$ • 0.33 methanol • 0.25 H_2O: C, 65.62; H, 7.13; N, 9.47. Found: C, 65.65; H, 6.90; N, 9.58; HRMS (ESI+) Calcd for $C_{32}H_{40}N_4O_6$ 577.3021, found 577.3001.

Preparation of Intermediate: 2-tert-Butoxycarbonylamino-4-dimethylcarbamoyl-butyric acid methyl ester



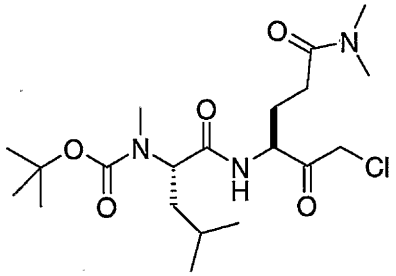
A solution of 2-tert-butoxycarbonylamino-pentanedioic acid 1-methyl ester (20.0 g, 76.6 mmol) in dichloromethane (385 mL) at 0 °C was treated successively with dimethylamine hydrochloride (7.50 g, 91.9 mmol), EDC-hydrochloric acid (22 g, 114.8 mmol), and NMM (16.8 mL, 153.1 mmol). The ice bath was then removed and the clear colorless solution was stirred at RT. After 17 hrs, the pale yellow solution was quenched with 1:1 ice:saturated aqueous $NaHCO_3$ and layers were separated. The organic layer was washed with 1.0 M hydrochloric acid (100 mL), watrer (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 20.1 g of the title compound as a white solid (90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, *J*=7.8 Hz, 1 H), 3.93 - 4.02 (m, 1 H), 3.61 (s, 3 H), 2.91 (s, 3 H), 2.79 (s, 3 H), 2.24 - 2.40 (m, 2 H), 1.84 - 1.95 (m, 1 H), 1.68 - 1.80 (m, 1 H), 1.36 (s, 9 H); MS (ESI+) for $C_{13}H_{24}N_2O_5$ *m/z* 289.2 $(M+H)^+$; HRMS (ESI+) Calcd for $(M+Na)^+$ 311.1577, found 311.1566.

Preparation of Intermediate: *tert*-butyl [(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]carbamate



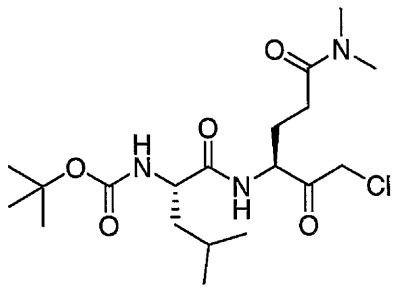
A 3-neck flame dried flask equipped with spinbar, nitrogen inlet, and internal thermometer was charged with methyl N^2-(*tert*-butoxycarbonyl)-N^5,N^5-dimethyl-L-glutaminate (10.6 g, 37 mmol), THF (200 mL), and chloroiodomethane (9.9 mL, 136 mmol) followed by cooling to -77 °C. LDA (114 mL, 185 mmol, 1.5 M mono-THF complex in cyclohexane) was added via pressure equalizing dropping funnel at such a rate to keep the internal temperature below –70 °C. After complete addition, the reaction was stirred for a further hour before quenching with a mixture of AcOH (30 mL) and THF (30mL), added at such a rate to maintain the internal temperature below –65 °C. After complete addition, the dark suspension was stirred for 10 minutes then warmed to ambient temperature. The reaction was diluted with ethyl acetate (450 mL) and the organics were washed with water (200 mL), satd. $NaHCO_3$ (2 x 150 mL), brine (2 x 150 mL) dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to yield the crude product as a dark oil which was purified by flash chromatography, eluting with ethyl acetate. This afforded a dark red oil, that was recrystalized from ether / hexane to afford the title compound as a pale yellow solid, 5.2 g, 50%. ^{1}H NMR (DMSO-d_6) δ 7.36 (d, *J* = 7 Hz, 1 H), 4.61 (d, *J* = 16 Hz, 1 H), 4.55 (d, *J* = 17 Hz, 1 H), 4.04 – 4.19 (m, 1 H), 2.91 (s, 3 H), 2.79 (s, 3 H), 2.30 (t, 2 H, *J* = 7 Hz), 1.87 – 1.99 (m, 1 H), 1.60 – 1.72 (m, 1 H), 1.37 (s, 9 H); Anal. Calcd for $C_{13}H_{23}ClN_2O_4$ • 0.34 H_2O: C, 49.90; H, 7.63; N, 8.95. Found: C, 49.97; H, 7.44; N, 8.77.

Preparation of Intermediate: N^2-(*tert*-butoxycarbonyl)-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide



To a solution of *tert*-butyl [(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]carbamate (2.88 g, 9.39 mmol) in dioxane (25 mL) at –15 °C was added 4 M hydrochloric acid / dioxane (50 mL) dropwise over 10 minute period. The resulting mixture was allowed to warm to ambient temperature over one hour. The solvents were removed *in vacuo* and the residue azeotroped with toluene (3 x 25 mL). The crude hydrochloride salt was taken into DMF (30 mL) and cooled to 0 °C. Boc-N-methyl-Leu-OH (2.53 g, 10.33 mmol), HATU (3.9 g, 10.33 mmol) and NMM (2.4 mL, 21.59 mmol) were added, and the resulting mixture stirred at 0 °C for 90 minutes before quenching with ice / satd. $NaHCO_3$ (100 mL each). The mixture was extracted with ethyl acetate (3 x 150 mL) and the combined organics washed with water (3 x 50 mL), 1 M hydrochloric acid (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated to provide a crude brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a pale orange oil, 2.14 g, 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (1 H, d, J = 6.8 Hz), 4.41 - 4.64 (3 H, m), 4.32 (1 H, s), 2.90 (3 H, s), 2.80 (3 H, s), 2.66 - 2.74 (4 H, m), 2.29 (2 H, t, J = 6.9 Hz), 2.00 (1 H, s), 1.74 (1 H, s), 1.49 - 1.66 (2 H, m), 1.39 (9 H, s), 0.83 - 0.95 (6 H, m).

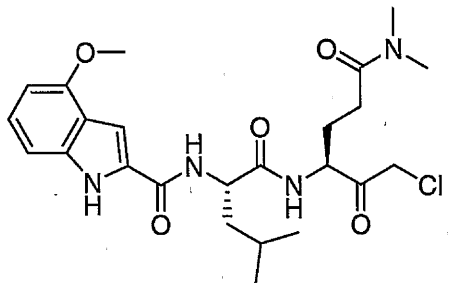
Preparation of Intermediate: {1-[3-Chloro-1-(2-dimethylcarbamoyl-ethyl)-2-oxo-propylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester



Following the procedure described for the preparation of N^2-(*tert*-butoxycarbonyl)-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide but substituting Boc-Leu-OH and making non critical variations provided a crude amber syrup. This material was purified by Biotage MPLC (40M column, 1-4% methanol/chloroform) to afford 1.76 g (64%) of the title compound

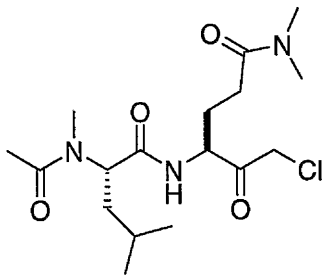
as a glass. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, *J*=7.3 Hz, 1 H), 7.00 (d, *J*=7.3 Hz, 1 H), 4.48 - 4.57 (m, 2 H), 4.25 - 4.36 (m, 1 H), 3.83 - 3.95 (m, 1 H), 2.90 (s, 3 H), 2.79 (s, 3 H), 2.24 - 2.32 (m, 2 H), 1.95 - 2.08 (m, 1 H), 1.65 - 1.76 (m, 1 H), 1.53 - 1.63 (m, 1 H), 1.38 - 1.47 (m, 2 H), 1.36 (s, 9 H), 0.87 (d, *J*=6.6 Hz, 3 H), 0.84 (d, *J*=6.6 Hz, 3 H); MS (ESI+) for $C_{19}H_{34}ClN_3O_5$ *m/z* 420.2 $(M+H)^+$.

Example 31: 4-Methoxy-1H-indole-2-carboxylic acid {1-[3-chloro-1-(2-dimethylcarbamoyl-ethyl)-2-oxo-propylcarbamoyl]-3-methyl-butyl}-amide



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting {1-[3-Chloro-1-(2-dimethylcarbamoyl-ethyl)-2-oxo-propylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester and making no other critical variations provided crude amber syrup. This material was purified by Biotage MPLC (40M column, 2-4% methanol/chloroform) to afford 1.25 g (71%) of the title compound as an off-white foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (d, *J*=2.0 Hz, 1 H), 8.51 (d, *J*=7.6 Hz, 1 H), 8.44 (d, *J*=7.6 Hz, 1 H), 7.35 (d, *J*=1.8 Hz, 1 H), 7.09 (t, *J*=8.0 Hz, 1 H), 6.96 - 7.03 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.51 - 4.66 (m, 2 H), 4.41 - 4.50 (m, 1 H), 4.33 - 4.40 (m, 1 H), 3.87 (s, 3 H), 2.86 (s, 3 H), 2.76 (s, 3 H), 2.29 (t, *J*=7.3 Hz, 2 H), 1.97 - 2.11 (m, 1 H), 1.66 - 1.77 (m, 3 H), 1.50 - 1.60 (m, 1 H), 0.93 (d, *J*=6.3 Hz, 3 H), 0.88 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{24}H_{33}ClN_4O_5$ *m/z* 493.2 $(M+H)^+$.

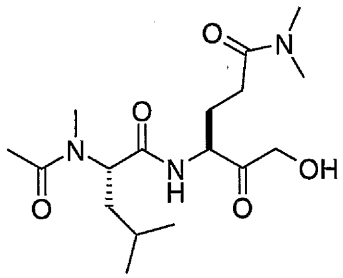
Example 32: N^2-acetyl-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide



To a solution of N^2-(*tert*-butoxycarbonyl)-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide (2.0g, 4.77 mmol) in dioxane (50 mL) at –15 °C was added 4 M hydrochloric

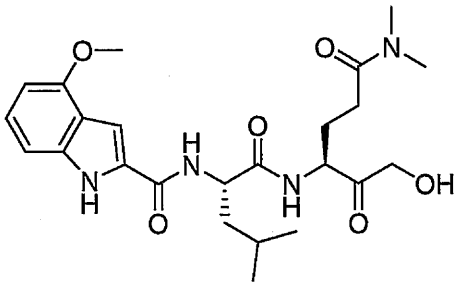
acid / dioxane (50 mL) dropwise over 10 minute period. The resulting mixture was allowed to warm to ambient temperature over one hour. The solvents were removed *in vacuo* and the residue azeotroped with toluene (3 x 25 mL). The crude hydrochloride salt was taken into DMF (15 mL) and cooled to 0 °C before adding acetyl chloride (339 µl, 4.77 mmol) followed by triethylamine (1.33 mL, 9.54 mmol). The resulting yellow suspension was stirred at 0 °C for 1 hour before quenching with water (30 mL). The mixture was saturated with NaCl and extracted with ethyl acetate (5 x 75 mL), and the combined organics dried over $MgSO_4$, filtered and concentrated to provide a pale brown oil. This material was purified by Biotage flash chromatography, eluting with methanol/dichloromethane to afford the title compound as a pale orange oil, 1.21 g, 69%. ^{1}H NMR (400 MHz, DMSO-d_6) 8.30 (1 H, d, J = 6.8 Hz), 5.00 (1 H, t, J = 7.8 Hz), 4.47 - 4.60 (2 H, m), 4.27 - 4.35 (1 H, m), 2.91 (3 H, s), 2.84 (3 H, s), 2.80 (3 H, s), 2.28 (2 H, t, J = 7.1 Hz), 1.92 - 2.07 (4 H, m), 1.64 - 1.81 (1 H, m), 1.51 - 1.62 (2 H, m), 1.31 - 1.45 (1 H, m), 0.89 (3 H, d, J = 6.6 Hz), 0.84 (3 H, d, J=6.6 Hz).

Example 33: *N*^{2}-acetyl-*N*^{1}-[(1*S*)-4-(dimethylamino)-1-glycoloyl-4-oxobutyl]-*N*^{2}-methyl-L-leucinamide



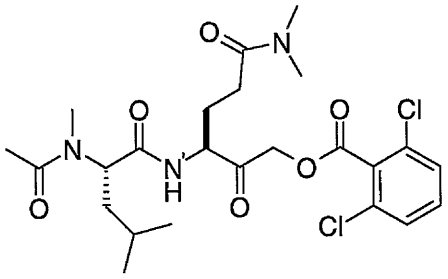
To a solution of *N*^{2}-acetyl-*N*^{1}-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-*N*^{2}-methyl-L-leucinamide (971 mg, 2.67 mmol) in DMF (25 mL) was added benzoyl formic acid (521 mg, 3.47 mmol) followed by freshly ground CsF (933 mg, 6.14 mmol) and the suspension placed in a pre-heated oil bath at 65 °C for 4 hours. The reaction was cooled to ambient temperature, diluted with ethyl acetate (200 mL), and washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. The residue was taken into methanol (120 mL), K_2CO_3 (38 mg, 0.27 mmol) added, and the suspension stirred at ambient temperature for 1 hour. The reaction was neutralized by the addition of 1M hydrochloric acid (273 µl, 0.27 mmol) and the solvents removed *in vacuo*. The crude product was purified by flash chromatography eluting with dichloromethane / methanol to afford the title compound (428 mg, 45%) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) 8.18 (1 H, d, J = 7.1 Hz), 4.98 - 5.06 (2 H, m), 4.23 - 4.30 (1 H, m), 4.04 - 4.23 (2 H, m), 2.90 (3 H, s), 2.83 (3 H, s), 2.80 (3 H, s), 2.28 (2 H, t, J = 7.2 Hz), 2.03 (3 H, s), 1.87 - 2.00 (1 H, m), 1.61 - 1.77 (1 H, m), 1.48 - 1.61 (2 H, m), 1.29 - 1.45 (1 H, m), 0.89 (3 H, d, J = 6.8 Hz), 0.83 (3 H, d, J = 6.6 Hz); MS (API-ES +) for $C_{17}H_{31}N_3O_5$ *m/z* 358.2 $(M+H)^+$.

Example 34: 4-Methoxy-1H-indole-2-carboxylic acid {1-[1-(2-dimethylcarbamoyl-ethyl)-3-hydroxy-2-oxo-propylcarbamoyl]-3-methyl-butyl}-amide



Following the procedure described for the preparation of N^2-acetyl-N^1-[(1*S*)-4-(dimethylamino)-1-glycoloyl-4-oxobutyl]-N^2-methyl-L-leucinamide but substituting 4-Methoxy-1H-indole-2-carboxylic acid {1-[3-chloro-1-(2-dimethylcarbamoyl-ethyl)-2-oxo-propylcarbamoyl]-3-methyl-butyl}-amide and making no other critical variations provided crude pale yellow foam. This material was purified by Biotage MPLC (40M column, 2-5% methanol/chloroform) to afford 460 mg (38%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (d, *J*=2.0 Hz, 1 H), 8.41 (d, *J*=7.8 Hz, 1 H), 8.35 (d, *J*=7.6 Hz, 1 H), 7.35 (d, *J*=1.5 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.98 - 7.01 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 5.01 (t, *J*=5.9 Hz, 1 H), 4.45 - 4.52 (m, 1 H), 4.31 - 4.38 (m, 1 H), 4.09 - 4.26 (m, 2 H), 3.87 (s, 3 H), 2.85 (s, 3 H), 2.76 (s, 3 H), 2.24 - 2.32 (m, 2 H), 1.92 - 2.04 (m, 1 H), 1.64 - 1.75 (m, 3 H), 1.49 - 1.57 (m, 1 H), 0.93 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{24}H_{34}N_4O_6$ *m/z* 475.2 $(M+H)^+$; HRMS (ESI+) Calcd for $(M+H)^+$ 475.2551, found 475.2534.

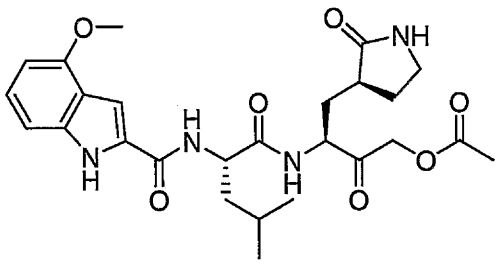
Example 35: 3*S*)-3-[(*N*-acetyl-*N*-methyl-L-leucyl)amino]-6-(dimethylamino)-2,6-dioxohexyl 2,6-dichlorobenzoate



To a solution of N^2-acetyl-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide (229 mg, 0.63 mmol) in DMF (6 mL) was added 2,6-dichloro benzoic acid (157 mg, 0.82 mmol) followed by freshly ground CsF (220 mg, 1.45 mmol) and the suspension placed in a pre-heated oil bath at 65 °C for 2 hours. The reaction was cooled to ambient temperature, diluted with ethyl acetate (100 mL), and washed with water (3 x 30 mL), brine (50 mL), dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude product was purified by flash chromatography eluting with dichloromethane / methanol to afford the title compound (252 mg, 75%) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6) 8.33 (1 H, d, *J* = 7.1 Hz), 7.51 - 7.64 (3 H, m), 5.14 (2 H, s), 5.01 - 5.07 (1

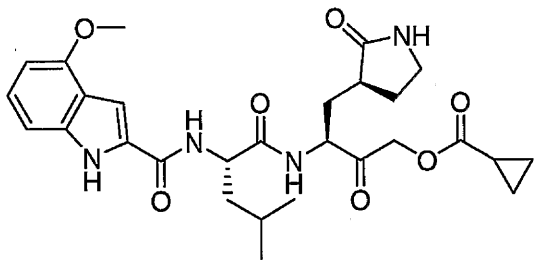
H, m), 4.32 - 4.41 (1 H, m), 2.91 (3 H, s), 2.85 (3 H, s), 2.81 (3 H, s), 2.68 - 2.75 (1 H, m), 2.32 (2 H, t, *J* = 7.1 Hz), 1.98 - 2.11 (4 H, m), 1.73 - 1.86 (1 H, m), 1.55 - 1.64 (2 H, m), 1.32 - 1.45 (1 H, m), 0.90 (3 H, d, *J* = 6.6 Hz), 0.84 (3 H, d, *J* = 6.3 Hz); HRMS (ESI+) Calcd for $C_{24}H_{33}Cl_2N_3O_6$+H1 530.1819, found 530.1805.

Example 36: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate



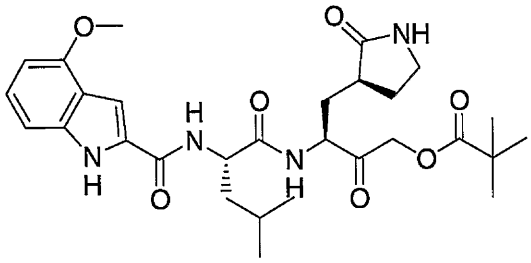
An oven-dried 40 mL scintillation vial with spinbar was charged with acetic acid (27 mg, 0.46 mmol) followed by a solution of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (172 mg, 0.35 mmol) in DMF (3.5 mL), and purged with N_2. This pale yellow solution was then treated with CsF (122 mg, 0.81 mmol), sealed with a Teflon-lined screwcap, and heated at 65 °C on a reaction block with vigorous stirring. After 3 h, the reaction was cooled to RT, diluted with water (30 mL), and extracted with dichloromethane (4 x 7 mL). The combined organic layers were washed with water (2 x 20 mL), brine (20 mL), and concentrated *in vacuo*. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 78 mg (45%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1 H), 8.57 (d, *J*=7.8 Hz, 1 H), 8.43 (d, *J*=7.6 Hz, 1 H), 7.64 (s, 1 H), 7.36 (d, *J*=1.8 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.99 (d, *J*=8.1 Hz, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.83 (d, *J*=3.0 Hz, 1 H), 4.76 - 4.95 (m, 1 H), 4.35 - 4.50 (m, 2 H), 3.87 (s, 3 H), 3.03 - 3.17 (m, 2 H), 2.22 - 2.35 (m, 1 H), 2.09 - 2.22 (m, 1 H), 2.07 (s, 3 H), 1.90 - 2.04 (m, 1 H), 1.65 - 1.77 (m, 2 H), 1.48 - 1.65 (m, 3 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{26}H_{34}N_4O_7$ *m/z* 515.2 $(M+H)^+$.

Example 37: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl cyclopropanecarboxylate



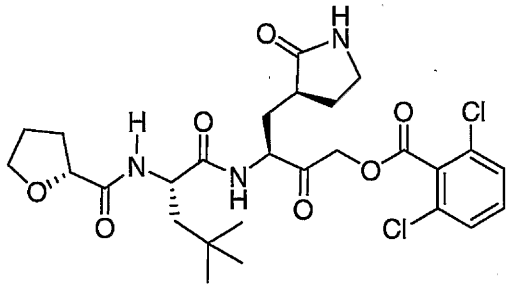
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting cyclopropanecarboxylic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 82 mg (43%) of the title compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (d, *J*=2.0 Hz, 1 H), 8.56 (d, *J*=7.8 Hz, 1 H), 8.43 (d, *J*=7.6 Hz, 1 H), 7.63 (s, 1 H), 7.36 (d, *J*=1.5 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.97 - 7.02 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.85 (d, 1 H), 4.78 - 4.96 (m, 1 H), 4.33 - 4.51 (m, 2 H), 3.87 (s, 3 H), 3.02 - 3.16 (m, 2 H), 2.22 - 2.35 (m, 1 H), 2.01 - 2.11 (m, 1 H), 1.89 - 2.00 (m, 1 H), 1.65 - 1.77 (m, 3 H), 1.46 - 1.65 (m, 3 H), 0.81 - 0.98 (m, 10 H); MS (ESI+) for $C_{28}H_{36}N_4O_7$ *m/z* 541.2 $(M+H)^+$.

Example 38: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl pivalate



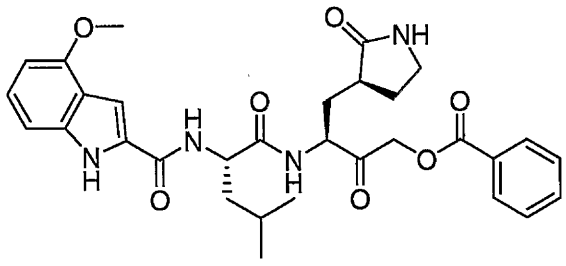
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting pivalic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 152 mg (78%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1 H), 8.56 (d, *J*=7.8 Hz, 1 H), 8.44 (d, *J*=7.8 Hz, 1 H), 7.64 (s, 1 H), 7.36 (s, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.99 (d, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.84 (s, 1 H), 4.77 - 4.94 (m, 1 H), 4.34 - 4.51 (m, 2 H), 3.87 (s, 3 H), 3.02 - 3.16 (m, 2 H), 1.91 - 2.36 (m, 3 H), 1.48 - 1.78 (m, 5 H), 1.16 (s, 9 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{29}H_{40}N_4O_7$ *m/z* 557.2 $(M+H)^+$.

Example 39: (3*S*)-3-({4-methyl-*N*-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide and 2,6-dichlorobenzoic acid and making non-critical variations provided a light amber residue. The residue was purified by preparative HPLC (Luna 10μ C18) eluting with a gradient of MeCN containing 0.1% AcOH in water containing 0.1% AcOH to give 0.155 g (54%) of the title compound as a cream colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (d, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.71 (s, 1H), 7.66 - 7.55 (m, 3H), 5.18 (s, 2H), 4.54 - 4.40 (m, 1H), 4.37 - 4.35 (m, 1H), 4.25 (m, 1H), 3.98 - 3.91 (m, 1H), 3.84 - 3.72 (m, 1H), 3.23 - 3.07 (m, 2H), 2.33 - 2.23 (m, 1H), 2.16 - 2.05 (m, 2H), 1.86 - 1.74 (m, 3H), 1.72 - 1.62 (m, 5H), 0.89 (s, 9H); MS (ESI+) for $C_{27}H_{35}Cl_2N_3O_7$ *m/z* 584 (M+H). Anal. Calcd for $C_{27}H_{35}Cl_2N_3O_7$ • 0.5 H_2O: C, 54.64; H, 6.11; N, 7.08. Found: C, 54.26; H, 6.00; N, 6.87. HRMS (ESI+) Calcd for $C_{27}H_{35}Cl_2N_3O_7$+H1 584.1925, found 584.1921.

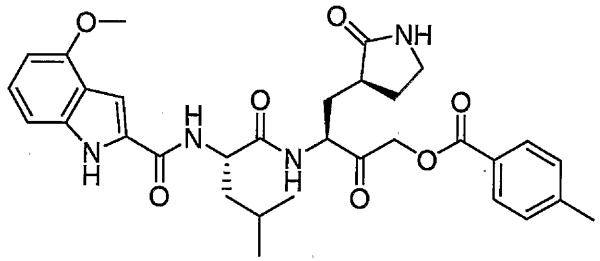
Example 40: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl benzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting benzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 183 mg (91%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1 H), 8.64 (d, J=8.1 Hz, 1 H), 8.46 (d, J=7.6

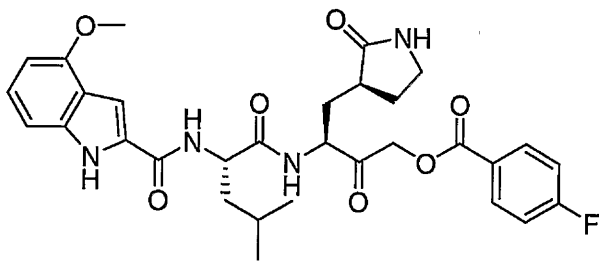
Hz, 1 H), 7.98 (d, *J*=8.1 Hz, 2 H), 7.91 - 7.95 (m, 1 H), 7.66 - 7.71 (m, 1 H), 7.66 (s, 1 H), 7.52 - 7.57 (m, 1 H), 7.37 (d, *J*=1.8 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.96 - 7.02 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 5.13 (s, 1 H), 5.06 - 5.24 (m, 1 H), 4.44 - 4.53 (m, 2 H), 3.87 (s, 3 H), 3.04 - 3.15 (m, 2 H), 2.34 (m, 1 H), 2.07 - 2.27 (m, 1 H), 1.98 - 2.07 (m, 1 H), 1.52 - 1.79 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{31}H_{36}N_4O_7$ *m/z* 577.2 $(M+H)^+$.

Example 41: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-methylbenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-methylbenzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 92 mg (44%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (d, *J*=1.8 Hz, 1 H), 8.63 (d, *J*=8.1 Hz, 1 H), 8.46 (d, *J*=7.6 Hz, 1 H), 7.87 (d, *J*=8.1 Hz, 2 H), 7.65 (s, 1 H), 7.37 (d, *J*=1.8 Hz, 1 H), 7.34 (d, *J*=8.3 Hz, 2 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.97 - 7.01 (m, 1 H), 6.50 (d, *J*=7.8 Hz, 1 H), 5.09 (s, 1 H), 5.03 - 5.20 (m, 1 H), 4.43 - 4.52 (m, 2 H), 3.87 (s, 3 H), 3.04 - 3.17 (m, 2 H), 2.38 (s, 3 H), 2.28 - 2.34 (m, 1 H), 2.06 - 2.14 (m, 1 H), 1.96 - 2.06 (m, 1 H), 1.51 - 1.78 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{32}H_{38}N_4O_7$ *m/z* 591.2 $(M+H)^+$.

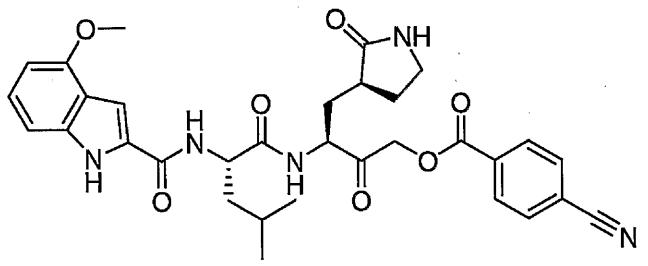
Example 42: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-fluorobenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-

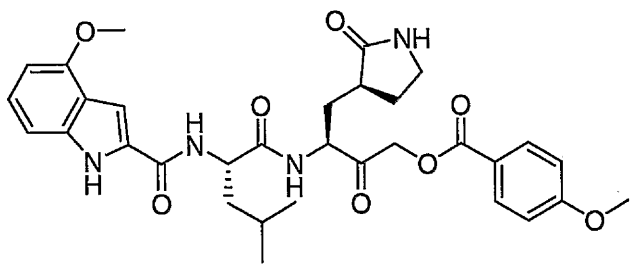
fluorobenzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 136 mg (65%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (d, *J*=2.0 Hz, 1 H), 8.63 (d, *J*=7.8 Hz, 1 H), 8.46 (d, *J*=7.6 Hz, 1 H), 8.04 (dd, *J*=8.6, 5.6 Hz, 2 H), 7.65 (s, 1 H), 7.35 - 7.41 (m, 3 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.99 (d, *J*=8.1 Hz, 1 H), 6.50 (d, *J*=7.6 Hz, 1 H), 5.12 (d, *J*=1.3 Hz, 1 H), 5.06 - 5.23 (m, 1 H), 4.44 - 4.52 (m, 2 H), 3.87 (s, 3 H), 3.04 - 3.17 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.07 - 2.26 (m, 1 H), 1.98 - 2.06 (m, 1 H), 1.52 - 1.79 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{31}H_{35}FN_4O_7$ *m/z* 595.2 $(M+H)^+$.

Example 43: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-cyanobenzoate



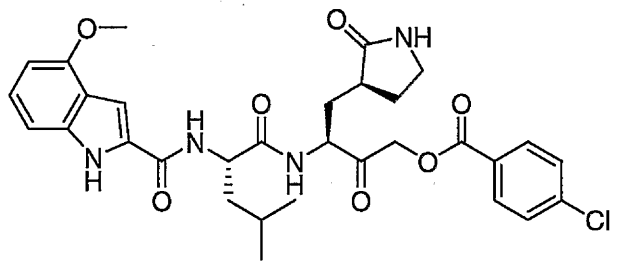
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-cyanobenzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 159 mg (75%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (d, *J*=2.0 Hz, 1 H), 8.64 (d, *J*=8.1 Hz, 1 H), 8.46 (d, *J*=7.6 Hz, 1 H), 8.09 - 8.14 (m, 2 H), 7.99 - 8.05 (m, 2 H), 7.66 (s, 1 H), 7.37 (d, *J*=1.5 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.99 (d, *J*=8.3 Hz, 1 H), 6.50 (d, *J*=7.6 Hz, 1 H), 5.17 (d, *J*=2.8 Hz, 1 H), 5.11 - 5.27 (m, 1 H), 4.44 - 4.53 (m, 2 H), 3.87 (s, 3 H), 3.04 - 3.17 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.07 - 2.26 (m, 1 H), 1.97 - 2.06 (m, 1 H), 1.51 - 1.78 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{32}H_{35}N_5O_7$ *m/z* 602.2 $(M+H)^+$.

Example 44: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-methoxybenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-methoxybenzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 145 mg (68%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (d, *J*=1.8 Hz, 1 H), 8.62 (d, *J*=7.8 Hz, 1 H), 8.46 (d, *J*=7.6 Hz, 1 H), 7.93 (d, *J*=9.1 Hz, 2 H), 7.65 (s, 1 H), 7.37 (d, *J*=2.0 Hz, 1 H), 7.04 - 7.11 (m, 2 H), 7.00 (dd, *J*=8.6, 3.0 Hz, 2 H), 6.50 (d, *J*=7.6 Hz, 1 H), 5.07 (s, 1 H), 5.01 - 5.18 (m, 1 H), 4.44 - 4.51 (m, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.04 - 3.17 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.07 - 2.25 (m, 1 H), 1.97 - 2.06 (m, 1 H), 1.50 - 1.79 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{32}H_{38}N_4O_8$ *m/z* 607.2 $(M+H)^+$.

Example 45: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-chlorobenzoate

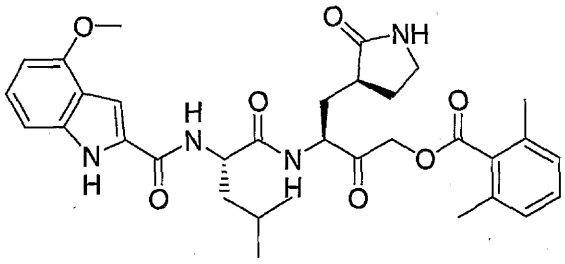


Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-chlorobenzoic acid and making non-critical variations provided a crude product. This material was purified by Biotage MPLC (25M, 2.5-4.5% methanol/dichloromethane) to afford 172 mg (80%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (d, *J*=1.8 Hz, 1 H), 8.63 (d, *J*=7.8 Hz, 1 H), 8.46 (d, *J*=7.6 Hz, 1 H), 7.98 (d, *J*=8.6 Hz, 2 H), 7.65 (s, 1 H), 7.62 (d, *J*=8.6 Hz, 2 H), 7.37 (d, *J*=1.8 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.99 (d, *J*=8.3 Hz, 1 H), 6.50 (d, *J*=7.6 Hz, 1 H), 5.13 (d, *J*=1.5 Hz, 1 H), 5.07 - 5.23 (m, 1 H), 4.44 - 4.52 (m, 2 H), 3.87 (s, 3 H), 3.04 - 3.14 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.06 - 2.26 (m, 1 H), 1.97 - 2.06 (m, 1 H), 1.51 - 1.78 (m, 5 H), 0.94 (d, *J*=6.3 Hz, 3 H), 0.89 (d, *J*=6.3 Hz, 3 H); MS (ESI+) for $C_{31}H_{35}ClN_4O_7$ *m/z* 611.1 $(M+H)^+$.

Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 2,6-dichlorobenzoic acid and making non-critical variations provided a crude product. This material was purified by LC (20 g 230-400 SiO_2, 3% methanol/chloroform) to afford 114 mg (65%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.57 (d, *J* = 2 Hz, 1 H), 8.62 (d, *J* = 8 Hz, 1 H), 8.46 (d, *J* = 4 Hz, 1 H), 7.65-7.53 (m, 4 H), 7.36 (s, 1 H), 7.08 (t, *J* = 8 Hz, 1 H), 6.99 (d, *J* = 8 Hz, 1

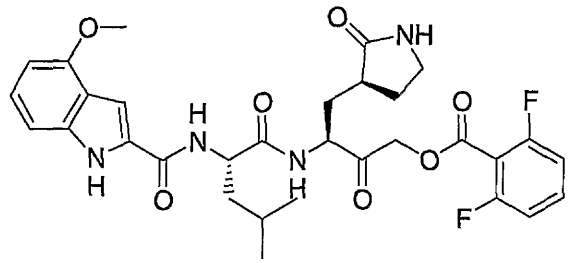
H), 6.49 (d, J = 8 Hz, 1 H), 5.19 (d, J = 20 Hz, 1 H), 5.15 (d, J = 20 Hz, 1 H), 4.51 (m, 2 H), 3.87 (s, 3 H), 3.11 (m, 2 H), 2.30 (m, 1 H), 2.06 (m, 2 H), 1.76-1.51 (m, 5 H), 0.94 (d, J = 8 Hz, 3 H), 0.89 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{31}H_{34}Cl_2N_4O_7$ *m/z* 645.1 $(M+H)^+$; Anal. Calcd for $C_{31}H_{34}Cl_2N_4O_7 \cdot 0.2\ H_2O$: C, 57.36; H, 5.34; N, 8.63. Found: C, 57.23; H, 5.55; N, 8.46. HRMS (ESI+) Calcd for $C_{31}H_{34}Cl_2N_4O_7$+H1 645.1877, found 645.1871.

Example 47: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dimethylbenzoate



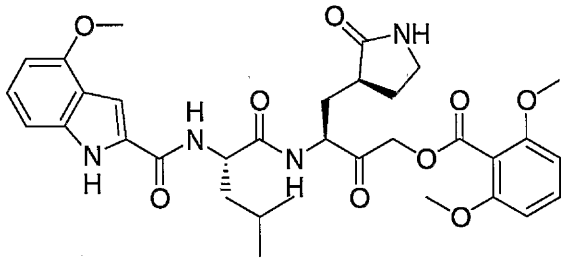
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 2,6-dimethylbenzoic acid and making non-critical variations provided a crude brown foam. This material was purified by Biotage MPLC (25M, 3-4% methanol/dichloromethane) to afford 177 mg (73%) of the title compound as an off-white glass. ^{1}H NMR (DMSO-d_6) δ 11.58 (d, J = 2 Hz, 1 H), 8.63 (d, J = 8 Hz, 1 H), 8.46 (d, J = 8 Hz, 1 H), 7.65 (s, 1H), 7.36 (s, 1H), 7.25 (t, J = 8 Hz, 1 H), 7.08 (m, 3 H), 7.00 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 5.11 (s, 2 H), 4.51 (m, 2 H), 3.87 (s, 3 H), 3.10 (m, 2 H), 2.32-2.21 (m, 7 H), 2.07 (m, 2 H), 1.78-1.53 (m, 5 H), 0.94 (d, J = 8 Hz, 3 H), 0.89 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{33}H_{40}N_4O_7$ *m/z* 605.2 $(M+H)^+$; Anal. Calcd for $C_{33}H_{40}N_4O_7 \cdot 0.3\ H_2O \cdot 0.2\ CHCl_3$: C, 62.90; H, 6.49; N, 8.84. Found: C, 62.95; H, 6.42; N, 8.72. HRMS (ESI+) Calcd for $C_{33}H_{40}N_4O_7$+H1 605.2970, found 605.2985.

Example 48: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-difluorobenzoate



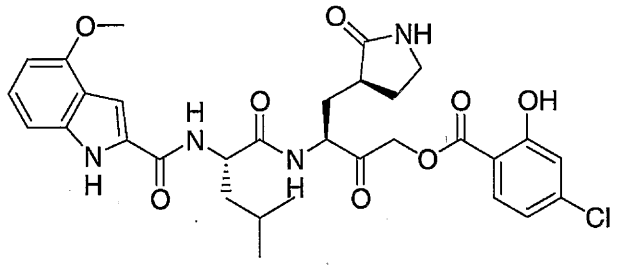
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 2,6-difluorolbenzoic acid and making non-critical variations provided a crude brown oily solid. This material was triturated with chloroform/ethyl acetate to afford 180 mg (75%) of the title compound as white solid. ^{1}H NMR (DMSO-d_6) δ 11.65 (d, J = 2 Hz, 1 H), 8.68 (d, J = 8 Hz, 1 H), 8.54 (d, J = 8 Hz, 1 H), 7.73-7.65 (m, 2H), 7.36 (s, 1H), 7.27 (t, J = 8 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 5.19 (d, J = 16 Hz, 1 H), 5.14 (d, J = 16 Hz, 1 H), 4.48 (m, 2H), 3.87 (s, 3 H), 3.11 (m, 2 H), 2.32 (m, 1 H), 2.11-1.91 (m, 2 H), 1.81-1.56 (m, 5 H), 0.94 (d, J = 4 Hz, 3 H), 0.89 (d, J = 4 Hz, 3 H); MS (ESI+) for $C_{31}H_{34}F_2N_4O_7$ *m/z* 613.2 $(M+H)^+$; HRMS (ESI+) Calcd for $C_{31}H_{34}F_2N_4O_7$+H1 613.2469, found 613.2476.

Example 49: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dimethoxybenzoate



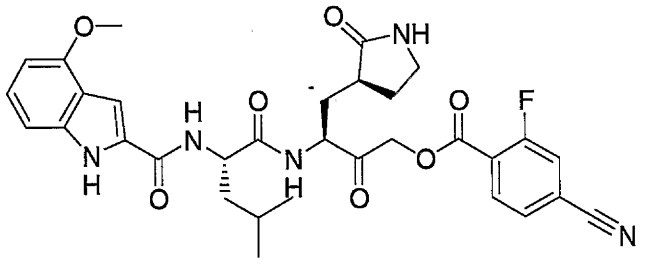
Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 2,6-dimethoxybenzoic acid and making non-critical variations provided a crude brown foam. This material was purified by Biotage MPLC (25M, 3-4% methanol/dichloromethane) to afford 169 mg (66%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.58 (d, J = 2 Hz, 1 H), 8.55 (d, J = 8 Hz, 1 H), 8.45 (d, J = 8 Hz, 1 H), 7.64 (s, 1H), 7.40-7.35 (m, 2H), 7.08 (t, J = 8 Hz, 1 H), 7.00 (d, J = 8 Hz, 1 H), 6.71 (d, J = 8 Hz, 1 H), 6.50 (d, J = 8 Hz, 1 H), 5.01 (d, J = 16 Hz, 1 H), 4.95 (d, J = 16 Hz, 1 H), 4.53-4.48 (m, 2H), 3.87 (s, 3 H), 3.75 (s, 6H), 3.08 (m, 2 H), 2.31 (m, 1 H), 2.11-1.90 (m, 2 H), 1.75-1.55 (m, 5 H), 0.94 (d, J = 8 Hz, 3 H), 0.89 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{33}H_{40}N_4O_9$ *m/z* 637.2 $(M+H)^+$; Anal. Calcd for $C_{33}H_{40}N_4O_9 \cdot 0.25\ H_2O \cdot 0.25\ CHCl_3$: C, 59.51; H, 6.12; N, 8.35. Found: C, 59.49; H, 6.08; N, 8.42.

Example 50: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-chloro-2-hydroxybenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-chlorosalicylic acid and making non-critical variations provided a crude brown syrup. This material was purified by Biotage MPLC (25M, 2-3% methanol/dichloromethane) to afford 64 mg (25%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1 H), 10.50 (bs, 1H), 8.65 (d, J = 8 Hz, 1 H), 8.46 (d, J = 8 Hz, 1 H), 7.81 (d, J = 8 Hz, 1H), 7.63 (m, 1H), 7.37 (s, 1H), 7.08 (m, 2 H), 7.00 (m, 2 H), 6.50 (d, J = 8 Hz, 1 H), 5.16 (d, J = 16 Hz, 2 H), 5.11 (d, J = 16 Hz, 2 H), 4.49 (m, 2H), 3.87 (s, 3 H), 3.13 (m, 2 H), 2.32 (m, 1 H), 2.11-1.98 (m, 2 H), 1.76-1.55 (m, 5 H), 0.94 (d, J = 6 Hz, 3 H), 0.89 (d, J = 6 Hz, 3 H); MS (ESI-) for $C_{31}H_{35}ClN_4O_8$ *m/z* 625.1 $(M-H)^-$; Anal Calcd for $C_{31}H_{35}ClN_4O_8 \cdot 0.1\ H_2O \cdot 0.14\ CHCl_3$: C, 57.93; H, 5.52; N, 8.68. Found: C, 58.04; H, 5.78; N, 8.74; HRMS (ESI+) Calcd for $C_{31}H_{35}ClN_4O_8$+H1 627.2216, found 627.2219.

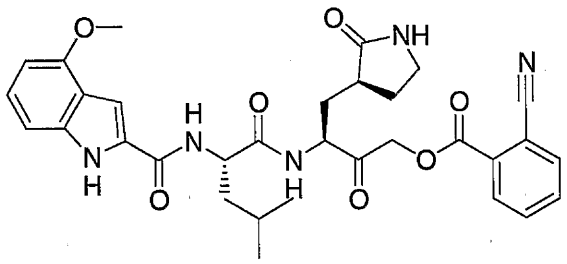
Example 51: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-cyano-2-fluorobenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 4-cyano-2-fluorobenzoic acid and making non-critical variations provided a crude oily brown solid. This material was purified by Biotage MPLC (25M, 2.5-3.5% methanol/dichloromethane) to afford 119 mg (48%) of the title compound as an off-white powder. ^{1}H NMR (DMSO-d_6) δ 11.58 (d, J = 2 Hz, 1 H), 8.63 (d, J = 8 Hz, 1 H), 8.46 (d, J = 8 Hz, 1 H), 8.06 (m, 2 H), 7.83 (d, J = 8 Hz, 1H), 7.65 (s, 1H), 7.36 (d, J = 2 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.50 (d, J = 8 Hz, 1 H), 5.16 (d, J =

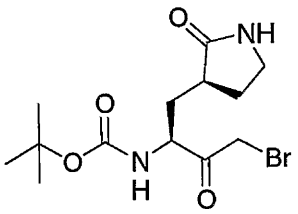
16 Hz, 1 H), 5.11 (d, *J* = 16 Hz, 1 H), 4.49 (m, 2H), 3.87 (s, 3 H), 3.11 (m, 2 H), 2.32 (m, 1 H), 2.10-1.98 (m, 2 H), 1.77-1.53 (m, 5 H), 0.94 (d, *J* = 6 Hz, 3 H), 0.89 (d, *J* = 6 Hz, 3 H); MS (ESI+) for $C_{32}H_{34}FN_5O_7$ *m/z* 620.1 $(M+H)^+$; Anal Calcd for $C_{32}H_{34}FN_5O_7 \cdot 0.3\ H_2O$: C, 61.49; H, 5.58; N, 11.20. Found: C, 61.47; H, 5.61; N, 10.98; HRMS (ESI+) Calcd for $C_{32}H_{34}FN_5O_7$+H1 620.2515, found 620.2532.

Example 52: (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2-cyanobenzoate



Following the procedure described for the preparation of (3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate but substituting 2-cyanobenzoic acid and making non-critical variations provided a crude brown oily solid. This material was triturated with chloroform/ethyl acetate to afford 91 mg (38%) of the title compound as white solid. ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1 H), 8.65 (d, *J* = 8 Hz, 1 H), 8.46 (d, *J* = 8 Hz, 1 H), 8.17 (m, 1H), 8.04 (m, 1H), 7.88 (m, 1H), 7.65 (s, 1H), 7.37 (s, 1H), 7.08 (t, *J* = 8 Hz, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 6.49 (d, *J* = 8 Hz, 1 H), 5.19 (m, 2 H), 4.50 (m, 2H), 3.87 (s, 3 H), 3.11 (m, 2 H), 2.32 (m, 1 H), 2.07-1.97 (m, 2 H), 1.76-1.56 (m, 5 H), 0.94 (d, *J* = 6 Hz, 3 H), 0.89 (d, *J* = 6 Hz, 3 H); MS (ESI+) for $C_{32}H_{35}N_5O_7$ *m/z* 602.2 $(M+H)^+$; Anal Calcd for $C_{32}H_{35}N_5O_7 \cdot 0.4\ H_2O$: C, 63.12, H, 5.93; N, 11.50. Found: C, 63.16; H, 5.96; N, 11.43; HRMS (ESI+) Calcd for $C_{32}H_{35}N_5O_7$+H1 602.2609, found 602.2610.

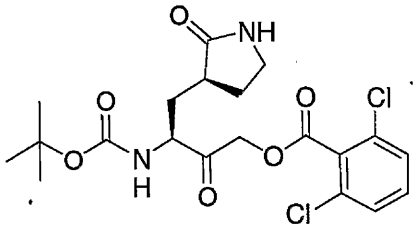
Preparation of Intermediate: *tert*-butyl ((1*S*)-3-bromo-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate



A solution of *tert*-butyl ((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate (1.26 g, 4.3 mmol) in dichloromethane (107 mL) at 0 °C under nitrogen was treated with 48%

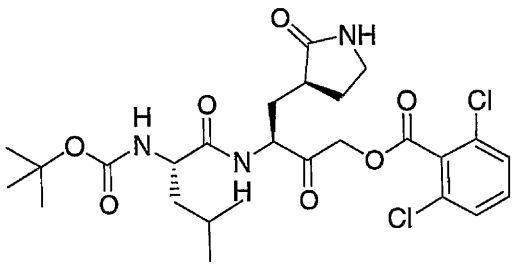
hydrobromic acid (0.48 mL, 4.3 mmol) with effervescence observed. The reaction was stirred at 0 °C for 1 hour, washed once with water (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford 1.23 g (83%) of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (s, 1 H), 7.51 (d, J = 8 Hz, 1H), 4.46 (d, J = 16 Hz, 1H), 4.41 (d, J = 16 Hz, 1H), 4.19 (m, 1 H), 3.13 (m, 2 H), 2.26 (m, 1 H), 2.13 (m, 1 H), 1.87 (m, 1 H), 1.63 (m, 2 H), 1.38 (s, 9 H); MS (ESI+) for $C_{13}H_{21}BrN_2O_4$ *m/z* 371.0 $(M+H)^+$.

Preparation of Intermediate: (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate



A solution of *tert*-butyl ((1*S*)-3-bromo-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)carbamate (1.17 g, 3.2 mmol) in DMF (16 mL) was treated with 2,6-dichloro benzoic acid (794 mg, 4.2 mmol) followed by cesium fluoride (1.18 g, 7.4 mmol). The resulting suspension was placed in a pre-heated oil bath at 65 °C for 2 hours. The reaction was cooled to ambient temperature, diluted with ethyl acetate (100 mL), and washed once with water (40 mL), once with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude yellow syrup. This material was purified by Biotage MPLC (25M, 4.5% methanol/dichloromethane) to afford 1.19 mg (80%) of the title compound as an off-white glass. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (m, 5 H), 5.35 (s, 2H), 4.32 (m, 1 H), 3.23 (m, 2 H), 2.24 (m, 1 H), 2.11 (m, 1 H), 1.86 (m, 1 H), 1.67 (m, 2 H), 1.35 (s, 9 H); MS (ESI+) for $C_{20}H_{24}Cl_2N_2O_6$ *m/z* 481.0 $(M+Na)^+$; HRMS (ESI+) Calcd for $C_{20}H_{24}Cl_2N_2O_6$+H 481.0903, found 481.0890.

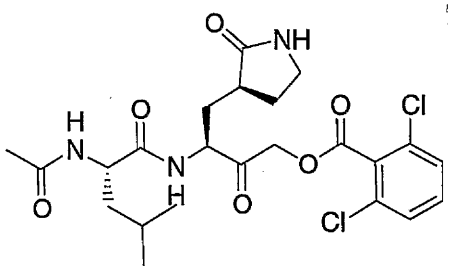
Preparation of Intermediate: (3*S*)-3-{[*N*-(*tert*-butoxycarbonyl)-L-leucyl]amino}-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate



Following the procedure described for the preparation of N^2-(*tert*-butoxycarbonyl)-N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-L-leucinamide but substituting (3*S*)-3-[(*tert*-

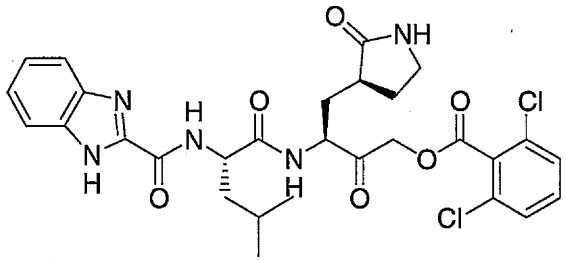
butoxycarbonyl)amino]-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate and making non-critical variations provided a brown foam. This material was purified by LC (50 g 230-400 SiO_2, 2.5-3.5% methanol/chloroform) to afford 413 mg (61%) of the title compound as a light yellow foam. ^{1}H NMR (DMSO-d_6) δ 8.47 (d, J = 8 Hz, 1 H), 7.60 (m, 4 H), 7.05 (d, J = 8 Hz, 1 H), 5.19 (d, J = 16 Hz, 1 H), 5.13 (d, J = 16 Hz, 1 H), 4.47 (m, 1 H), 3.95 (m, 1 H), 3.16 (m, 1 H), 3.08 (m, 1 H), 2.27 (m, 1 H), 2.10 (m, 1 H), 2.03 (m, 1 H), 1.65 (m, 2 H), 1.47-1.37 (m, 11 H), 0.89 (d, J = 4 Hz, 3H), 0.85 (d, J = 4 Hz, 3H); MS (ESI+) for $C_{26}H_{35}Cl_2N_3O_7$ *m/z* 572.1 $(M+H)^+$. Anal. Calcd for $C_{26}H_{35}Cl_2N_3O_7 \cdot 0.5\ H_2O$: C, 53.70; H, 6.24; N, 7.23. Found: C, 53.74; H, 6.31; N, 7.31; HRMS (ESI+) Calcd for $C_{26}H_{35}Cl_2N_3O_7$+Na 594.1744, found 594.1729.

Example 53: (3*S*)-3-[(*N*-acetyl-L-leucyl)amino]-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate



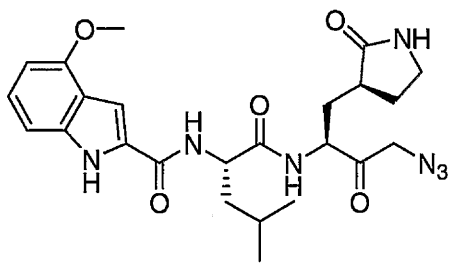
Following the procedure described for the preparation of N^2-acetyl-N^1-[(1*S*)-1-(chloroacetyl)-4-(dimethylamino)-4-oxobutyl]-N^2-methyl-L-leucinamide but substituting (3*S*)-3-{[*N*-(*tert*-butoxycarbonyl)-L-leucyl]amino}-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate and making non-critical variations provided a pale yellow oil. This material was purified by Biotage MPLC (25M, 3.5-4.5% methanol/dichloromethane) to afford 161 mg (78%) of the title compound as a white foam. ^{1}H NMR (DMSO-d_6) δ 8.56 (d, J = 8 Hz, 1 H), 8.06 (d, J = 8 Hz, 1 H), 7.65-7.53 (m, 4 H), 5.17 (d, J = 16 Hz, 1 H), 5.10 (d, J = 16 Hz, 1 H), 4.44 (m, 1 H), 4.25 (m, 1H), 3.12 (m, 2 H), 2.25 (m, 1 H), 2.06 (m, 1 H), 1.97 (m, 1 H), 1.84 (s, 3 H), 1.63 (m, 3 H), 1.45 (m, 2 H), 0.90 (d, J = 8 Hz, 3 H), 0.85 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{23}H_{29}Cl_2N_3O_6$ *m/z* 514.0 $(M+H)^+$; Anal. Calcd for $C_{23}H_{29}Cl_2N_3O_6 \cdot 0.25\ H_2O \cdot 0.1$ EtOAc: C, 53.26; H, 5.79; N, 7.96. Found: C, 53.27; H, 5.82; N, 7.84. HRMS (ESI+) Calcd for $C_{23}H_{29}Cl_2N_3O_6$+H1 514.1506, found 514.1508.

Example 54: (3*S*)-3-{[*N*-(1*H*-benzimidazol-2-ylcarbonyl)-L-leucyl]amino}-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate



Following the procedure described for the preparation of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide but substituting (3*S*)-3-{[*N*-(*tert*-butoxycarbonyl)-L-leucyl]amino}-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate and 1H-benzimidazole-2-carboxylic acid and making non-critical variations provided a crude yellow oil. This material was purified by Biotage MPLC (25M, 3-4% methanol/dichloromethane) to afford 95 mg (72%) of the title compound as an off-white foam. ^{1}H NMR (DMSO-d_6) δ 13.32 (s, 1 H), 8.89 (d, J = 8 Hz, 1 H), 8.60 (d, J = 8 Hz, 1 H), 7.74 (d, J = 8 Hz, 1 H), 7.59 (m, 5 H), 7.29 (m, 2 H), 5.20 (d, J = 20 Hz, 1 H), 5.15 (d, J = 20 Hz, 1 H), 4.56 (m, 2 H), 3.12 (m, 2 H), 2.30 (m, 1 H), 2.01 (m, 2 H), 1.83 (m, 1H), 1.65 (m, 4 H), 0.92 (d, J = 8 Hz, 3 H), 0.89 (d, J = 8 Hz, 3 H); MS (ESI+) for $C_{29}H_{31}Cl_2N_5O_6$ *m/z* 616.0 $(M+H)^+$. Anal. Calcd for $C_{29}H_{31}Cl_2N_5O_6$: C, 56.50; H, 5.07; N, 11.36. Found: C, 57.28; H, 5.32; N, 11.35. HRMS (ESI+) Calcd for $C_{29}H_{31}Cl_2N_5O_6$+H1 616.1724, found 616.1729.

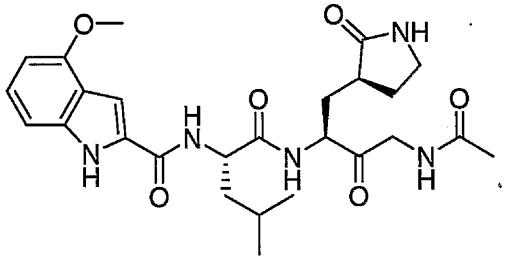
Example 55: *N*-((1*S*)-1-{[((1*S*)-3-azido-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



A solution of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (200 mg, 0.41 mmol) in methanol (2.9 mL) was treated with a solution of NaN_3 (212 mg, 3.26 mmol) in water (0.7 mL). The reaction mixture was stirred at RT for 27 hrs followed by concentration *in vacuo*. The resulting residue was diluted with water (20 mL) followed by extraction with chloroform (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a crude

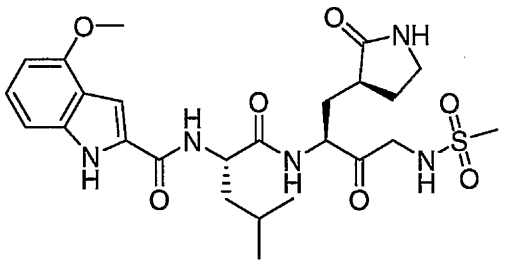
product. This material was purification by column chromatography {2-5% methanol-(1:1 ethyl acetate:chloroform)} to afford 78 mg (39%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1 H), 8.57 (d, *J*=7.8 Hz, 1 H), 8.44 (d, *J*=7.6 Hz, 1 H), 7.64 (s, 1 H), 7.36 (d, *J*=1.5 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.93 - 7.03 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.41 - 4.49 (m, 1 H), 4.37 (m, 1 H), 4.22 (s, 1 H), 4.16 - 4.31 (m, 1 H), 3.87 (s, 3 H), 3.02 - 3.17 (m, 2 H), 2.27 (m, 1 H), 2.03 - 2.22 (m, 1 H), 1.90 - 2.02 (m, 1 H), 1.46 - 1.79 (m, 5 H), 0.94 (d, *J*=8.0 Hz, 3 H), 0.89 (d, *J*=8.0 Hz, 3 H); MS (ESI+) for $C_{24}H_{31}N_7O_5$ *m/z* 498.1 $(M+H)^+$.

Example 56: *N*-((1*S*)-1-{[((1*S*)-3-(acetylamino)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



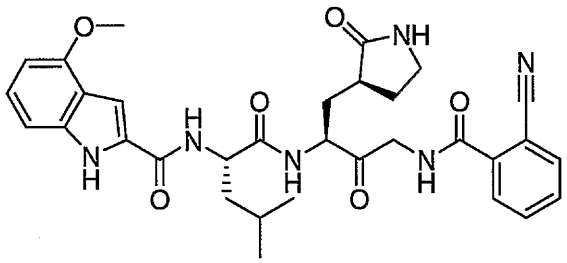
A solution of *N*-((1*S*)-1-{[((1*S*)-3-azido-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (200 mg, 0.40 mmol) in 1,4-dioxane (4 mL) was treated with 10% Pd/C (200 mg) and acetic anhydride (0.19 mL, 2.01 mmol). The resulting black suspension was stirred at RT for 4 hrs under atmospheric H_2, filtered thru celite, rinsed with ethyl acetate, and concentrated to give a crude product. This material was purified by column chromatography {5-15% methanol-(1:1 ethyl acetate:chloroform)} to afford 115 mg (56%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1 H), 8.55 (d, *J*=7.8 Hz, 1 H), 8.42 (d, *J*=7.6 Hz, 1 H), 8.07 (t, *J*=5.6 Hz, 1 H), 7.63 (s, 1 H), 7.35 (d, *J*=1.5 Hz, 1 H), 7.08 (t, *J*=8.0 Hz, 1 H), 6.96 - 7.02 (m, 1 H), 6.49 (d, *J*=7.6 Hz, 1 H), 4.43 - 4.53 (m, 1 H), 4.35 (m, 1 H), 3.99 (d, *J*=5.6 Hz, 2 H), 3.87 (s, 3 H), 3.01 - 3.16 (m, 2 H), 2.24 - 2.36 (m, 1 H), 2.02 - 2.15 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.83 (s, 3 H), 1.65 - 1.77 (m, 2 H), 1.49 - 1.64 (m, 3 H), 0.94 (d, *J*=8.0 Hz, 3 H), 0.89 (d, *J*=8.0 Hz, 3 H); MS (APCI+) for $C_{26}H_{35}N_5O_6$ *m/z* 514.2 $(M+H)^+$.

Example 57: 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-[(methylsulfonyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide



A mixture of *N*-((1*S*)-1-{[((1*S*)-3-azido-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (497 mg, 1.0 mmol), Pd black (106 mg, 1.0 mmol), hydrochloric acid (1.0 mL, 2.0 M in Et_2O, 2.0 mmol), and EtOH (4.4 mL) was stirred at room temperature for 22 hrs under atmospheric H_2. The black suspension was filtered thru celite, rinsed with EtOH, and concentrated to give a crude product. A portion of this hydrochloric acid salt (242 mg, 0.48 mmol) was taken up in dichloromethane (4 mL) and treated with methanesulfonyl chloride (0.07 mL, 0.95 mmol) followed by Et_3N (0.07 mL, 0.48 mmol). The reaction mixture was stirred at RT for 4.5 hrs, quenched with water, and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a crude product. This material was purified by column chromatography (2-6% methanol-dichloromethane gradient) to afford 75 mg (28%) of the title compound as a white solid. MS (ESI+) for $C_{25}H_{35}N_5O_7S$ *m/z* 550.2 $(M+H)^+$.

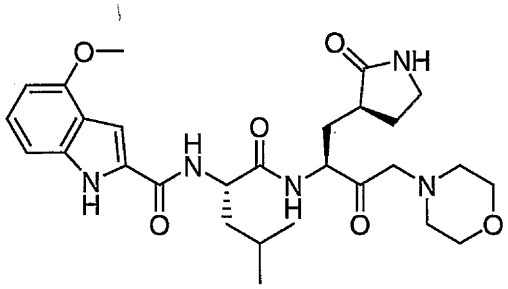
Example 58: *N*-((1*S*)-1-{[((1*S*)-3-[(2-cyanobenzoyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-[(methylsulfonyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide of but treating the intermediate hydrochloric acid salt with 2-cyanobenzoic acid (77 mg, 0.52 mmol), NMM (0.12 mL, 1.05 mmol), and HATU (198 mg, 0.52 mmol) in DMF (2 mL) at 0 °C for 1 hr 40 min. The reaction was quenched with 1:1 saturated aqueous $NaHCO_3$: ice /water, extracted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude product. This material was purifed by column chromatography (2-6% methanol-

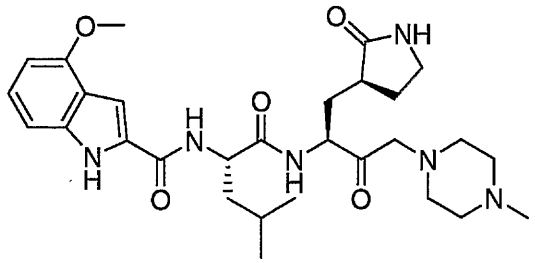
dichloromethane gradient) to afford 45 mg (16%) of the title compound as a pale yellow solid (note: mixture of diastereomers. MS (ESI+) for $C_{32}H_{36}N_6O_6$ *m/z* 601.2 $(M+H)^+$.

Example 59: 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-morpholin-4-yl-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide



A solution of *N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide (100 mg, 0.20 mmol) in THF (2 mL) was treated with morpholine (17 µL, 0.20 mmol) and stirred at RT 5 h. The resulting opaque off-white reaction mixture was quenched with water, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give a crude product. This material was purified by reverse-phase chromatography (CH_3CN-water gradient) followed by lyophilization afforded 39 mg (35%) of the title compound as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.53 (d, *J*=1.8 Hz, 1 H), 8.73 - 8.81 (m, 1 H), 8.46 (d, *J*=7.1 Hz, 1 H), 7.70 (s, 1 H), 7.37 (d, *J*=1.8 Hz, 1 H), 7.10 (t, *J*=8.0 Hz, 1 H), 6.96 - 7.04 (m, 1 H), 6.50 (d, *J*=7.8 Hz, 1 H), 4.39 - 4.47 (m, 1 H), 4.31 - 4.39 (m, 1 H), 3.87 (s, 3 H), 3.07 - 3.19 (m, 4 H), 2.27 - 2.37 (m, 1 H), 2.07 - 2.17 (m, 1 H), 1.92 - 2.04 (m, 1 H), 1.60 - 1.78 (m, 4 H), 1.49 - 1.59 (m, 1 H), 0.94 (d, *J*=8.0 Hz, 3 H), 0.89 (d, *J*=8.0 Hz, 3 H); MS (ESI+) for $C_{28}H_{39}N_5O_6$ *m/z* 542.2 $(M+H)^+$.

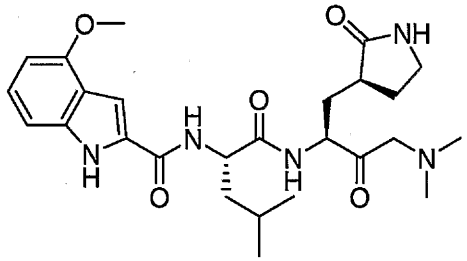
Example 60: 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-(4-methylpiperazin-1-yl)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-morpholin-4-yl-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-

carboxamide but substituting *N*-methyl piperazine and making non-critical variations provided a crude product. This material was purified by reverse-phase chromatography (CH_3CN-water gradient) followed by lyophilization to afford 28 mg (26%) of the title compound. MS (ESI+) for $C_{29}H_{42}N_6O_5$ *m/z* 555.3 $(M+H)^+$.

Example 61: *N*-((1*S*)-1-{[((1*S*)-3-(dimethylamino)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide



Following the procedure described for the preparation of 4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-morpholin-4-yl-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide but substituting dimethylamine and making non-critical variations provided a crude product. This material was purified by reverse-phase chromatography (CH_3CN-water gradient) followed by lyophilization to afford 22 mg (22%) of the title compound. MS (ESI+) for $C_{26}H_{37}N_5O_5$ *m/z* 500.2 $(M+H)^+$.

The compounds described above where analyzed by a FRET biochemical assay and by invitro virological assays using cell culture techniques.

Protection from SARS Infection: Neutral Red Endpoint

The ability of compounds to protect cells against infection by the SARS coronavirus is measured by a cell viability assay similar to that described in Borenfreund, E., and Puerner, J. 1985. Toxicity determined in vitro by morphological alterations and neutral red absorption Toxicology Letters. 24:119-124, utilizing neutral red staining as an endpoint. Briefly, medium containing appropriate concentrations of compound or medium only is added to Vero cells. Cells are infected with SARS-associated virus or mock-infected with medium only. One to seven days later, the medium is removed and medium containing neutral red is added to the test plates. Following incubation at 37°C for two hours, cells are washed twice with PBS and a 50% EtOH, 1% acetic acid solution is added. The cells are shaken for 1 to 2 minutes and incubated at 37°C for 5 to 10 minutes. The amount of neutral red is quantified spectrophotometrically at 540nm. Data is expressed as the percent of neutral red in wells of compound-treated cells compared to neutral red in wells of uninfected, compound-free cells. The fifty percent effective concentration (EC50) is calculated as the concentration of compound that increases the percent of neutral red production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50%

cytotoxicity concentration (CC50) is calculated as the concentration of compound that decreases the percentage of neutral red produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells. The therapeutic index is calculated by dividing the cytotoxicity (CC50) by the antiviral activity (EC50).

Protection from SARS Infection: Glo endpoint

The ability of compounds to protect cells against infection by the SARS coronavirus can also be measured by a cell viability assay utilizing luciferase to measure intracellular ATP as an endpoint. Briefly, medium containing appropriate concentrations of compound or medium only is added to Vero cells. Cells are infected with SARS-associated virus or mock-infected with medium only. One to seven days later, the medium is removed and the amount of intracellular ATP is measured as per Promega Technical Bulletin No. 288: CellTiter-Glo® Luminescent Cell Viability Assay (Promega, Madison, WI). The CellTiter-Glo® reagent is added to the test plates and following incubation at 37°C for 1.25 hours, the amount of signal is quantified using a luminometer at 490nm. Data is expressed as the percent of luminescent signal from wells of compound-treated cells compared to the luminescent signal from wells of uninfected, compound-free cells. The fifty percent effective concentration (EC50) is calculated as the concentration of compound that increases the percent of the luminescent signal from infected, compound-treated cells to 50% of the luminescent signal from uninfected, compound-free cells. The 50% cytotoxicity concentration (CC50) is calculated as the concentration of compound that decreases the percentage of the luminescent signal from uninfected, compound-treated cells to 50% of the luminescent signal from uninfected, compound-free cells. The therapeutic index is calculated by dividing the cytotoxicity (CC50) by the antiviral activity (EC50).

Cytotoxicity

The ability of compounds to cause cytotoxicity in cells is measured by a cell viability assay similar to that described in Weislow, O.S., Kiser, R., Fine, D.L., Bader, J., Shoemaker, R.H., and Boyd, M.R.1989. New Soluble-Formazan Assay for HIV-1 Cytopathic Effects: Application to High-Flux Screening of Synthetic and Natural Products for AIDS-Antiviral Activity. Journal of the National Cancer Institute 81(08): 577-586), utilizing formazan as an endpoint. Briefly, Vero cells are resuspended in medium containing appropriate concentrations of compound or medium only. One to seven days later, XTT and PMS are added to the test plates and following incubation at 37°C for two hours the amount of formazan produced is quantified spectrophotometrically at 540nm. Data is expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of compound-free cells. The 50% cytotoxicity concentration (CC50) is calculated as the concentration of compound that decreases the percentage of formazan produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells.

Protection from Coronavirus 229E Infection

The ability of compounds to protect cells against infection by human coronavirus 229E is measured by a cell viability assay similar to that described in Weislow, O.S., Kiser, R., Fine, D.L., Bader, J., Shoemaker, R.H., and Boyd, M.R.1989. New Soluble-Formazan Assay for HIV-1 Cytopathic Effects: Application to High-Flux Screening of Synthetic and Natural Products for AIDS-Antiviral Activity. Journal of the National Cancer Institute 81(08): 577-586), utilizing formazan as an endpoint. Briefly, medium containing appropriate concentrations of compound or medium only is added to MRC-5 cells. Cells are infected with human coronavirus 229E or mock-infected with medium only. One to seven days later, XTT and PMS are added to the test plates and following incubation at 37°C for two hours the amount of formazan produced is quantified spectrophotometrically at 540nm. Data is expressed as the percent of formazan in wells of compound-treated cells compared to formazan in wells of uninfected, compound-free cells. The fifty percent effective concentration (EC50) is calculated as the concentration of compound that increases the percent of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50% cytotoxicity concentration (CC50) is calculated as the concentration of compound that decreases the percentage of formazan produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells. The therapeutic index is calculated by dividing the cytotoxicity (CC50) by the antiviral activity (EC50).

Coronavirus 3C Protease FRET Assay and Analysis

Proteolytic activity of Coronavirus 3C protease is measured using a continuous fluorescence resonance energy transfer assay. The SARS $3CL^{pro}$ FRET assay measures the protease catalyzed cleavage of TAMRA- SITSAVL**QS**GFRKMK-(DABCYL)-OH to TAMRA - SITSAVL**Q** and **S**GFRKMK-(DABCYL)-OH . The fluorescence of the cleaved TAMRA (ex. 558 nm / em. 581 nm) peptide was measured using a TECAN SAFIRE fluorescence plate reader over the course of 10 min. Typical reaction solutions contained 20 mM HEPES (pH 7.0), 1 mM EDTA, 4.0 uM FRET substrate, 4% DMSO and 0.005% Tween-20. Assays were initiated with the addition of 25 nM SARS $3CL^{pro}$ (nucleotide sequence 9985-10902 of the Urbani strain of SARS coronavirus complete genome sequence (NCBI accession number AY278741)). Percent inhibition was determined in duplicate at 0.001mM level of inhibitor.

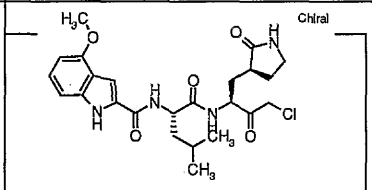
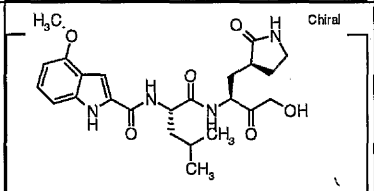
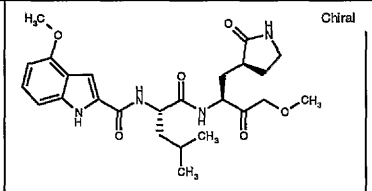
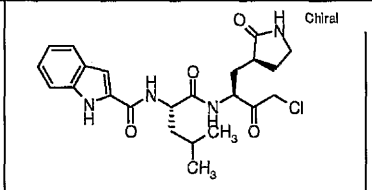
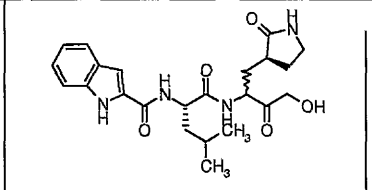
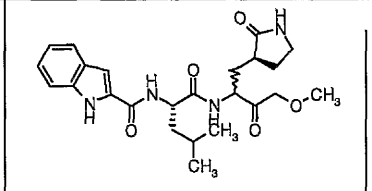
Data was analyzed with the non-linear regresssion analysis program Kalidagraph using the equation:

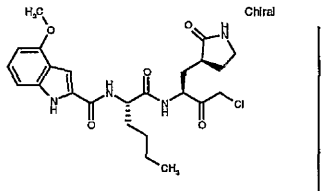
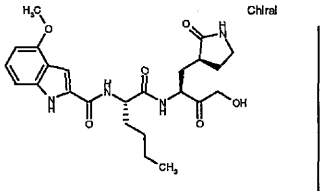
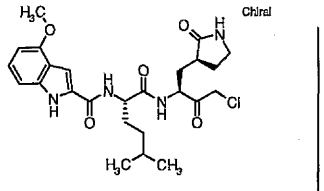
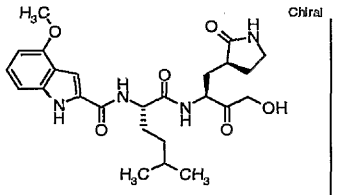
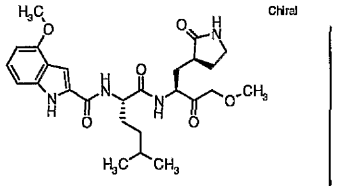
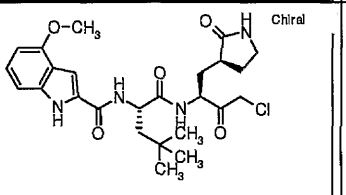
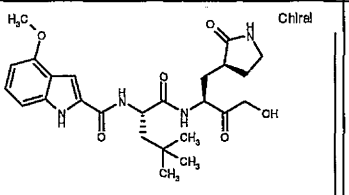
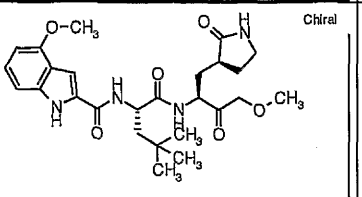
$$FU = \text{offset} + (\text{limit})(1 - e^{-(kobs)t})$$

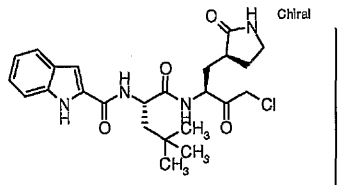
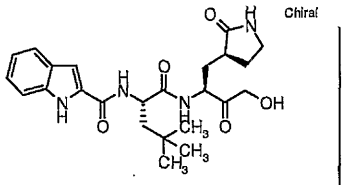
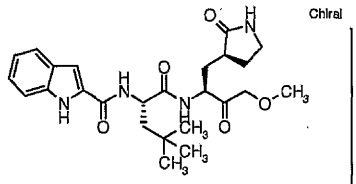
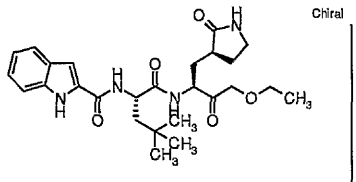
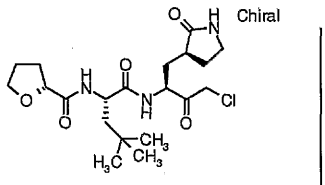
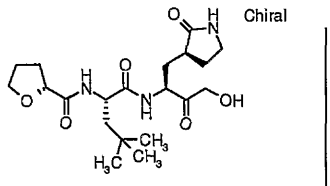
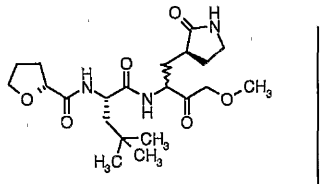
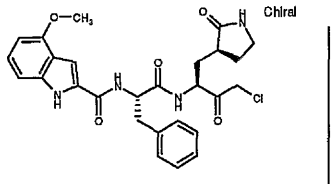
where offset equals the fluorescence signal of the uncleaved peptide substrate, and limit equals the fluorescence of fully cleaved peptide substrate. The kobs is the first order rate constant for this reaction, and in the absence of any inhibitor represents the utilization of substrate. In an enzyme start reaction which contains an irreversible inhibitors, and where the calculated limit is less than 20% of the theoretical maximum limit, the calculated kobs represents the rate of inactivation of coronavirus 3C protease. The slope (kobs/ I) of a plot of kobs vs. [I] is a measure of the avidity of the inhibitor for

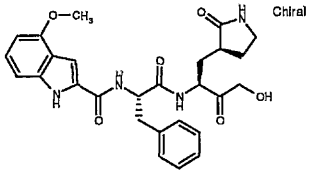
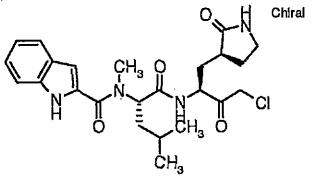
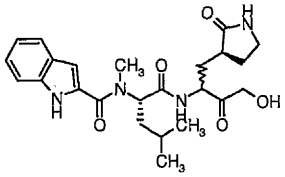
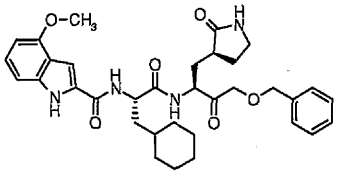
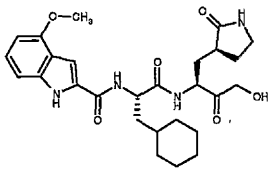
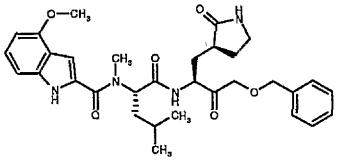
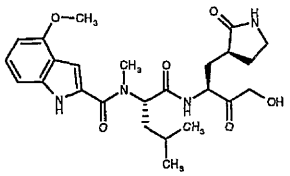
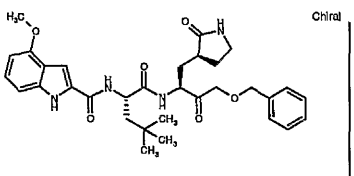
an enzyme. For very fast irreversible inhibitors, kobs/I is calculated from observations at only one or two [I] rather than as a slope.

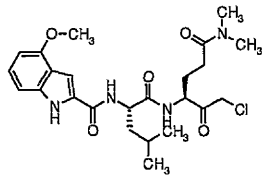
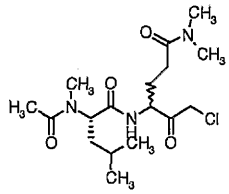
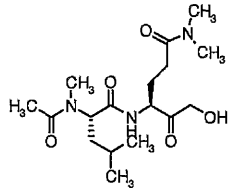
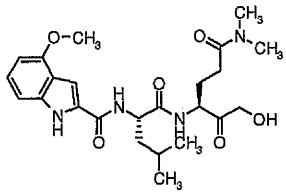
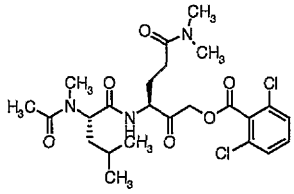
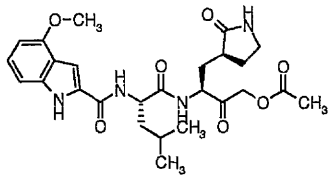
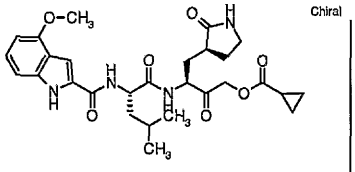
The following table describe the mean antiviral EC50 and the inhibition of the C3 like protease in the FRET assay.

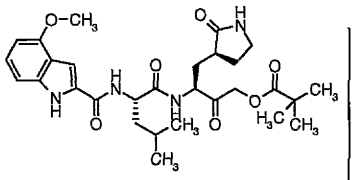
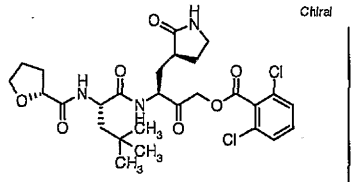
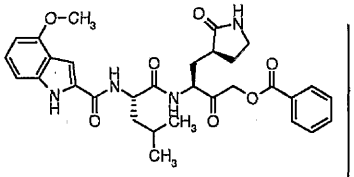
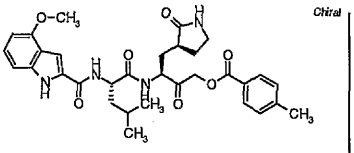
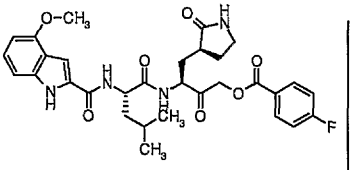
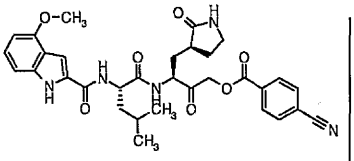
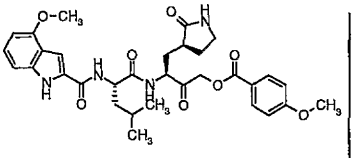
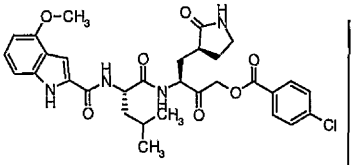
Example #	Structure	FRET Assay % Inh @ 1 uM	FRET Assay IC50 uM	FRET Assay kobs/I	Mean antiviral EC50
Example-01				283039	10
Example-02		100	0.004		5.1
Example-03		97	0.051		31
Example-04		100			
Example-05		99	0.038		20
Example-06		90	0.131		45

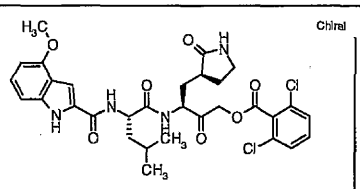
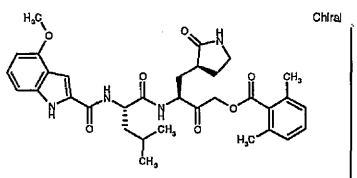
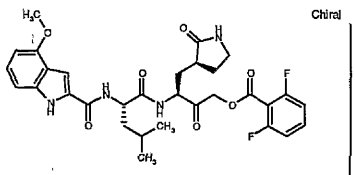
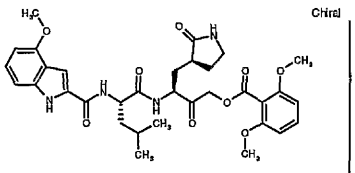
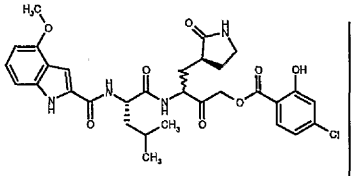
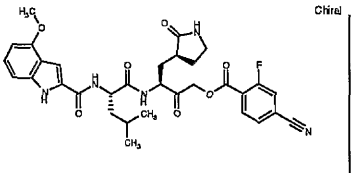
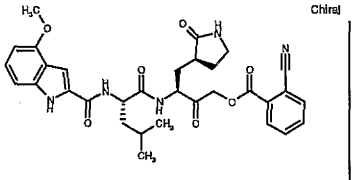
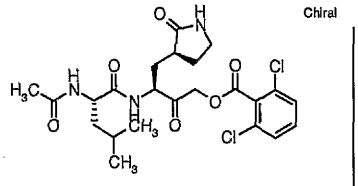
Example-07		100		213658	>42
Example-08		100	0.02		10
Example-09		100			
Example-10		100	0.034		33
Example-11		95	0.036		50
Example-12		100			
Example-13		100	0.023		11
Example-14		96	0.054		32

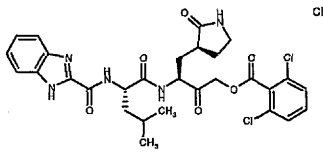
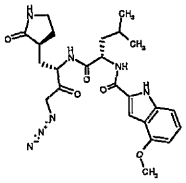
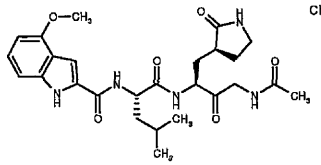
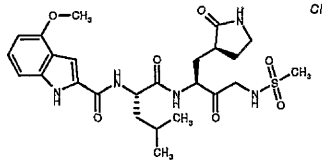
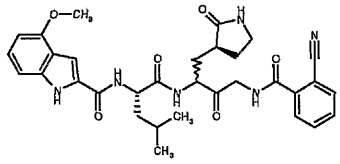
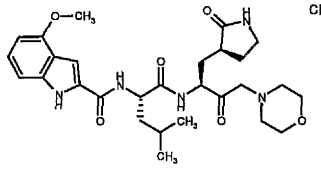
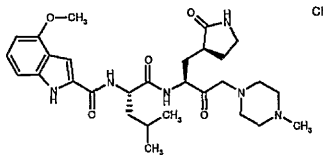
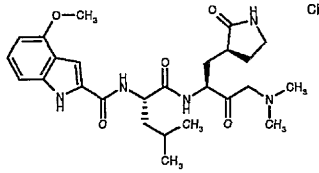
Example-15		100			
Example-16		100	0.02		17
Example-17		92	0.105		46
Example-18		92	0.112		20
Example-19					
Example-20		95	0.091		33
Example-21		50	1.08		>100
Example-22		100		155175	7.5

Example-23		91	0.103		47
Example-24		100			
Example-25		90	0.152		39
Example-26		95	0.133		5.8
Example-27		100	0.025		14
Example-28		51	0.927		26
Example-29		94	0.105		19
Example-30		99	0.032		4.1

Example-31					
Example-32					
Example-33		0			
Example-34		86	0.19		
Example-35		0			
Example-36		87	0.22		6.7
Example-37		89	0.18		9.3

Example-38		85	0.23		5.4
Example-39		80	0.133		2.3
Example-40		95	0.086		5.0
Example-41		94	0.087		4.4
Example-42		95	0.082		5.9
Example-43		98	0.053		6.4
Example-44		95	0.079		5.3
Example-45		95			5.3

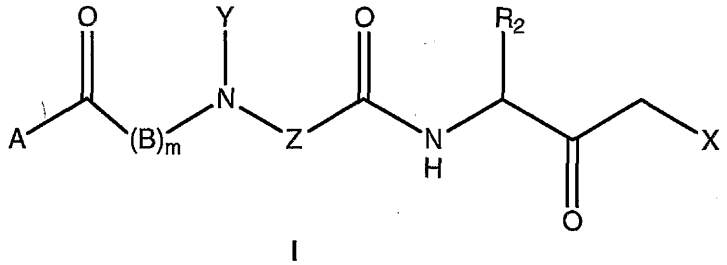
Example-46				62993	.35
Example-47		88	0.16		
Example-48				12766	14
Example-49		86	0.21		
Example-50				10148	32
Example-51				13321	30
Example-52		100	0.017		10
Example-53		44	1.28		7.0

Example-54		99		30287	10
Example-55		95	0.101		94
Example-56		64	2.65		>100
Example-57		93	0.107		20
Example-58		56			>100
Example-59		23			
Example-60		7			
Example-61		17			>100

While the invention has been described in terms of various preferred embodiments and specific examples, the invention should be understood as not being limited by the foregoing detailed description, but as being defined by the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound comprising the following structure:



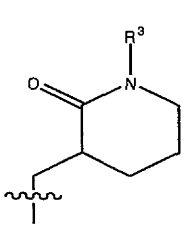
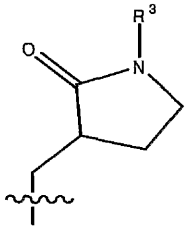
I

wherein:

m is an integer selected from 0 and 1;

Y is selected from the group consisting of H, $-CH_3$, and $-CH_2CH_3$;

R^1 is C_1 to C_7 alkyl, C_3 to C_{10} cycloalkyl, and benzyl wherein said alkyl, benzyl and cycloalkyl is unsubstituted or independently substituted with 1 to 3 R^7 substituents;

R^2 is selected from  ,  , and 

R^3 is independently selected from H and C_1 to C_3 alkyl;

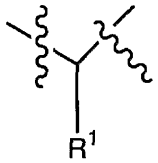
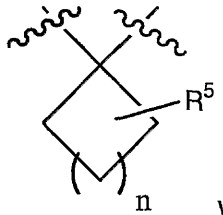
each R^4 and $R^{4'}$ is independently H, C_1 to C_3 alkyl or C_3 to C_6 cycloalkyl, wherein each alkyl and cycloalkyl is unsubstituted or substituted with oxo, 1 to 3 halogens or 1 to 3 hydroxyls;

R^5 is H or selected from R^7 substituents;

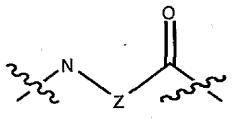
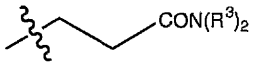
R^6 is C_6 to C_{10} aryl, benzyl, C_3 to C_{10} cycloalkyl, 4 to 10 member heterocycle or C_1 to C_7 alkyl wherein the foregoing R^6 substituents are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

each R^7 is independently selected from halogen, oxo, C_1 to C_4 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_6 cycloalkyl, $-OR^4$, $-NR^4C(O)R^4$, $-NR^4R^{4'}$, SR^4, $-SOR^4$, $-SO^2R^4$, $-C(O)R^4$, $-CO_2R^4$, $-SO_2NR^4R^{4'}$, $-C(O)NR^4R^{4'}$, $-NR^4SO_2R^4$, 4 to 10 member heterocycle and $-OC(O)R^4$, wherein the

foregoing alkyl, alkenyl, alkynyl, cycloalkyl and heterocycle groups are each optionally substituted with halogen, hydroxy, C_1 to C_6 alkoxy, and oxo;

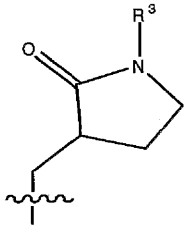
Z is selected from the group consisting of  and  wherein n is 0 to 3;

A is 4 to 10 member heterocycle, C_3 to C_{10} cycloalkyl, C_6 to C_{10} aryl and C_1 to C_7 alkyl , wherein said heterocycle, cycloalkyl, alkyl and aryl are unsubstituted or independently substituted with 1 to 3 R^7 substituents;

B is  with the proviso that when R^2 is  then m is 0; and

X is selected from –OH, -OR^6, Cl, Br, I, and -$OC(O)R^6$;

and the solvates and pharmaceutically active salts thereof.

2. The compound of claim 1 wherein R^2 is  .

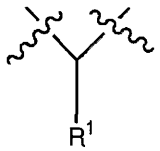
3. The compound of claim 2 wherein A is a C_4 to C_{10} heterocycle unsubstituted or independently substituted with 1 to 3 of the following substituents: halogen, C_1 to C_4 alkyl, -OR^4, -$NR^4C(O)R^4$, -$NR^4R^{4'}$, SR^4, SOR^4, SO^2R^4, -$C(O)R^4$, -CO_2R^4, -$SO_2NR^4R^{4'}$, -$NR^4SO_2NR^4R^{4'}$ and –$OC(O)R^4$.

4. The compound of claim 3 wherein X is –OH, Cl and OC(O)aryl wherein said aryl isindependently substituted with 0 to 2 of the following moieties chlorine, fluorine cyano, methoxy, hydroxyl.

5. The compound of claim 3 wherein said heterocycle is an indole or benzimidazole said indole or benzamidazole is unsubstituted or substituted with –OH, -OR^4 or 1-3 halogens.

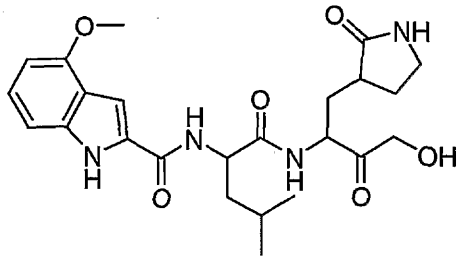
6. The compound of claim 3 wherein Y is H.

7. The compound of claim 3 wherein m is 0.

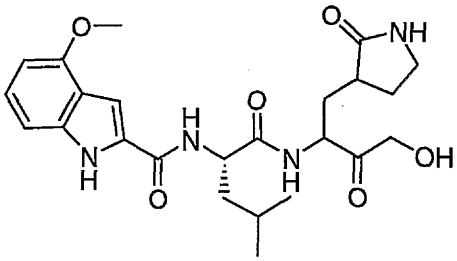
8. The compound of claim 7 wherein Z is 

9. The compound of claim 8 wherein R^1 is C_1 to C_7 alkyl, said alkyl is unsubstituted or substituted with C_3 to C_6 cycloalkyl.

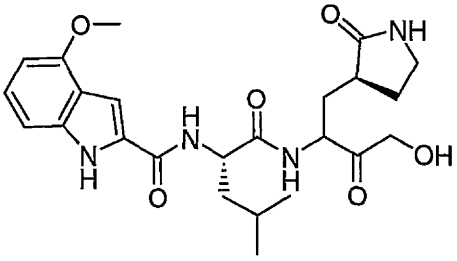
10. A compound having the following structure:



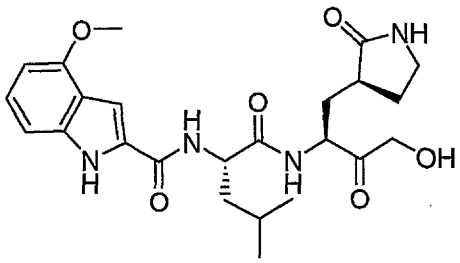
11. The compound of claim 10 wherein the compound is



12. The compound of claim 11 wherein the compound is



13. The compound of claim 12 wherein the compound is



14. A method of interfering with or preventing SARS related coronavirus viral replication activity comprising contacting a SARS related coronavirus protease with a therapeutically effective amount of a compound of claim 1.

15. A method of treating a SARS related infection in a patient, comprising administering to said patient a pharmaceutically effective amount of a compound of claim 1.

16. A method of treating a SARS related infection in a patient, comprising administering to said patient a pharmaceutically effective amount of a compound of claim 12.

17. A pharmaceutical composition for the treatment of a coronavirus in a mammal comprising administering a therapeutic amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

18. A method of treating a coronavirus infection in a mammal, comprising administering a pharmaceutically effective amount of a compound of claim 1.

19. The pharmaceutical composition of claim 17 wherein the coronavirus is a SARS coronavirus.

20. The pharmaceutical composition of claim 19 wherein the pharmaceutical composition includes at least one of a pharmaceutically acceptable interferon, p-glycoprotein inhibitor and CYP3A4 inhibitor.

21. A compound selected from the group consisting of :
N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,
N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,

4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide,

.*N*-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}pentyl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}pentyl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-4-methoxy-1*H*-indole-2-carboxamide,

4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-4-methylpentyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,

4-methoxy-*N*-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-ethoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-1*H*-indole-2-carboxamide,

N^1-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide,

N^1-((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide,

N^1-((1*S*)-3-methoxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-4-methyl-N^2-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucinamide,

N-((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-phenylalaninamide,

N-((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)-*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-phenylalaninamide,

N-((1*S*)-1-{[((1*S*)-3-chloro-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-*N*-methyl-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-*N*-methyl-1*H*-indole-2-carboxamide,

N-[(1*S*)-2-[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-1-(cyclohexylmethyl)-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide,

N-{(1*S*)-1-(cyclohexylmethyl)-2-[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]-2-oxoethyl}-4-methoxy-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-hydroxy-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide,

N-((1*S*)-1-{[((1*S*)-3-(benzyloxy)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3,3-dimethylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,

4-Methoxy-1H-indole-2-carboxylic acid {1-[3-chloro-1-(2-dimethylcarbamoyl-ethyl)-2-oxo-propylcarbamoyl]-3-methyl-butyl}-amide,

4-Methoxy-1H-indole-2-carboxylic acid {1-[1-(2-dimethylcarbamoyl-ethyl)-3-hydroxy-2-oxo-propylcarbamoyl]-3-methyl-butyl}-amide,

(3*S*)-3-[(*N*-acetyl-*N*-methyl-L-leucyl)amino]-6-(dimethylamino)-2,6-dioxohexyl 2,6-dichlorobenzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl acetate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl cyclopropanecarboxylate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl pivalate,

(3*S*)-3-({4-methyl-*N*-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl benzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-methylbenzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-fluorobenzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-cyanobenzoate,

(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-methoxybenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-chlorobenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dimethylbenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-difluorobenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dimethoxybenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-chloro-2-hydroxybenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 4-cyano-2-fluorobenzoate,
(3*S*)-3-({*N*-[(4-methoxy-1*H*-indol-2-yl)carbonyl]-L-leucyl}amino)-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2-cyanobenzoate,
(3*S*)-3-[(*N*-acetyl-L-leucyl)amino]-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate,
(3*S*)-3-{[*N*-(1*H*-benzimidazol-2-ylcarbonyl)-L-leucyl]amino}-2-oxo-4-[(3*S*)-2-oxopyrrolidin-3-yl]butyl 2,6-dichlorobenzoate,
N-((1*S*)-1-{[((1*S*)-3-azido-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,
N-((1*S*)-1-{[((1*S*)-3-(acetylamino)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,
4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-[(methylsulfonyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide,
N-((1*S*)-1-{[((1*S*)-3-[(2-cyanobenzoyl)amino]-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide,
4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-morpholin-4-yl-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide,
4-methoxy-*N*-((1*S*)-3-methyl-1-{[((1*S*)-3-(4-methylpiperazin-1-yl)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}butyl)-1*H*-indole-2-carboxamide, and
N-((1*S*)-1-{[((1*S*)-3-(dimethylamino)-2-oxo-1-{[(3*S*)-2-oxopyrrolidin-3-yl]methyl}propyl)amino]carbonyl}-3-methylbutyl)-4-methoxy-1*H*-indole-2-carboxamide.

22. A method of treating a SARS related infection in a patient, comprising administering to said patient a pharmaceutically effective amount of a compound of claim 13.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001289

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/10 A61K38/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORRIS ET AL.: "In Vitro and Ex Vivo Inhibition of Hepatitis A Virus 3C Proteinase by a Peptidyl Monofluromethyl Ketone" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 5, May 1997 (1997-05), pages 797-807, XP002339902 Cpds. 13a, 13b	1
Y	the whole document	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2005	05/09/2005

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	XUE WU ZHANG ET AL: "EXPLORING THE BINDING MECHANISM OF THE MAIN PROTEINASE IN SARS-ASSOCIATED CORONAVIRUS AND ITS IMPLICATION TO ANTI-SARS DRUG DESIGN" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 12, no. 9, 1 May 2004 (2004-05-01), pages 2219-2223, XP001202604 ISSN: 0968-0896 abstract	1
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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